Gemeinsamer Bundesausschuss

Anlage zur Zusammenfassenden Dokumentation

Beratungsverfahren nach § 137e SGB V über eine Richtlinie zur Erprobung der

Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

infolge der Bewertung nach § 137h Absatz 1 Satz 4 SGB V Absatz 1 Satz 4 SGB V

Unterausschuss Methodenbewertung
des Gemeinsamen Bundesausschusses

Korrespondenzadresse:
Gemeinsamer Bundesausschuss
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Inhaltsverzeichnis

Informationsergänzung zu einer neuen Untersuchungs- oder Behandlungsmethode mit einem Medizinprodukt hoher Risikoklasse gemäß § 137h SGB V

Methode	Medikamentenbeschichteter Ballonkatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Krankenhaus/ Medizinproduktehersteller	Urotronic Inc. Xenium Lane North Plymouth, MN 55441 USA Vertreten durch (Vollmacht anbei): Kalms Consulting GmbH Rheinstraße 45-46 12161 Berlin kschroeder@kalmconsulting.com 0172 362 4522
Datum	14.12.2020

Informationsergänzung zum Formular

Orientieren Sie sich bei Ihrer Informationsergänzung an der Struktur und den Angaben im vom anfragenden Krankenhaus eingereichten Formular. Das Formular hat der Gemeinsame Bundesausschuss auf seiner Internetseite eingestellt. Informationen, die bereits im eingereichten Formular angegeben sind, müssen Sie nicht wiederholen.

Abschnitt, Nummer des Formulars	**Informationsergänzung** Bitte begründen Sie Ihre Informationsergänzung möglichst durch Literatur (z. B. relevante Studien), listen Sie die Literatur unter dem „Literaturverzeichnis“ (siehe unten) auf und übermitteln Sie die zugehörigen Volltexte.
II 1.1 Symptomatik und Spontanverlauf	Das Methodenpapier 6.0 des IQWiG wurde am 5.11. und somit nach Übermittlung von Informationen zur gegenständlichen Methode veröffentlicht. Aus den Ausführungen unter *3.8.2 § 137h-Bewertung* geht hervor, dass Schädlichkeit einem höheren Schaden im Vergleich zu einer Nichtbehandlung entspricht. Daher möchten wir die Ausführungen hinsichtlich des Spontanverlaufs von Harnröhrenstrikturen präzisieren. Mundy, 2010 erläutern in einem Übersichtsartikel die Komplikationen unbehandelter Harnröhrenstrikturen und haben dies übersichtlich in Tabelle 2 zusammengefasst:

	Tabelle 2 Komplikationen unbehandelter Strikturen **Komplikation** / **Inzidenz %** Verdickung der Blasenwand, trabekulierte Blase (auch Trabekel- oder Balkenblase) / 85 Akuter Harnverhalt / 60 Prostatitis / 50 Epididymo-Orchitis / 25 Periurethraler Abscess / 15 Steine (Blase, Harnröhre) / 10 Hydronephrose / 20 Diese hohe Rate an Komplikationen von unbehandelten Harnröhrenstrikturen haben zur Folge, dass heutzutage keine Studien durchgeführt werden, die eine neue Behandlungsmethode mit dem Spontanverlauf der Erkrankung vergleichen. Um die Wiederholung bereits übermittelter Informationen zu vermeiden, verzichten wir auf eine detaillierte Darstellung des Vergleichs der oben aufgeführten Komplikationen mit den im Abschnitt IIIb der Informationsübermittlungen erläuterten Resultaten der klinischen Studien.
Bitte tragen Sie hier die Nummer des Abschnitts und die Nummer des Feldes ein, auf die sich Ihre Informationsergänzung bezieht (z. B. II 1.1).	Bitte tragen Sie hier Ihre ergänzenden Informationen ein.
Bitte tragen Sie hier die Nummer des Abschnitts und die Nummer des Feldes ein, auf die sich Ihre Informationsergänzung bezieht (z. B. II 1.1).	Bitte tragen Sie hier Ihre ergänzenden Informationen ein.

Informationenergänzung zu allgemeinen Aspekten

Allgemeine Anmerkung Bitte begründen Sie Ihre Informationsergänzung möglichst durch Literatur (z. B. relevante Studien), listen Sie die Literatur unter dem „Literaturverzeichnis“ (siehe unten) auf und übermitteln Sie die zugehörigen Volltexte.
Bitte tragen Sie hier nur allgemeine Anmerkungen ein, die nicht einem konkreten Abschnitt des Formulars zur Übermittlung von Informationen über den Stand der wissenschaftlichen Erkenntnisse zugeordnet werden können.

Literaturverzeichnis

Mundy AR, Andrich DE. Urethral strictures. BJU Int. 2011 Jan;107(1):6-26. doi: 10.1111/j.1464-410X.2010.09800.x. PMID: 21176068.

Bundesanzeiger
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Bekanntmachung
Veröffentlicht am Dienstag, 6. April 2021
BAnz AT 06.04.2021 B6

Bundesministerium für Gesundheit

Bekanntmachung des Gemeinsamen Bundesausschusses 1. über die Aufnahme von Beratungen über eine Richtlinie zur Erprobung des medikamentenbeschichteten Ballondilatationskatheters zur transurethralen Behandlung von Harnröhrenstrikturen sowie 2. zur Ermittlung weiterer betroffener Medizinprodukthersteller und 3. zur Aufforderung der betroffenen Medizinprodukthersteller, die Sicherheitsberichte sowie weitere klinische Daten einzureichen

Vom 1. April 2021

1. Aufnahme von Beratungen über eine Richtlinie zur Erprobung

Mit Beschluss vom 1. April 2021 hat der Gemeinsame Bundesausschuss (G-BA) als Ergebnis eines Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 des Fünften Buches Sozialgesetzbuch (SGB V) festgestellt, dass für die Methode

– Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

weder der Nutzen noch die Schädlichkeit oder Unwirksamkeit als belegt anzusehen ist. Mit dem vorgenannten Beschluss hat der G-BA zugleich ein Beratungsverfahren über eine Richtlinie zur Erprobung gemäß § 137e SGB V für die gegenständliche Methode sowie das Einschätzungsverfahren nach 2. Kapitel § 6 der Verfahrensordnung des G-BA (VerfO) eingeleitet. Der Beschluss sowie die Tragenden Gründe sind auf den Internetseiten des G-BA veröffentlicht https://www.g-ba.de/beschluesse/4757.

Gemäß § 137h Absatz 4 Satz 1 SGB V trifft der G-BA die Entscheidung über eine Richtlinie zur Erprobung nach § 137e SGB V innerhalb von sechs Monaten nach dem Beschluss über das Bewertungsergebnis im Verfahren nach § 137h Absatz 1 Satz 4 SGB V. Die Erprobung dient dem Zweck, die notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode zu gewinnen, an denen es nach dem eingangs genannten Feststellungsbeschluss bislang fehlt. In der Erprobungs-Richtlinie konkretisiert der G-BA gemäß 2. Kapitel § 22 VerfO die Eckpunkte der klinischen Studie, die die Bewertung des Nutzens der Methode auf einem für eine spätere Richtlinienentscheidung ausreichend sicheren Erkenntnisniveau erlauben soll. Darüber hinaus regelt der G-BA die in die Erprobung einzubeziehenden Indikationen und die sächlichen, personellen und sonstigen Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung. Er legt zudem Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung fest. Für Krankenhäuser, die nicht an der Erprobung teilnehmen, kann der G-BA nach den §§ 136 bis 136b SGB V Anforderungen an die Qualität der Leistungserbringung regeln.

Es ist aber auch möglich, dass der G-BA dieses Beratungsverfahren vor dem Hintergrund bereits laufender oder geplanter Studien, die Erkenntnisse für eine abschließende Nutzenbewertung liefern können, aussetzt.

Außerdem kann der G-BA gemäß 2. Kapitel § 37 Absatz 7 VerfO die Voraussetzungen für die Abrechnungsfähigkeit des Medizinprodukts regeln, insbesondere einen befristeten Zeitraum für dessen Abrechnungsfähigkeit festlegen.

Mit diesem ersten Teil dieser Veröffentlichung soll insbesondere Sachverständigen der medizinischen Wissenschaft und Praxis, Dachverbänden von Ärztegesellschaften, Spitzenverbänden der Selbsthilfegruppen und Patientenvertretungen sowie Spitzenorganisationen der Hersteller von Medizinprodukten und den betroffenen Herstellern von Medizinprodukten Gelegenheit gegeben werden, durch Beantwortung eines Fragebogens erste Einschätzungen zur Erprobung der oben genannten Methode einschließlich der vorgenannten möglichen Regelungsgegenstände einer Erprobungs-Richtlinie abzugeben.

Die Einschätzungen anhand des Fragebogens sind innerhalb einer Frist von einem Monat nach der Veröffentlichung im Bundesanzeiger (bis zum 5. Mai 2021) in elektronischer Form an folgende E-Mail-Adresse zu senden:

erprobung137e@g-ba.de

Den Fragebogen sowie weitere Erläuterungen finden Sie auf der Internetseite des G-BA unter https://www.g-ba.de/beschluesse/4757.

2. Ermittlung weiterer betroffener Medizinprodukthersteller – Aufforderung zur Meldung –

Gemäß 2. Kapitel § 37 Absatz 4 Satz 5 VerfO werden mit diesem zweiten Teil dieser Veröffentlichung weitere, von der vorgenannten Richtlinienentscheidung des G-BA zu der gegenständlichen Methode betroffene Hersteller aufgefordert, sich beim G-BA zu melden. Als betroffen gilt gemäß 2. Kapitel § 32 Absatz 3 VerfO ein Hersteller, wenn er ein auf dem deutschen Markt verkehrsfähiges Medizinprodukt hoher Risikoklasse verantwortlich produziert, welches für die zu erprobende Methode maßgeblich ist.

Die Beteiligungsmöglichkeiten der betroffenen Hersteller im Rahmen des Beratungsverfahrens über eine Richtlinie zur Erprobung gemäß § 137e SGB V umfassen:

- Berücksichtigung bei einer etwaigen Bestimmung von Kernmerkmalen der gegenständlichen Methode nach 2. Kapitel § 36 Satz 2 VerfO,
- Berücksichtigung bei einer etwaigen Bestimmung von Regelungen zur Abrechnungsfähigkeit des Medizinprodukts gemäß § 137h Absatz 4 Satz 6 SGB V,
- Möglichkeit zur Einbeziehung in die Beratungen zur Erprobungs-Richtlinie im Übrigen gemäß 2. Kapitel § 22 Absatz 1 Satz 3 VerfO sowie
- Berücksichtigung nach § 92 Absatz 7d Satz 1 Halbsatz 2 SGB V im Stellungnahmeverfahren zur Entscheidung über die Erprobungs-Richtlinie.

Um die Prüfung der Voraussetzungen der Betroffenheit eines Medizinprodukteherstellers zu ermöglichen, sind im Zuge der Meldung aussagekräftige Unterlagen einzureichen. Diese umfassen Ausführungen in deutscher Sprache

- zur Bezeichnung und Beschreibung des Medizinprodukts,
- zur Beschreibung der Einbindung des Medizinprodukts in die Methode und
- zur Zweckbestimmung, für die das Medizinprodukt in Verkehr gebracht wurde.

Es sind außerdem

- die medizinprodukterechtliche Konformitätserklärung bzw. das Konformitätszertifikat des Medizinprodukts für das Inverkehrbringen in der Bundesrepublik Deutschland sowie
- die technische Gebrauchsanweisung

beizufügen. Auf der Grundlage der eingereichten Unterlagen prüft der G-BA, ob die Voraussetzungen für die vorgenannten Beteiligungsmöglichkeiten vorliegen.

Hersteller, die bereits im Rahmen der Informationsübermittlung nach § 137h Absatz 1 Satz 1 SGB V ihr Einvernehmen erklärt haben sowie betroffene Hersteller, die sich im Rahmen der Bekanntmachung der Informationsübermittlung nach § 137h Absatz 1 Satz 1 SGB V zu der gegenständlichen Methode als solche gemeldet haben, sind bereits auf dieser Grundlage in das Verfahren einbezogen. Eine gesonderte Meldung ist in diesem Fall nicht erforderlich.

Die Unterlagen sind bis zum 5. Mai 2021 der Geschäftsstelle des G-BA – nach Möglichkeit in elektronischer Form (z. B. als Word- oder PDF-Dokumente) per E-Mail – an die folgende Korrespondenzadresse zu übermitteln. Des Weiteren ist die Korrespondenz-Post- und E-Mail-Adresse des betroffenen Herstellers unter Angabe einer Kontaktperson mitzuteilen.

Korrespondenzadresse

Gemeinsamer Bundesausschuss
Abteilung Methodenbewertung & Veranlasste Leistungen
Postfach 12 06 06
10596 Berlin
E-Mail: erprobung137e@g-ba.de

Nachmeldungen sind zulässig. Insoweit ist zu beachten, dass bis zu der Entscheidung über die Nachmeldung die Wahrnehmung der oben genannten Beteiligungsrechte nicht möglich ist.

3. Aufforderung der betroffenen Medizinprodukthersteller, die Sicherheitsberichte sowie weitere klinische Daten einzureichen

Die betroffenen Medizinprodukthersteller werden hiermit zudem aufgefordert, gemäß § 137h Absatz 4 Satz 7 SGB V dem G-BA unverzüglich nach Fertigstellung die Sicherheitsberichte nach Artikel 86 der Verordnung (EU) 2017/745 des Europäischen Parlaments und des Rates vom 5. April 2017 über Medizinprodukte, zur Änderung der Richtlinie 2001/83/EG, der Verordnung (EG) Nr. 178/2002 und der Verordnung (EG) Nr. 1223/2009 und zur Aufhebung der Richtlinien 90/385/EWG und 93/42/EWG des Rates (ABl. L 117 vom 5.5.2017, S. 1) sowie weitere klinische Daten, die sie im Rahmen der ihnen nach Artikel 83 der Verordnung (EU) 2017/745 obliegenden Überwachung nach dem Inverkehrbringen oder aus klinischen Prüfungen nach dem Inverkehrbringen gewonnen haben,

zu übermitteln. Bei Vorliegen neuer derartiger Erkenntnisse sind diese Angaben fortlaufend und unverzüglich bis zu einer abschließenden Beschlussfassung zu übersenden.

Die vorstehend beschriebenen Unterlagen sind erstmals bis zum 5. Mai 2021 der Geschäftsstelle des G-BA – nach Möglichkeit in elektronischer Form (z. B. als Word- oder PDF-Dokumente) entweder auf einer DVD oder per E-Mail – an die oben genannte Korrespondenzadresse zu übermitteln.

Berlin, den 1. April 2021

Gemeinsamer Bundesausschuss
Unterausschuss Methodenbewertung

Die Vorsitzende
Lelgemann

Gelegenheit zur Abgabe erster Einschätzungen

Gemeinsamer Bundesausschuss

zu Beratungen des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Mit Beschluss vom 1. April 2021 hat der Gemeinsame Bundesausschuss (G-BA) als Ergebnis eines Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 des Fünften Buches Sozialgesetzbuch (SGB V) festgestellt, dass für die Methode

- Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

weder der Nutzen noch die Schädlichkeit oder Unwirksamkeit als belegt anzusehen ist.

Für eine Methode nach § 137h Absatz 1 Satz 4 Nummer 3 SGB V entscheidet der G-BA innerhalb von sechs Monaten nach dem Beschluss nach Absatz 1 Satz 4 über eine Richtlinie zur Erprobung nach § 137e. Eine Prüfung des Potentials der Methode erfolgt nicht. Deshalb hat der G-BA mit dem vorgenannten Beschluss zugleich ein Beratungsverfahren über eine Richtlinie zur Erprobung gemäß § 137e SGB V für die gegenständliche Methode eingeleitet. Der Beschluss sowie die Tragenden Gründe sind auf den Internetseiten des G-BA veröffentlicht.

Das Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 SGB V erfolgte auf der Grundlage der von einem Krankenhaus mit der Informationsübermittlung nach § 137h Absatz 1 Satz 1 SGB V eingereichten Angaben und Unterlagen.

Um den G-BA in die Lage zu versetzen, eine abschließende Bewertung des Nutzens der vorgenannten Methode durchzuführen, sollen im Wege der Erprobung die hierfür nach den §§ 135 und 137c SGB V i. V. m. den Vorgaben der Verfahrensordnung des G-BA (VerfO) notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode gewonnen werden. Die zu diesem Zweck notwendigen Studien sollen durch eine unabhängige wissenschaftliche Institution (UWI) nach Maßgabe dieser Richtlinie entworfen, durchgeführt und ausgewertet werden. Die Ausgestaltung des Studiendesigns ist – soweit nicht im Folgenden näher bestimmt – von der UWI auf der Basis des Standes der wissenschaftlichen Erkenntnisse vorzunehmen und zu begründen.

Gemäß 2. Kapitel § 6 der Verfahrensordnung des G-BA erhalten Sie Gelegenheit zur Abgabe einer ersten Einschätzung zum angekündigten Beratungsgegenstand. Bitte verwenden Sie zur Abgabe Ihrer Einschätzung den nachfolgenden Fragebogen.

Bitte belegen Sie Ihre Ausführungen jeweils durch Angabe von Quellen unter Nutzung der beigefügten Literaturliste (siehe Anlage). Bitte fügen Sie die Publikationen – soweit möglich – in Kopie bei.

Wir bitten Sie, den Fragebogen als Word-Dokument und alle weiteren Unterlagen als PDF-Dokumente per E-Mail an erprobung137e@g-ba.de zu übersenden. Die Frist zur Abgabe Ihrer Einschätzung endet am 5. Mai 2021.

Fragebogen

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Mit der Abgabe Ihrer Einschätzung erklären Sie sich damit einverstanden, dass diese, auch auszugsweise, in einem Bericht des G-BA wiedergegeben werden kann, der mit Abschluss der Beratung zu jedem Thema erstellt und der Öffentlichkeit via Internet zugänglich gemacht wird.

Funktion des Einschätzenden

Bitte geben Sie an, in welcher Funktion Sie diese Einschätzung abgeben (z. B. Verband, Institution, Hersteller, Leistungserbringer, Privatperson).

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Mit der Erprobungsstudie soll nachgewiesen werden, dass bei erwachsenen Männern mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre die Behandlung mittels eines medikamentenbeschichteten Ballondilatationskatheters bezüglich des primären Endpunktes aus dem International Prostate Symptom Score (IPSS) und der Strikturfreiheitsrate überlegen ist.

Überlegungen des G-BA	**Fragen des G-BA**	**Einschätzung**
Population		
In die Erprobungsstudie einzuschließen sind erwachsene Männer mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre.	Ist dies die aus Ihrer Sicht treffende Beschreibung der Studienpopulation? Wenn nicht, wie sollte die Studienpopulation definiert werden? Sollten Subpopulationen gebildet werden? (z.B. entsprechend der Genese der Harnröhrenstrikturen?	Klicken Sie hier, um einen Text einzugeben.
Intervention		
Im Rahmen der Studienplanung durch eine UWI soll unter Einbezug klinischer Expertise konkretisiert werden, ob und ggf. mit welchem Verfahren bei stark stenotischen Strikturen unmittelbar vor der Behandlung mit einem medikamentenbeschichteten	Verfahren zur Prädilatation stellen die Urethrotomia interna, die Dilatation mit unbeschichteten Ballonkathetern und die Aufbougierung mit Kathetern zunehmender Größe dar. Im deutschen Versorgungskontext kommt in erster Linie die	Klicken Sie hier, um einen Text einzugeben.

Ballondilatationskatheter eine Prädilatation der Striktur erfolgen soll.	Urethrotomia interna für die Prädilatation zum Einsatz. Stimmen Sie mit der Überlegung des G-BA überein, dass im Rahmen der Studienplanung durch eine UWI festgelegt werden sollte, ob und ggf. mit welchem Verfahren eine Prädilatation von stark stenotischen Strikturen erfolgen soll? Falls nein, welche Vorgaben zur Prädilatation sollten Ihrer Meinung nach definiert werden?	
Die Prüfintervention ist die Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter.	Stimmen Sie mit der Überlegung des G-BA zur Intervention überein? Falls nein, wie würden Sie die Intervention definieren?	Klicken Sie hier, um einen Text einzugeben.
Vergleichsintervention (Kontrolle)		
Die Vergleichsintervention ist die Urethrotomia interna.	Stimmen Sie mit der Überlegung des G-BA zur Vergleichsintervention überein? Falls nein, wie würden Sie die Vergleichsintervention definieren? Sollten andere/weitere Vergleichsinterventionen berücksichtigt werden?	Klicken Sie hier, um einen Text einzugeben.

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	Inwieweit sollten Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichstherapie als möglicherweise hierfür relevante Faktoren berücksichtigt werden?	
Endpunkte		
Der primäre Endpunkt ist der Anteil an Patienten, die • nach 12 Monaten eine Verbesserung im IPSS-Score im Vergleich zum Ausgangswert aufweisen (Verbesserung um mindestens sechs Punkte [>15% der Skalenspannweite]) und • sich innerhalb dieses Zeitraums keiner klinisch-indizierten Reintervention aufgrund des Wiederauftretens der Striktur einschließlich entsprechender Symptomatikunterziehen müssen (Strikturfreiheit).	Stimmen Sie mit der Überlegung des G-BA zum primären Endpunkt und der vorgeschlagenen Responseschwelle überein? Falls nein, was ist aus Ihrer Sicht ein angemessener primärer Endpunkt für die Erprobungsstudie und welche validierten Erhebungsinstrumente gibt es nach Ihrer Kenntnis für diesen von Ihnen vorgeschlagenen Endpunkt? Bitte beschreiben Sie bezüglich der von Ihnen vorgeschlagenen Erhebungsinstrumente die minimale klinische Differenz zur Beurteilung des Behandlungsergebnisses und belegen Sie Ihre Aussagen nach Möglichkeit mit geeigneten Studien.	Klicken Sie hier, um einen Text einzugeben.
Als sekundäre Endpunkte sind (unter anderem) zu erheben:	Stimmen Sie mit der Überlegung des G-BA zu den sekundären Endpunkten	Klicken Sie hier, um einen Text einzugeben.

• Morbidität (z. B. klinisch-indizierte Reinterventionen, Wiederauftreten der Striktursymptomatik, wiederkehrende Harnwegsinfekte), • gesundheitsbezogene Lebensqualität, • unerwünschte Ereignisse.	überein? Welche validierten Erhebungsinstrumente zu diesen Endpunkten halten Sie für geeignet? Sollten Ihrer Meinung nach weitere bzw. andere sekundäre Endpunkte ergänzend in der Erprobungsstudie untersucht werden? In diesem Fall benennen Sie bitte die entsprechenden validierten Erhebungsinstrumente.	
Studientyp und Beobachtungszeitraum		
Die Erprobungsstudie ist als randomisierte, kontrollierte Studie (RCT) multizentrisch durchzuführen.	Stimmen Sie mit der Überlegung des G-BA zum Studientyp überein? Falls nein, welche Vorgaben zum Studientyp sollten definiert werden?	Klicken Sie hier, um einen Text einzugeben.
Die Randomisierung sollte im Verhältnis 1:1 erfolgen.	Stimmen Sie mit der Überlegung des G-BA zur Randomisierung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Klicken Sie hier, um einen Text einzugeben.

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Die Studienteilnehmer und die weiterbehandelnden Personen sowie die Endpunkterheber sollen verblindet sein.	Stimmen Sie mit der Überlegung des G-BA zur Verblindung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bezüglich dieser Vorgaben?	Klicken Sie hier, um einen Text einzugeben.
Die patientenindividuelle Nachbeobachtungszeit soll 12 Monate betragen.	Eine Nachbeobachtungszeit von 12 Monaten (nach der Intervention) wird als angemessen angesehen, da bei Patienten mit Rezidivstrikturen das Auftreten eines erneuten Rezidivs nach einer Urethrotomia interna oft bereits innerhalb dieses Zeitraums erfolgt. Stimmen Sie mit dieser Überlegung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Klicken Sie hier, um einen Text einzugeben.

Erfassung und Dokumentation bestimmter Parameter		
Die Art und Anzahl weiterer therapeutischer Interventionen mit Bezug zur Grunderkrankung oder mit möglichen Einfluss auf die zu erfassenden Endpunkte sollten dokumentiert werden.	Stimmen Sie mit der Überlegung des G-BA überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Klicken Sie hier, um einen Text einzugeben.

Fragebogen

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Ergänzende Fragen	
Wie viele Studienzentren in Deutschland kämen für die Studie in Frage?	Klicken Sie hier, um einen Text einzugeben.
Wie viele Studienzentren sollten initiiert werden, um die Studie in angemessener Zeit abzuschließen?	Klicken Sie hier, um einen Text einzugeben.
Welche Maßnahmen wären erforderlich, um eine zügige Rekrutierung zu gewährleisten?	Klicken Sie hier, um einen Text einzugeben.
Gibt es aus Ihrer Sicht Aspekte zu berücksichtigen, welche die geplante Studiendurchführung erschweren könnten? (Beispielsweise geplante oder laufende Studien mit Rekrutierung derselben Patientengruppen im Indikationsgebiet der Erprobungsstudie)	Klicken Sie hier, um einen Text einzugeben.
Welche Anforderungen, insbesondere hinsichtlich der personellen, technischen und räumlichen Ausstattung, sind aus Ihrer Sicht zur Erbringung der Methode im Rahmen einer Studie zu stellen? Bitte berücksichtigen Sie hierbei auch mögliche periprozedurale Risiken ihrer Anwendung.	Klicken Sie hier, um einen Text einzugeben.
Wird bei den genannten Eckpunkten die Versorgungsrealität in Hinblick auf die Durchführbarkeit der Erprobung und der Leistungserbringung angemessen berücksichtigt?	Klicken Sie hier, um einen Text einzugeben.
Bitte benennen Sie ggf. zusätzliche Aspekte, die im Rahmen der Erstellung der Erprobungs-Richtlinie berücksichtigt werden sollten.	Klicken Sie hier, um einen Text einzugeben.

Fragebogen

Gemeinsamer Bundesausschuss

Überlegungen des G-BA zur näherungsweisen Fallzahlschätzung	Wie lautet Ihre Einschätzung?
Für die Fallzahl ist die Größe des nachzuweisenden Effekts maßgeblich. Diese wiederum hängt maßgeblich von der Operationalisierung des primären Endpunkts (hier: IPSS Score und Strikturfreiheit) ab. Unter Annahme einer Effektstärke von beispielsweise 15 % (80 % der Teilnehmer erreichen den primären Endpunkt in der Interventionsgruppe, 65 % in der Kontrollgruppe), abgeleitet aus den Ergebnissen der Studien ROBUST- I[1] und ROBUST-II[2] sowie aus Daten zur Strikturfreiheit nach 12 Monaten in Abhängigkeit der Anzahl vorheriger Interventionen[3], ergibt sich als grobe Approximation eine Fallzahl in der Kategorie einer mittleren Studie (100 bis < 500).	Klicken Sie hier, um einen Text einzugeben.

Schätzung der Overheadkosten der Erprobungsstudie (Beispiel)	Wie lautet Ihre Einschätzung?
Für Studien mit mittlerer Fallzahl (hier: 400 Studienteilnehmer als Kalkulationsgrundlage) und mittlerem Aufwand lässt sich ein studienspezifischer Aufwand in Höhe von etwa 5500 € je Teilnehmer beziffern. Auf der Basis dieser Annahmen lassen sich geschätzte Studienkosten von 2,2 Millionen € berechnen.	Klicken Sie hier, um einen Text einzugeben.

[1]Urotronic. ROBUST I Pilot Study (ROBUST) [online]. 2020 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03014726.

[2]Urotronic. Re-establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease (ROBUST-II) [online]. 2019 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03270384.

[3]Heyns CF, Steenkamp JW, De Kock ML et al. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998; 160(2): 356-358. https://dx.doi.org/10.1016/s0022-5347(01)62894-5.

Gelegenheit zur Abgabe erster Einschätzungen

Gemeinsamer Bundesausschuss

zu Beratungen des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Mit Beschluss vom 1. April 2021 hat der Gemeinsame Bundesausschuss (G-BA) als Ergebnis eines Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 des Fünften Buches Sozialgesetzbuch (SGB V) festgestellt, dass für die Methode

- Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

weder der Nutzen noch die Schädlichkeit oder Unwirksamkeit als belegt anzusehen ist.

Für eine Methode nach § 137h Absatz 1 Satz 4 Nummer 3 SGB V entscheidet der G-BA innerhalb von sechs Monaten nach dem Beschluss nach Absatz 1 Satz 4 über eine Richtlinie zur Erprobung nach § 137e. Eine Prüfung des Potentials der Methode erfolgt nicht. Deshalb hat der G-BA mit dem vorgenannten Beschluss zugleich ein Beratungsverfahren über eine Richtlinie zur Erprobung gemäß § 137e SGB V für die gegenständliche Methode eingeleitet. Der Beschluss sowie die Tragenden Gründe sind auf den Internetseiten des G-BA veröffentlicht.

Das Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 SGB V erfolgte auf der Grundlage der von einem Krankenhaus mit der Informationsübermittlung nach § 137h Absatz 1 Satz 1 SGB V eingereichten Angaben und Unterlagen.

Um den G-BA in die Lage zu versetzen, eine abschließende Bewertung des Nutzens der vorgenannten Methode durchzuführen, sollen im Wege der Erprobung die hierfür nach den §§ 135 und 137c SGB V i. V. m. den Vorgaben der Verfahrensordnung des G-BA (VerfO) notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode gewonnen werden. Die zu diesem Zweck notwendigen Studien sollen durch eine unabhängige wissenschaftliche Institution (UWI) nach Maßgabe dieser Richtlinie entworfen, durchgeführt und ausgewertet werden. Die Ausgestaltung des Studiendesigns ist – soweit nicht im Folgenden näher bestimmt – von der UWI auf der Basis des Standes der wissenschaftlichen Erkenntnisse vorzunehmen und zu begründen.

Gemäß 2. Kapitel § 6 der Verfahrensordnung des G-BA erhalten Sie Gelegenheit zur Abgabe einer ersten Einschätzung zum angekündigten Beratungsgegenstand. Bitte verwenden Sie zur Abgabe Ihrer Einschätzung den nachfolgenden Fragebogen.

Bitte belegen Sie Ihre Ausführungen jeweils durch Angabe von Quellen unter Nutzung der beigefügten Literaturliste (siehe Anlage). Bitte fügen Sie die Publikationen – soweit möglich – in Kopie bei.

Wir bitten Sie, den Fragebogen als Word-Dokument und alle weiteren Unterlagen als PDF-Dokumente per E-Mail an erprobung137e@g-ba.de zu übersenden. Die Frist zur Abgabe Ihrer Einschätzung endet am 5. Mai 2021.

Fragebogen

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Mit der Abgabe Ihrer Einschätzung erklären Sie sich damit einverstanden, dass diese, auch auszugsweise, in einem Bericht des G-BA wiedergegeben werden kann, der mit Abschluss der Beratung zu jedem Thema erstellt und der Öffentlichkeit via Internet zugänglich gemacht wird.

Funktion des Einschätzenden

Bitte geben Sie an, in welcher Funktion Sie diese Einschätzung abgeben (z. B. Verband, Institution, Hersteller, Leistungserbringer, Privatperson).

Prof. Dr. med. Tilman Kälble
Direktor der Klinik für Urologie und Kinderurologie
Klinikum Fulda
Pacelliallee 4
36043 Fulda

Meine nun folgende Einschätzung erfolgt als der von der Deutschen Gesellschaft für Urologie e.V. (Fachgesellschaft) dazu ermächtigte klinische Experte.

Fragebogen

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Mit der Erprobungsstudie soll nachgewiesen werden, dass bei erwachsenen Männern mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre die Behandlung mittels eines medikamentenbeschichteten Ballondilatationskatheters bezüglich des primären Endpunktes aus dem International Prostate Symptom Score (IPSS) und der Strikturfreiheitsrate überlegen ist.

Überlegungen des G-BA	**Fragen des G-BA**	**Einschätzung**
Population		
In die Erprobungsstudie einzuschließen sind erwachsene Männer mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre.	Ist dies die aus Ihrer Sicht treffende Beschreibung der Studienpopulation? Wenn nicht, wie sollte die Studienpopulation definiert werden? Sollten Subpopulationen gebildet werden? (z.B. entsprechend der Genese der Harnröhrenstrikturen?	Max. 2cm lange Rezidivstrikturen der anterioren Harnröhre sind die korrekte Studienpopulation. Bezüglich Subpopulationen sollte die Ätiologie „traumatisch vs. iatrogen“ (z. B. Katheterisierung, endoskopischer Eingriff) ebenso erfasst werden wie „Striktur geht nahtlos in den Sphinkter über“ oder „ist vom Sphinkter externus entfernt“. Die Subpopulationen müssen jedoch bei der Randomisierung keine Berücksichtigung finden.
Intervention		
Im Rahmen der Studienplanung durch eine UWI soll unter Einbezug klinischer Expertise konkretisiert werden, ob und ggf. mit welchem Verfahren bei stark stenotischen Strikturen unmittelbar vor der Behandlung mit einem medikamentenbeschichteten	Verfahren zur Prädilatation stellen die Urethrotomia interna, die Dilatation mit unbeschichteten Ballonkathetern und die Aufbougierung mit Kathetern zunehmender Größe dar. Im deutschen Versorgungskontext kommt in erster Linie die	Als Verfahren zur Prädilatation sollte standardisiert die Urethrotomia interna bis in das Schleimhautniveau angegeben werden, um eine einheitliche „Prädilatation“ zu erreichen und gleichzeitig die genaue Länge der Enge noch einmal endoskopisch ermitteln zu können.

Fragebogen

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Ballondilatationskatheter eine Prädilatation der Striktur erfolgen soll.	Urethrotomia interna für die Prädilatation zum Einsatz. Stimmen Sie mit der Überlegung des G-BA überein, dass im Rahmen der Studienplanung durch eine UWI festgelegt werden sollte, ob und ggf. mit welchem Verfahren eine Prädilatation von stark stenotischen Strikturen erfolgen soll? Falls nein, welche Vorgaben zur Prädilatation sollten Ihrer Meinung nach definiert werden?	
Die Prüfintervention ist die Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter.	Stimmen Sie mit der Überlegung des G-BA zur Intervention überein? Falls nein, wie würden Sie die Intervention definieren?	Ja.
Vergleichsintervention (Kontrolle)		
Die Vergleichsintervention ist die Urethrotomia interna.	Stimmen Sie mit der Überlegung des G-BA zur Vergleichsintervention überein? Falls nein, wie würden Sie die Vergleichsintervention definieren? Sollten andere/weitere Vergleichsinterventionen berücksichtigt werden?	s. oben, d.h. die Urethrotomia interna ist die sinnvollste Vergleichsintervention.

	Inwieweit sollten Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichstherapie als möglicherweise hierfür relevante Faktoren berücksichtigt werden?	s. oben, d.h. die Genese traumatisch vs. instrumentell (DK, Katheterisierung, endoskopischer Eingriff) sollte ebenso dokumentiert werden wie die Lage der Striktur zum Sphinkter. Darüber hinaus sollte die Anzahl der Rezidive sowie die Strikturlänge dokumentiert werden, ohne dass dies bei der Randomisierung berücksichtigt werden muss.
Endpunkte		
Der primäre Endpunkt ist der Anteil an Patienten, die • nach 12 Monaten eine Verbesserung im IPSS-Score im Vergleich zum Ausgangswert aufweisen (Verbesserung um mindestens sechs Punkte [>15% der Skalenspannweite]) und • sich innerhalb dieses Zeitraums keiner klinisch-indizierten Reintervention aufgrund des Wiederauftretens der Striktur einschließlich entsprechender Symptomatik unterziehen müssen (Strikturfreiheit).	Stimmen Sie mit der Überlegung des G-BA zum primären Endpunkt und der vorgeschlagenen Responseschwelle überein? Falls nein, was ist aus Ihrer Sicht ein angemessener primärer Endpunkt für die Erprobungsstudie und welche validierten Erhebungsinstrumente gibt es nach Ihrer Kenntnis für diesen von Ihnen vorgeschlagenen Endpunkt? Bitte beschreiben Sie bezüglich der von Ihnen vorgeschlagenen Erhebungsinstrumente die minimale klinische Differenz zur Beurteilung des Behandlungsergebnisses und belegen Sie Ihre Aussagen nach Möglichkeit mit geeigneten Studien.	12 Monate sind ein guter Endpunkt, unbedingt sollte dieser jedoch nach 24 Monaten noch einmal wiederholt werden. Die IPSS-Score-Verbesserung um mindestens 6 Punkte ist ein sinnvolles Maß, sollte jedoch nicht das alleinige Maß sein, da der IPSS-Score rein subjektive Verbesserungen misst und die Angaben somit zwangsläufig intra- und interindividuelle Schwankungen aufweisen. Unbedingt sollte die Uroflowmetrie präoperativ sowie nach 12 und 24 Monaten herangezogen werden zusammen mit der sonographischen Restharnbestimmung. Für die Beurteilung relevante Messergebnisse bei diesen beiden Erhebungs-instrumenten leiten sich aus deren Definition ab: Klinisch relevanter Restharn liegt dann vor, wenn mehr als 10% des Miktionsvolumens im Anschluss an die Miktion in der Blase verbleiben oder einfacher, wenn der Restharn höher als 100ml beträgt. Insofern sollte der Restharn nach der Intervention < als 10% des Miktionsvolumens oder <100ml absolut betragen. Bezüglich der Uroflowmetrie würde ich die Parameter „max. Flussgeschwindigkeit in ml/s“ sowie „Flusszeit“ prä- und

		postoperativ messen und die Differenzen dann als Studienergebnis ausweisen. Im Vorhinein anzugeben, welche Verbesserung beispielsweise der max. Flussgeschwindigkeit signifikant ist oder nicht, ist schwierig bis unmöglich, da unter anderem von der präoperativen Situation und auch von psychovegetativen Einflüssen abhängig. So wäre beispielsweise der Anstieg der max. Flussgeschwindigkeit von 3 auf 8ml/s eine Verbesserung um über 100%, wäre klinisch jedoch immer noch als hoch obstruktiv zu werten, wohingegen eine Verbesserung von 10 auf 15ml/s klinisch eine deutliche Verbesserung darstellt, obwohl die Verbesserung nur 50% beträgt.
Als sekundäre Endpunkte sind (unter anderem) zu erheben: • Morbidität (z. B. klinisch-indizierte Reinterventionen, Wiederauftreten der Striktursymptomatik, wiederkehrende Harnwegsinfekte), • gesundheitsbezogene Lebensqualität, • unerwünschte Ereignisse.	Stimmen Sie mit der Überlegung des G-BA zu den sekundären Endpunkten überein? Welche validierten Erhebungsinstrumente zu diesen Endpunkten halten Sie für geeignet? Sollten Ihrer Meinung nach weitere bzw. andere sekundäre Endpunkte ergänzend in der Erprobungsstudie untersucht werden? In diesem Fall benennen Sie bitte die entsprechenden validierten Erhebungsinstrumente.	Ein sekundärer Endpunkt, wie schon angegeben, wäre nach 24 Monaten, dann gleiche Messinstrumente wie nach 12 Monaten. Zu registrieren sind unerwünschte Ereignisse wie Harnverhalt, Harnwegsinfekte, Reinterventionen, wobei bezüglich letzteren die Latenzzeiten zwischen einer konventionellen Sachse-Urethrotomie und einer Sachse-Urethrotomie mit Ballondilatation bis zu einer Reintervention verglichen werden können.
Studientyp und Beobachtungszeitraum		

Fragebogen

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Die Erprobungsstudie ist als randomisierte, kontrollierte Studie (RCT) multizentrisch durchzuführen.	Stimmen Sie mit der Überlegung des G-BA zum Studientyp überein? Falls nein, welche Vorgaben zum Studientyp sollten definiert werden?	Ja.
Die Randomisierung sollte im Verhältnis 1:1 erfolgen.	Stimmen Sie mit der Überlegung des G-BA zur Randomisierung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Ja.
Die Studienteilnehmer und die weiterbehandelnden Personen sowie die Endpunkterheber sollen verblindet sein.	Stimmen Sie mit der Überlegung des G-BA zur Verblindung überein? Falls nein, welche Einwände oder Vorschläge haben Sie gegen diese Vorgaben?	Die Studienteilnehmer sollten verblindet sein, für die weiterbehandelnden Personen sowie die Endpunkterheber ist dies jedoch nicht notwendig.
Die patientenindividuelle Nachbeobachtungszeit soll 12 Monate betragen.	Eine Nachbeobachtungszeit von 12 Monaten (nach der Intervention) wird als angemessen angesehen, da bei Patienten mit Rezidivstrikturen das Auftreten eines erneuten Rezidivs nach einer Urethrotomia interna oft bereits innerhalb dieses Zeitraums erfolgt. Stimmen Sie mit dieser Überlegung überein? Falls nein, welche Einwände	s. o.

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	oder Vorschläge haben Sie bzgl. dieser Vorgabe?	

Erfassung und Dokumentation bestimmter Parameter		
Die Art und Anzahl weiterer therapeutischer Interventionen mit Bezug zur Grunderkrankung oder mit möglichen Einfluss auf die zu erfassenden Endpunkte sollten dokumentiert werden.	Stimmen Sie mit der Überlegung des G-BA überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Ja

Ergänzende Fragen	
Wie viele Studienzentren in Deutschland kämen für die Studie in Frage?	Mindestens 20.
Wie viele Studienzentren sollten initiiert werden, um die Studie in angemessener Zeit abzuschließen?	Mindestens 10.
Welche Maßnahmen wären erforderlich, um eine zügige Rekrutierung zu gewährleisten?	Es sollte ein Studienleiter bestimmt werden, der wiederum direkt verschiedene Klinikleiter anspricht. Da sich die Klinikleiter der größeren deutschen urologischen Kliniken gut kennen und sich in aller Regel gerne gegenseitig bei wissenschaftlichen Fragestellungen unterstützen, wäre damit die entscheidende Voraussetzung gegeben.
Gibt es aus Ihrer Sicht Aspekte zu berücksichtigen, welche die geplante Studiendurchführung erschweren könnten? (Beispielsweise geplante oder	Geplante laufende Studien überregionaler Art dürfte es im Moment nicht geben. Da bisher zur Sachse-Urethrotomie sowie

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Ergänzende Fragen	
laufende Studien mit Rekrutierung derselben Patientengruppen im Indikationsgebiet der Erprobungsstudie)	zur offenen Urethraplastik keine sinnvollen etablierten Alternativen existieren, dürfte die Studiendurchführung nicht durch andere Studien erschwert werden.
Welche Anforderungen, insbesondere hinsichtlich der personellen, technischen und räumlichen Ausstattung, sind aus Ihrer Sicht zur Erbringung der Methode im Rahmen einer Studie zu stellen? Bitte berücksichtigen Sie hierbei auch mögliche periprozedurale Risiken ihrer Anwendung.	Für die Studie sind keinerlei besondere Anforderungen erforderlich. Jede urologische Klinik hat einen Röntgen-Arbeitsplatz mit Durchleuchtungsmöglichkeit, so dass die Studie in jeder urologischen Klinik sofort begonnen werden kann.
Wird bei den genannten Eckpunkten die Versorgungsrealität in Hinblick auf die Durchführbarkeit der Erprobung und der Leistungserbringung angemessen berücksichtigt?	s. oben.
Bitte benennen Sie ggf. zusätzliche Aspekte, die im Rahmen der Erstellung der Erprobungs-Richtlinie berücksichtigt werden sollten.	/

Überlegungen des G-BA zur näherungsweisen Fallzahlschätzung	**Wie lautet Ihre Einschätzung?**
Für die Fallzahl ist die Größe des nachzuweisenden Effekts maßgeblich. Diese wiederum hängt maßgeblich von der Operationalisierung des primären Endpunkts (hier: IPSS Score und Strikturfreiheit) ab. Unter Annahme einer Effektstärke von beispielsweise 15 % (80 % der Teilnehmer erreichen den primären Endpunkt in der Interventionsgruppe, 65 % in der Kontrollgruppe), abgeleitet aus den Ergebnissen der Studien ROBUST-I[1] und	Eine Studie mit mehr als 100 auswertbaren Teilnehmern erscheint mir unrealistisch. In Deutschland ist es zunehmend schwierig, manchmal fast unmöglich, prospektiv randomisierte Studien durchzuführen – insbesondere, wenn wie im vorliegenden Fall der Patient eine Überlegenheit der Dilatation zusätzlich zur Sichturethrotomie vermuten könnte. Insofern

[1]Urotronic. ROBUST I Pilot Study (ROBUST) [online]. 2020 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03014726.

Fragebogen

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Überlegungen des G-BA zur näherungsweisen Fallzahlschätzung	Wie lautet Ihre Einschätzung?
ROBUST-II[2] sowie aus Daten zur Strikturfreiheit nach 12 Monaten in Abhängigkeit der Anzahl vorheriger Interventionen[3], ergibt sich als grobe Approximation eine Fallzahl in der Kategorie einer mittleren Studie (100 bis < 500).	erscheinen mir 100 Patienten sowohl von der Realisierungsmöglichkeit als auch inhaltlich ausreichend.

Schätzung der Overheadkosten der Erprobungsstudie (Beispiel)	Wie lautet Ihre Einschätzung?
Für Studien mit mittlerer Fallzahl (hier: 400 Studienteilnehmer als Kalkulationsgrundlage) und mittlerem Aufwand lässt sich ein studienspezifischer Aufwand in Höhe von etwa 5500 € je Teilnehmer beziffern. Auf der Basis dieser Annahmen lassen sich geschätzte Studienkosten von 2,2 Millionen € berechnen.	Dies hängt stark vom vorgesehenen Studienhonorar ab. Die minimalen Kosten bei 100 Teilnehmern wären die Kosten des Ballons für 50 Teilnehmer, die zusätzlichen Kosten richten sich dann in erster Linie nach dem Honorar.

[2]Urotronic. Re-establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease (ROBUST-II) [online]. 2019 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03270384.

[3]Heyns CF, Steenkamp JW, De Kock ML et al. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998; 160(2): 356-358. https://dx.doi.org/10.1016/s0022-5347(01)62894-5.

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Beratungsverfahren über eine Richtlinie zur Erprobung gemäß § 137e SGB V in Folge einer Bewertung nach § 137h Absatz 1 Satz 4 SGB V: Medikamenten-beschichteter Ballonkatheter zur transurethralen Behandlung von Harnröhrenstrikturen (BVh-20-002)
Einreichung weiterer klinischer Daten, Information zur einer geplanten RCT, Einschätzung zu Eckpunkten einer Erprobungsstudie.

Sehr geehrte Frau Dr. Schuhrke,

mit diesem Schreiben kommt Urotronic der Aufforderung des G-BA zur Einreichung weiterer klinischer Daten nach.
Darüber hinaus können Sie diesem Schreiben Informationen über die Planung einer weiteren RCT in Kooperation mit NIHR (National Institute of Health Research https://www.nihr.ac.uk/) in UK entnehmen.
Darüber hinaus finden Sie als Anlage die Einschätzung von Urotronic zu den Eckpunkten einer Erprobungsstudie.

Zunächst zu den noch unveröffentlichten Resultaten der ROBUST-Studienserie:

ROBUST I-Studie 3-Jahresdaten:
Diesem Schreiben sind Abstracts beigefügt, die bei den Kongressen der AUA (American Urology Association), ICS (International Continence society) und WCE (World congress of Endourology) 2021 eingereicht wurden.
Ausgewählte Resultate seien hier in Kürze erläutert: Nach 3 Jahren konnten 43 der 53 ursprünglich in die Studie eingeschlossenen Patienten nachuntersucht werden.

- Es gab keine schwerwiegenden unerwünschten Ereignisse im Zusammenhang mit der Behandlung nach 3 Jahren.
- Die Freiheit von erneuten Eingriffen an der Studienstriktur nach 1, 2 und 3 Jahren betrug 83 % (40/48), 81 % (38/47) bzw. 77 % (33/43).
- Die Erfolgsrate (≥ 50% Verbesserung des IPSS und Freiheit von Reinterventionen) nach 3 Jahren betrug 67 % (29/43), was mit den 2-Jahres-Ergebnissen (68 %, 32/47) übereinstimmt.

- Der IPSS verbesserte sich von einem Mittelwert von 25,2 bei Studienbeginn auf 5,5 nach 3 Jahren (ungepaarter t-Test, p<0,001).

Weitere Resultate nach 3 Jahren Nachbeobachtungszeit bitten wir, den beigefügten Abstracts zu entnehmen.

ROBUST III-Studie vorläufige Daten:
Diesem Schreiben sind Abstracts beigefügt, die bei den Kongressen der AUA (American Urology Association), ICS (International Continence society) und WCE (World Congress of Endourology) 2021 eingereicht wurden. Außerdem finden Sie als Anlage den Studienbericht vom 20. April 2021. Diese Dokumente bittet Urotronic bis auf Weiteres vertraulich zu behandeln. Die Kongressabstracts werden im September/Oktober veröffentlicht werden. Urotronic geht davon aus, dass die Resultate der ROBUST III Studie gegen Ende des 2. oder Anfang des 3. Quartals publiziert werden.

Ausgewählte verfügbare Resultate seien hier in Kürze erläutert:
Insgesamt wurden 127 Patienten (79 Optilume, 48 Kontrolle) mit einer Strikturlänge $\leq$ 3 cm und $\geq$ 2 vorherigen endoskopischen Strikturbehandlungen im Verhältnis 2:1 (Intervention:Kontrolle) randomisiert. Patienten waren bis zu 6 Monate nach dem Eingriff verblindet. Der primäre Endpunkt, die Freiheit von Strikturen (als Passierbarkeit für ein 16 F flexibles Zystoskop, oder eine 14 F Katheter), wurde nach 6 Monaten erhoben. Die Resultate nach 6 Monaten Nachbeobachtungszeit liegen vollständig vor. Der 12-Monatsdatensatz ist zurzeit noch unvollständig. Es ist zu erwarten, dass die Resultate in Verlauf der Beratung zu einer Erprobungsrichtlinie zur Verfügung stehen werden.

- Der Anteil der Probanden, die nach 6 Monaten strikturfrei blieben, betrug 74,6 % (50/67) in der Optilume DCB-Gruppe im Vergleich zu 26,8 % (11/41) in der Kontrollgruppe (p<0,001). Die Ergebnisse waren in den Untergruppen mit ≥5 versus <5 vorherigen Strikturbehandlungen und für Längen <2cm versus ≥2cm konsistent.
- Die Kaplan-Meier-Schätzung für die Rate der Freiheit von Wiederholungseingriffen bis zum 1-Jahres-Follow-up war für den Optilume DCB im Vergleich zur Kontrolle signifikant höher. Details zu dem Endpunkt Freiheit von Reinterventionen sind unter 9.4.8 auf Seite 62 des Studienberichts der ROBUST III-Studie dargestellt (Studienbericht RP1076rA ROBUST III Interim Clinical Study Report_27Apr21 – signed.pdf).
- In beiden Gruppen verbesserte sich der Symptomscore sofort nach dem Eingriff. In der Kontrollgruppe näherten sie sich nach einem Jahr jedoch wieder dem Ausgangswert an.
- Bei keinem Probanden trat eine schwerwiegende auf das Medizinprodukt zurückzuführende Komplikation auf.

Weitere Resultate bitten wir den Abstracts sowie dem Studienbericht zu entnehmen.

- Darüber hinaus haben wir diesem Brief eine **Übersicht der ROBUST-Studien** beigefügt, die ausgewählte Aspekte vergleichend darstellt (LA1093rA Optilume® DCB Clinical Program summary):
  - Mittlere Anzahl an vorherigen Strikturbehandlungen
  - Länge der Strikturen, Ätiologie, anatomische Lokalisierung, Anteil Patienten mit Harnverhalt vor dem Eingriff
  - Gewählte Verfahren für die Prädilation
  - Im Fall von ROBUST-III die Vergleichsintervention
  - Anatomischer Erfolg nach 6 Monaten im Vergleich

- Freiheit von Wiederholungseingriffen, soweit Resultate verfügbar sind.
- Durchschnittliche Resultate im IPSS.

Besteht die Notwendigkeit einer Erprobung der gegenständlichen Methode?
Aus der Sicht von Urotronic ist eine Erprobung nicht notwendig, da die ROBUST III-Studie nicht nur läuft, sondern bereits wesentliche Resultate vorliegen.
Bei der mit dem Ziel der FDA-Zulassung durchgeführten ROBUST III-Studie handelt es sich um eine hochwertige RCT. Dies möchten wir im Folgenden kurz ausführen.

- Die Randomisierung erfolgte stratifiziert durch permutierte Blöcke innerhalb eines Studienzentrums unter Verwendung eines elektronischen Datenerfassungssystems (EDC). Sie erfolgte unmittelbar vor Beginn des Behandlungs-/Kontrollverfahrens randomisiert. Damit sind die adäquate Erzeugung der Randomisierungssequenz und die Verdeckung der Gruppenzuteilung gewährleistet.
- Die Studienteilnehmer waren bis zur Erhebung des primären Studienendpunktes verblindet.
- Urotronic ist bewusst, dass die Nachuntersuchungen nicht verblindet waren.
    - Der primäre Endpunkt „Strikturfreiheit“ als ungehinderte Passage eines 16F Zystoskops ist jedoch ein objektives Kriterium, das ein Verzerrungspotenzial ohne Verblindung des Nachuntersuchers eher theoretisch erscheinen lässt.
    - Bei dem IPSS handelt es sich um einen patientenberichteten Endpunkt. Ein erhöhtes Verzerrungspotenzial ist für diesen Endpunkt nur durch den Patienten zu erwarten, der jedoch verblindet ist.
    - Ebenso geht Urotronic davon aus, dass der Bedarf für eine Reintervention unabhängig von der Verblindung des Nachuntersuchers ist.
- Urotronic ist sich der Tatsache bewusst, dass die Definition des Behandlungsverfahrens in der Kontrollgruppe (Ballondilatation, Urethrotomia interna oder Bougierung nach Ermessen des Behandlers) dazu führt, dass diese nicht genau dem Standardvorgehen im deutschen Gesundheitswesen (Urethrotomia interna) entspricht. Aufgrund der wegweisenden Publikation von Steenkamp, 1997 geht man jedoch davon aus, dass sich die Wirksamkeit und die Rezidivraten von Ballondilatation, Urethrotomia interna oder Bougierung bei der Behandlung von Strikturen nicht wesentlich unterscheiden. Diese Studie von Steenkamp ist nach wie vor wichtig für die aktuell gültigen Leitlinien, in denen Empfehlungen bezüglich Urethrotomia interna und Dilatationsverfahren ohne Unterscheidung zwischen den Verfahren ausgesprochen werden (Leitlinien der EAU, SIU und AUA). Aus diesem Grund ist Urotronic davon überzeugt, dass die Resultate der ROBUST III-Studie trotz der Vergleichsintervention, die scheinbar nicht dem Standardvorgehen in Deutschland entspricht, als Grundlage für eine Nutzenbewertung herangezogen werden sollten.

Als Schlussfolgerung hält Urotronic aufgrund der Studienqualität der ROBUST III-Studie und den bereits oder in Kürze vorliegenden Resultaten eine Erprobungsstudie für nicht notwendig.

Geplante RCT: Adjunctive Local Drug Treatment at the Time of Endoscopic Surgery for Recurrent Bulbar Urethral Stricture in Men (ReBUS)

Informationen zur geplanten ReBUS-Studie bitten wir dem angefügten Dokument „ReBUS Study“, einer Art Studiensynopse, zu entnehmen.

Die Studie wurde durch die Studiengruppe initiiert, die auch die OPEN-Studie durchgeführt hat, eine ebenfalls durch NIHR geförderte RCT, in der Urethrotomia interna und die Harnröhrenrekonstruktion verglichen wurde.
Zur Information bzgl. der zu erwartenden Studienqualität haben wir das Protokoll der OPEN-Studie, sowie die publizierten Resultate beigefügt (Stephenson, 2015 und Goulao, 2020).

Zeitplan der ReBUS-Studie:
Die Studie soll am 1.1.2022 begonnen werden. Für Set-up, eine interne Pilotierung, Rekrutierung, Nachbeobachtungszeit (der primäre Endpunkt soll wie in der Open-Studie nach 24 Monaten erhoben werden) und Analyse der Studiendaten sind in Summe nach 64 Monaten geplant.

Urotronic wird dem G-BA weitere Resultate der ROBUST III-Studie sowie Informationen zur Planung der ReBUS-Studie zur Verfügung stellen, sobald sie Urotronic vorliegen.

Mit freundlichen Grüßen

Marco Kalms
Geschäftsführer

Anlagen

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Vergleichende Übersicht ROBUST-Studien
- LA1093rA Optilume® DCB Clinical Program summary

Ordner: ReBUS-Studie
- ReBUS-Study.pdf

- Stephenson, R., Carnell, S., Johnson, N., Brown, R., Wilkinson, J., Mundy, A., . . . Pickard, R. (2015). Open urethroplasty versus endoscopic urethrotomy--clarifying the management of men with recurrent urethral stricture (the OPEN trial): study protocol for a randomised controlled trial. Trials, 16, 600. doi:10.1186/s13063-015-1120-4
- Goulao, B., Carnell, S., Shen, J., MacLennan, G., Norrie, J., Cook, J., . . . Pickard, R. (2020). Surgical Treatment for Recurrent Bulbar Urethral Stricture: A Randomised Open-label Superiority Trial of Open Urethroplasty Versus ndoscopic Urethrotomy (the OPEN Trial). Eur Urol. doi:10.1016/j.eururo.2020.06.003

Ordner: Weitere Publikation und Leitlinien

- Chapple, C., Andrich, D., Atala, A., Barbagli, G., Cavalcanti, A., Kulkarni, S., . . . Nakajima, Y. (2014). SIU/ICUD Consultation on Urethral Strictures: The management of anterior urethral stricture disease using substitution urethroplasty. Urology, 83(3 Suppl), S31-47. doi:10.1016/j.urology.2013.09.012
- Lumen, N., Campos-Juanatey, F., Dimitropoulos, K., Greenwell, T., Martins, F. E., Osman, N., . . . Verla, W. (2021). EAU Guidelines on Urethral Stricture. Retrieved from https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urethral-Strictures1-2021.pdf
- Steenkamp, J. W., Heyns, C. F., & de Kock, M. L. (1997). Internal urethrotomy versus dilation as treatment for male urethral strictures: a prospective, randomized comparison. J Urol, 157(1), 98-101.
- Wessells, H., Angermeier, K. W., Elliott, S., Gonzalez, C. M., Kodama, R., Peterson, A. C., . . . Santucci, R. A. (2017). Male Urethral Stricture: American Urological Association Guideline. J Urol, 197(1), 182-190. doi:10.1016/j.juro.2016.07.087

Gelegenheit zur Abgabe erster Einschätzungen

Gemeinsamer Bundesausschuss

zu Beratungen des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Mit Beschluss vom 1. April 2021 hat der Gemeinsame Bundesausschuss (G-BA) als Ergebnis eines Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 des Fünften Buches Sozialgesetzbuch (SGB V) festgestellt, dass für die Methode

- Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

weder der Nutzen noch die Schädlichkeit oder Unwirksamkeit als belegt anzusehen ist.

Für eine Methode nach § 137h Absatz 1 Satz 4 Nummer 3 SGB V entscheidet der G-BA innerhalb von sechs Monaten nach dem Beschluss nach Absatz 1 Satz 4 über eine Richtlinie zur Erprobung nach § 137e. Eine Prüfung des Potentials der Methode erfolgt nicht. Deshalb hat der G-BA mit dem vorgenannten Beschluss zugleich ein Beratungsverfahren über eine Richtlinie zur Erprobung gemäß § 137e SGB V für die gegenständliche Methode eingeleitet. Der Beschluss sowie die Tragenden Gründe sind auf den Internetseiten des G-BA veröffentlicht.

Das Bewertungsverfahrens nach § 137h Absatz 1 Satz 4 SGB V erfolgte auf der Grundlage der von einem Krankenhaus mit der Informationsübermittlung nach § 137h Absatz 1 Satz 1 SGB V eingereichten Angaben und Unterlagen.

Um den G-BA in die Lage zu versetzen, eine abschließende Bewertung des Nutzens der vorgenannten Methode durchzuführen, sollen im Wege der Erprobung die hierfür nach den §§ 135 und 137c SGB V i. V. m. den Vorgaben der Verfahrensordnung des G-BA (VerfO) notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode gewonnen werden. Die zu diesem Zweck notwendigen Studien sollen durch eine unabhängige wissenschaftliche Institution (UWI) nach Maßgabe dieser Richtlinie entworfen, durchgeführt und ausgewertet werden. Die Ausgestaltung des Studiendesigns ist – soweit nicht im Folgenden näher bestimmt – von der UWI auf der Basis des Standes der wissenschaftlichen Erkenntnisse vorzunehmen und zu begründen.

Gemäß 2. Kapitel § 6 der Verfahrensordnung des G-BA erhalten Sie Gelegenheit zur Abgabe einer ersten Einschätzung zum angekündigten Beratungsgegenstand. Bitte verwenden Sie zur Abgabe Ihrer Einschätzung den nachfolgenden Fragebogen.

Bitte belegen Sie Ihre Ausführungen jeweils durch Angabe von Quellen unter Nutzung der beigefügten Literaturliste (siehe Anlage). Bitte fügen Sie die Publikationen – soweit möglich – in Kopie bei.

Wir bitten Sie, den Fragebogen als Word-Dokument und alle weiteren Unterlagen als PDF-Dokumente per E-Mail an erprobung137e@g-ba.de zu übersenden. Die Frist zur Abgabe Ihrer Einschätzung endet am 5. Mai 2021.

Fragebogen

Gemeinsamer Bundesausschuss

Mit der Abgabe Ihrer Einschätzung erklären Sie sich damit einverstanden, dass diese, auch auszugsweise, in einem Bericht des G-BA wiedergegeben werden kann, der mit Abschluss der Beratung zu jedem Thema erstellt und der Öffentlichkeit via Internet zugänglich gemacht wird.

Funktion des Einschätzenden

Bitte geben Sie an, in welcher Funktion Sie diese Einschätzung abgeben (z. B. Verband, Institution, Hersteller, Leistungserbringer, Privatperson).

Urotronic Inc. als Hersteller des für die Methode maßgeblichen Medizinprodukts *Optilume Drug-coated urology balloon catheter*

Urotronic Inc.
2495 Xenium Lane North
Plymouth, MN 55441 USA
USA

Kalms Consulting ist bevollmächtigt, im Rahmen des Verfahrens nach §137h SGB V zu vertreten. Diese Vollmacht umfasst laut Nachricht des Gemeinsamen Bundesausschusses vom 13. April 2021 auch das Folgeverfahren.

Fragebogen

Gemeinsamer Bundesausschuss

Mit der Erprobungsstudie soll nachgewiesen werden, dass bei erwachsenen Männern mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre die Behandlung mittels eines medikamentenbeschichteten Ballondilatationskatheters bezüglich des primären Endpunktes aus dem International Prostate Symptom Score (IPSS) und der Strikturfreiheitsrate überlegen ist.

Überlegungen des G-BA	**Fragen des G-BA**	**Einschätzung**
Population		
In die Erprobungsstudie einzuschließen sind erwachsene Männer mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre.	Ist dies die aus Ihrer Sicht treffende Beschreibung der Studienpopulation? Wenn nicht, wie sollte die Studienpopulation definiert werden? Sollten Subpopulationen gebildet werden? (z.B. entsprechend der Genese der Harnröhrenstrikturen?	Gemäß aktueller Gebrauchsanweisung vom Februar 2021 wird der Optilume medikamentenbeschichtete Ballonkatheter (DCB) für die Behandlung von Männern ≥ 18 Jahren mit störenden Harnwegssymptomen bei Rezidivstrikturen der anterioren Harnröhre verwendet. Er dient zur Verwendung als Dilatationsballon für Einzel-, Tandem- oder diffuse Harnröhrenstrikturen mit einer Länge von **≤3 cm** oder als Ergänzungstherapie mit anderen Dilatationsprodukten und/oder -verfahren.[1] Die Studienpopulation sollte diesen Kriterien, also der aktuellen Zweckbestimmung, folgen und wäre somit im Einklang mit den vorliegenden Studienprotokollen der ROBUST-Studienserien, insbesondere der Studien I, II und III[2].

[1] Siehe Gebrauchsanweisung

[2] Informationen zu den Studien ROBUST I und II sind der übermittelten Information im Rahmen des §137h-Verfahrens zu entnehmen. Das Protokoll der ROBUST III Studie ist dem Fragebogen beigefügt.

		Urotronic möchte an dieser Stelle auf die neue, im April 2021 veröffentlichte Leitlinie der European Association of Urology hinweisen. Unter 6.2.1.3.5 auf Seite 28 findet sich die „strong recommendation“, penile Harnröhrenstrikturen nicht mittels Urethrotomia interna zu behandeln.[3] Urotronic schlägt vor, dieser Empfehlung zu folgen und eine penile Lokalisierung der Striktur als Ausschlusskriterium aufzunehmen. Diese Einschränkung spiegelt weitestgehend die diesbezüglichen Patientencharakteristika in der ROBUST-Studienserie wider, die zu 100% bulbäre Strikturen in ROBUST I und II und zu lediglich 10,1% penile Strikturen in ROBUST III umfasste.[4]
Intervention		
Im Rahmen der Studienplanung durch eine UWI soll unter Einbezug klinischer Expertise konkretisiert werden, ob und ggf. mit welchem Verfahren bei stark stenotischen Strikturen unmittelbar vor der Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter eine Prädilatation der Striktur erfolgen soll.	Verfahren zur Prädilatation stellen die Urethrotomia interna, die Dilatation mit unbeschichteten Ballonkathetern und die Aufbougierung mit Kathetern zunehmender Größe dar. Im deutschen Versorgungskontext kommt in erster Linie die Urethrotomia interna für die Prädilatation zum Einsatz.	Das Produkt hat erst im September 2020 die CE-Zertifizierung erhalten. Anschließend stand die Covid-19 Situation einer schnellen Einführung in Markt entgegen. Daher ist es zu früh, von einem Standardvorgehen zur Prädilatation im Kontext der gegenständlichen Methode im deutschen Versorgungskontext zu sprechen. Im Gegensatz zu dem Vorgehen in den USA, ist die Verwendung unbeschichteter Ballons zur Dilatation von Harnröhrenstrikturen in Deutschland nicht als Standard etabliert. Daher ist zu erwarten, dass die Prädilatation, falls notwendig, überwiegend durch eine

[3] Lumen, N., Campos-Juanatey, F., Dimitropoulos, K., Greenwell, T., Martins, F. E., Osman, N., . . . Verla, W. (2021). EAU Guidelines on Urethral Stricture. Retrieved from https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urethral-Strictures1-2021.pdf

[4] Übersicht ROBUST-Studien: LA1093rA Optilume® DCB Clinical Program summary - Siehe Übersicht auf Seite 4.

	Stimmen Sie mit der Überlegung des G-BA überein, dass im Rahmen der Studienplanung durch eine UWI festgelegt werden sollte, ob und ggf. mit welchem Verfahren eine Prädilatation von stark stenotischen Strikturen erfolgen soll? Falls nein, welche Vorgaben zur Prädilatation sollten Ihrer Meinung nach definiert werden?	Urethrotomia interna, bei Nähe zum Harnröhrensphinkter als Aufbougierung durchgeführt werden wird. Aus diesem Grund schlagen wir vor, die Wahl des Verfahrens zur Prädilatation dem Ermessen der behandelnden Urologen zu überlassen. Eine Subgruppenanalyse des Interventionsarms der ROBUST-III-RCT[5] auf Basis der Resultate nach 6 Monaten ergab, dass das gewählte Prädilationsverfahren keinen Einfluss auf die Rate an Patienten, die frei von Strikturen waren, hatte. Auch diese Beobachtung spricht dafür, den behandelnden Studienzentren keine Vorgaben zu machen und die Wahl des Vorgehens dem Ermessen der Studienärzte zu überlassen.
Die Prüfintervention ist die Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter.	Stimmen Sie mit der Überlegung des G-BA zur Intervention überein? Falls nein, wie würden Sie die Intervention definieren?	Wir stimmen der Überlegung des G-BA zur Intervention uneingeschränkt zu.
Vergleichsintervention (Kontrolle)		
Die Vergleichsintervention ist die Urethrotomia interna.	Stimmen Sie mit der Überlegung des G-BA zur Vergleichsintervention überein? Falls nein, wie würden Sie die Vergleichsintervention definieren?	Wir stimmen mit der Überlegung der G-BA zur Vergleichstherapie überein. Aus der Sicht von Urotronic ist es nicht notwendig, dass Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichsintervention eine Rolle spielen.

[5] Siehe Dokument: Subgruppenanalyse Prädilatationsverfahren: t11-2_primary_subgroup_dilation_pool_ITT.pdf

	Sollten andere/weitere Vergleichsinterventionen berücksichtigt werden? Inwieweit sollten Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichstherapie als möglicherweise hierfür relevante Faktoren berücksichtigt werden?	So zeigt beispielsweise die aktuelle Auswertung der ROBUST III-Studie konsistente Resultate bzgl. der Outcomes unabhängig davon, ob die Strikturen < 2 cm oder ≥ 2 cm (Einschlusskriterium war eine Länge von ≤ 3m) waren, bzw. ob < oder ≥ 5 vorherige Dilatationsverfahren durchgeführt worden waren[6].
Endpunkte		
Der primäre Endpunkt ist der Anteil an Patienten, die • nach 12 Monaten eine Verbesserung im IPSS-Score im Vergleich zum Ausgangswert aufweisen (Verbesserung um mindestens sechs Punkte [>15% der Skalenspannweite]) und • sich innerhalb dieses Zeitraums keiner klinisch-indizierten Reintervention aufgrund des	Stimmen Sie mit der Überlegung des G-BA zum primären Endpunkt und der vorgeschlagenen Responseschwelle überein? Falls nein, was ist aus Ihrer Sicht ein angemessener primärer Endpunkt für die Erprobungsstudie und welche validierten Erhebungsinstrumente gibt es nach Ihrer Kenntnis für diesen von Ihnen vorgeschlagenen Endpunkt?	Urotronic stimmt dem Endpunkt, der eine Kombination von Symptomverbesserung und Freiheit von klinisch indizierten Reinterventionen vorsieht, zu. Urotronic möchte darauf hinweisen, dass bei dem IPSS-Score die minimale klinisch relevante Differenz vom Ausgangswert abhängen kann (Barry et al J Urol 1995)[7], ist sich allerdings der Tatsache bewusst, dass sich diese Publikation auf die gutartige Vergrößerung der Prostata und deren Symptomatik bezieht. Ein klinisch bedeutsamer Schwellenwert hängt also vom Ausgangswert des IPSS ab. Urotronic schlägt deshalb vor, einen Schwellenwert von ≥30% Verbesserung im Vergleich zum

[6] ROBUST III 3 Abstract_ICS 2021, eingereicht.

[7] Barry, M. J., Williford, W. O., Chang, Y., Machi, M., Jones, K. M., Walker-Corkery, E., & Lepor, H. (1995). Benign Prostatic Hyperplasia Specific Health Status Measures in Clinical Research: How Much Change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is Perceptible to Patients? The Journal of Urology, 154(5), 1770-1774. doi:10.1016/s0022-5347(01)66780-6

Wiederauftretens der Striktur einschließlich entsprechender Symptomatikunterziehen müssen (Strikturfreiheit).	Bitte beschreiben Sie bezüglich der von Ihnen vorgeschlagenen Erhebungsinstrumente die minimale klinische Differenz zur Beurteilung des Behandlungsergebnisses und belegen Sie Ihre Aussagen nach Möglichkeit mit geeigneten Studien.	Ausgangswert zu wählen, der auch von der United States Food and Drug Administration für Studien mit Produkten zur Behandlung der BPH empfohlen wird[8]. Dieser Schwellenwert basiert auf der Arbeit von Roehrborn und Kollegen aus dem Jahr 2012, die die Beziehung von Symptomverbesserung gemäß IPSS und Patientenzufriedenheit ermittelt haben.[9]
Als sekundäre Endpunkte sind (unter anderem) zu erheben: • Morbidität (z. B. klinisch-indizierte Reinterventionen, Wiederauftreten der Striktursymptomatik, wiederkehrende Harnwegsinfekte), • gesundheitsbezogene Lebensqualität, • unerwünschte Ereignisse.	Stimmen Sie mit der Überlegung des G-BA zu den sekundären Endpunkten überein? Welche validierten Erhebungsinstrumente zu diesen Endpunkten halten Sie für geeignet? Sollten Ihrer Meinung nach weitere bzw. andere sekundäre Endpunkte ergänzend in der Erprobungsstudie untersucht werden? In diesem Fall benennen Sie bitte die entsprechenden validierten Erhebungsinstrumente.	Urotronic hält die Erhebung mehrerer sekundärer Endpunkte für geeignet: Sicherheit: • Häufigkeit der berichteten Arten von unerwünschten Ereignissen (z. B. Harnwegsinfektion, Hämaturie, Harnsymptome, akuter Harnverhalt) • Häufigkeit von Wiederholungseingriffen, einschließlich intermittierendem Katheterismus und Wiederholung der Dilatation/Urethrotomie oder Durchführung einer Urethroplastik. Wirksamheit

[8] FDA-Dokument *Select Updates for Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/select-updates-guidance-non-clinical-and-clinical-investigation-devices-used-treatment-benign

[9] Roehrborn CG, Wilson TH, Black LK. Quantifying the contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia: 4-year data from the CombAT trial. J Urol. 2012 May;187(5):1732-8. doi: 10.1016/j.juro.2011.12.083. Epub 2012 Mar 15. PMID: 22425127.

		• Verwendung eines Patient Reported Outcome Measure, der speziell für Harnröhrenstrikturen entwickelt wurde.[10] Dieser Fragebogen ist auch in deutscher Sprache validiert.[11] • Berichterstattung über Symptom-Scores (IPSS, PROM) im Zeitverlauf, mit der Maßgabe, dass bei Patienten mit einer Reintervention der studierten Striktur keine weitere Symptombeurteilung erfolgt oder der schlechteste vorherige Wert zugewiesen wird, um das klinische Versagen der ersten Intervention zu reflektieren.
Studientyp und Beobachtungszeitraum		
Die Erprobungsstudie ist als randomisierte, kontrollierte Studie (RCT) multizentrisch durchzuführen.	Stimmen Sie mit der Überlegung des G-BA zum Studientyp überein? Falls nein, welche Vorgaben zum Studientyp sollten definiert werden?	Zustimmung
Die Randomisierung sollte im Verhältnis 1:1 erfolgen.	Stimmen Sie mit der Überlegung des G-BA zur Randomisierung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Zustimmung

[10] Jackson, M. J., Sciberras, J., Mangera, A., Brett, A., Watkin, N., N'Dow J, M., . . . Mundy, A. R. (2011). Defining a patient-reported outcome measure for urethral

[11] Kluth, L. A., Dahlem, R., Becker, A., Schmid, M., Soave, A., Rosenbaum, C., . . . Ahyai, S. A. (2016). Psychometric validation of a German language version of a PROM for urethral stricture surgery and preliminary testing of supplementary ED and UI constructs. World J Urol, 34(3), 369-375. doi: 1007/s00345-015-1610-8

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Die Studienteilnehmer und die weiterbehandelnden Personen sowie die Endpunkterheber sollen verblindet sein.	Stimmen Sie mit der Überlegung des G-BA zur Verblindung überein? Falls nein, welche Einwände oder Vorschläge haben Sie gegen diese Vorgaben?	Wir stimmen zu, dass Patienten, behandelnde Ärzte und die Erhebung der Endpunkte so weit wie möglich verblindet werden sollten. Urotronic ist sich jedoch auch bewusst, dass diese Anforderung erheblichen zusätzlichen Aufwand für die Kliniken, die Patienten in die Studie einbringen, nach sich zieht
Die patientenindividuelle Nachbeobachtungszeit soll 12 Monate betragen.	Eine Nachbeobachtungszeit von 12 Monaten (nach der Intervention) wird als angemessen angesehen, da bei Patienten mit Rezidivstrikturen das Auftreten eines erneuten Rezidivs nach einer Urethrotomia interna oft bereits innerhalb dieses Zeitraums erfolgt. Stimmen Sie mit dieser Überlegung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Urotronic ist der Meinung, dass der primäre Endpunkt nach 12 Monaten erhoben werden sollte, jedoch sollte auch eine längerfristige Nachbeobachtung (z.B. 3 Jahre) in Betracht gezogen werden, um die Dauerhaftigkeit der Ergebnisse besser bewerten zu können.

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Erfassung und Dokumentation bestimmter Parameter		
Die Art und Anzahl weiterer therapeutischer Interventionen mit Bezug zur Grunderkrankung oder mit möglichen Einfluss auf die zu erfassenden Endpunkte sollten dokumentiert werden.	Stimmen Sie mit der Überlegung des G-BA überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	Urotronic stimmt zu, dass die Häufigkeit und die Art vorheriger Interventionen mit Bezug auf die in der Studie untersuchte Harnröhrenstriktur erhoben werden sollte. Urotronic empfiehlt außerdem, weitere wichtige Informationen zur Krankengeschichte zu erfassen, wie z. B. die Ätiologie der Strikturentwicklung, die Vorgeschichte anderer urologischer Erkrankungen (z. B. Krebserkrankungen, BPH, Kontrakturen des Blasenhalses, überaktive Blase, Inkontinenz usw.)

Ergänzende Fragen	
Wie viele Studienzentren in Deutschland kämen für die Studie in Frage?	Laut NUB-Aufstellung des InEK haben 85 Kliniken die NUB-Anfrage „Medikamentebeschichteter Ballonkatheter bei symptomatischer Harnröhrenstriktur“ eingereicht. Diese kommen also grundsätzlich als Studienzentren in Frage. Laut Weiße Liste (www.weisse-liste.de) behandelten im Jahr 2019 39 Kliniken in Deutschland 60 oder mehr Patienten mit einer Hauptdiagnose der Gruppe N35, also einer Harnröhrenverengung. Insgesamt behandelten 539 Kliniken Patienten mit dieser Indikation. Hinzu kommen deutschlandweit 3.411 Fälle mit der Hauptdiagnose N99.1 *Harnröhrenstriktur nach medizinischen Maßnahmen*. Die Fallzahlen der 4-Steller der Diagnosecodes sind der weißen Liste jedoch nicht zu entnehmen,

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Ergänzende Fragen	
Wie viele Studienzentren sollten initiiert werden, um die Studie in angemessener Zeit abzuschließen?	Um eine Effektgröße von 15% detektieren können, wäre eine Stichprobengröße von etwa 350 Probanden notwendig. Um diese Anzahl in einem überschaubaren Zeitraum rekrutieren zu können, würde Urotronic empfehlen, ca. 35 Zentren mit jeweils 10 Patienten in die Studie einzubeziehen. Wird die durchschnittliche Anzahl von Probanden je Studienzentrum aus der ROBUST III-Studie zugrunde gelegt (5,77), wären 61 Studienzentren notwendig, um die oben genannte Anzahl an Probanden zu rekrutieren. Urotronic möchte an dieser Stelle darauf hinweisen, dass die NUB-Anfrage zu der neuen Methode überraschend den Status 2 erhalten hat. Kliniken können also kein zusätzliches Budget für die Methode verhandeln, und können die Methode im Rahmen des DRG-Systems nicht wirtschaftlich erbringen. Diese Situation könnte der Rekrutierung einer höheren Anzahl an Probanden je Zentrum im Weg stehen.
Welche Maßnahmen wären erforderlich, um eine zügige Rekrutierung zu gewährleisten?	Es wäre erforderlich solche Zentren in die Studie einzubeziehen, die eine hohe Anzahl von Patienten mit Harnröhrenstriktur behandeln bzw. die eine relevante Anzahl an Urethrotomien durchführen.
Gibt es aus Ihrer Sicht Aspekte zu berücksichtigen, welche die geplante Studiendurchführung erschweren könnten? (Beispielsweise geplante oder	Patienten könnten aufgrund ihrer rezidivierenden Erkrankung der Randomisierung kritisch gegenüberstehen, nachdem sie sich zuvor einer oder mehreren Urethrotomien unterzogen haben.

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Ergänzende Fragen	
laufende Studien mit Rekrutierung derselben Patientengruppen im Indikationsgebiet der Erprobungsstudie)	Dies kann dazu führen, dass die Patienten eher versuchen, eine Behandlung mit der gegenständlichen Methode außerhalb der Studie zu erhalten, oder dass sie sich für die invasivere, aufwändigere plastische Rekonstruktion der Harnröhre entscheiden. Urotronic weist auch an dieser Stelle darauf hin, dass die NUB-Anfrage zu der neuen Methode überraschend mit dem Status 2 beschieden wurde. Kliniken können also kein zusätzliches Budget für die Methode verhandeln, und können daher die Methode im Rahmen des DRG-Systems nicht wirtschaftlich erbringen. Diese Situation kann die geplante Studiendurchführung erschweren.
Welche Anforderungen, insbesondere hinsichtlich der personellen, technischen und räumlichen Ausstattung, sind aus Ihrer Sicht zur Erbringung der Methode im Rahmen einer Studie zu stellen? Bitte berücksichtigen Sie hierbei auch mögliche periprozedurale Risiken ihrer Anwendung.	Die Anforderungen der Prozedur sind vergleichbar mit denen der Urethrotomia interna.
Wird bei den genannten Eckpunkten die Versorgungsrealität in Hinblick auf die Durchführbarkeit der Erprobung und der Leistungserbringung angemessen berücksichtigt?	Insgesamt berücksichtigen die genannten Eckpunkte aus Sicht von Urotronic die Versorgungsrealität in angemessener Weise.
Bitte benennen Sie ggf. zusätzliche Aspekte, die im Rahmen der Erstellung der Erprobungs-Richtlinie berücksichtigt werden sollten.	Klicken Sie hier, um einen Text einzugeben.

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Überlegungen des G-BA zur näherungsweisen Fallzahlschätzung	Wie lautet Ihre Einschätzung?
Für die Fallzahl ist die Größe des nachzuweisenden Effekts maßgeblich. Diese wiederum hängt maßgeblich von der Operationalisierung des primären Endpunkts (hier: IPSS Score und Strikturfreiheit) ab. Unter Annahme einer Effektstärke von beispielsweise 15 % (80 % der Teilnehmer erreichen den primären Endpunkt in der Interventionsgruppe, 65 % in der Kontrollgruppe), abgeleitet aus den Ergebnissen der Studien ROBUST- I[12] und ROBUST-II[13] sowie aus Daten zur Strikturfreiheit nach 12 Monaten in Abhängigkeit der Anzahl vorheriger Interventionen[14], ergibt sich als grobe Approximation eine Fallzahl in der Kategorie einer mittleren Studie (100 bis < 500).	Urotronic erwartet eine Erfolgsrate zwischen 70% und 80% für Optilume und zwischen 55% und 65% für die Urethrotomie je nach Charakteristik der Patientenpopulation. Daraus leitet sich ebenfalls eine Studiengröße in der mittleren Kategorie ab.

Schätzung der Overheadkosten der Erprobungsstudie (Beispiel)	Wie lautet Ihre Einschätzung?
Für Studien mit mittlerer Fallzahl (hier: 400 Studienteilnehmer als Kalkulationsgrundlage) und mittlerem Aufwand lässt sich ein studienspezifischer Aufwand in Höhe von etwa 5500 € je Teilnehmer beziffern. Auf der Basis dieser Annahmen lassen sich geschätzte Studienkosten von 2,2 Millionen € berechnen.	Urotronic stimmt der Kalkulation der Kosten für den studien-spezifischen Aufwand im Rahmen der obigen Annahmen zu den Fallzahlschätzungen zu.

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[13]Urotronic. Re-establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease (ROBUST-II) [online]. 2019 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03270384.

[14]Heyns CF, Steenkamp JW, De Kock ML et al. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998; 160(2): 356-358. https://dx.doi.org/10.1016/s0022-5347(01)62894-5.

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Aktuelle Dokumente zum maßgeblichen Medizin-Produkt und Literatur

1. Gebrauchsanweisung Stand Februar 2021: *Optilume manual_all languages_Feb2021_RevD_v3.pdf*

2. Protokoll ROBUST III-Studie: *PR1076rH_ROBUST_III_Protocol_20Dec2019.pdf*

3. Lumen, N., Campos-Juanatey, F., Dimitropoulos, K., Greenwell, T., Martins, F. E., Osman, N., . . . Verla, W. (2021). EAU Guidelines on Urethral Stricture. Retrieved from https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urethral-Strictures1-2021.pdf

4. Übersicht ROBUST-Studien: *LA1093rA Optilume® DCB Clinical Program summary.pdf*

5. Subgruppenanalyse Prädilatationsverfahren ROBUST-III: *t11-2_primary_subgroup_dilation_pool_ITT.pdf*

6. Resultate ROBUST-III: *ROBUST III Abstract_ICS 2021.pdf*

7. Barry, M. J., Williford, W. O., Chang, Y., Machi, M., Jones, K. M., Walker-Corkery, E., & Lepor, H. (1995). Benign Prostatic Hyperplasia Specific Health Status Measures in Clinical Research: How Much Change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is Perceptible to Patients? The Journal of Urology, 154(5), 1770-1774. doi:10.1016/s0022-5347(01)66780-6

8. FDA-Dokument *Select Updates for Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/select-updates-guidance-non-clinical-and-clinical-investigation-devices-used-treatment-benign

9. Roehrborn CG, Wilson TH, Black LK. Quantifying the contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia: 4-year data from the CombAT trial. J Urol. 2012 May;187(5):1732-8. doi: 10.1016/j.juro.2011.12.083. Epub 2012 Mar 15. PMID: 22425127.

10. Jackson, M. J., Sciberras, J., Mangera, A., Brett, A., Watkin, N., N'Dow J, M., . . . Mundy, A. R. (2011). Defining a patient-reported outcome measure for urethral

11. Kluth, L. A., Dahlem, R., Becker, A., Schmid, M., Soave, A., Rosenbaum, C., . . . Ahyai, S. A. (2016). Psychometric validation of a German language version of a PROM for urethral stricture surgery and preliminary testing of supplementary ED and UI constructs. World J Urol, 34(3), 369-375. doi: 1007/s00345-015-1610-8Roehrborn et al., 2012

OPTILUME®

URETHRAL DRUG COATED BALLOON CATHETER

ENGLISH

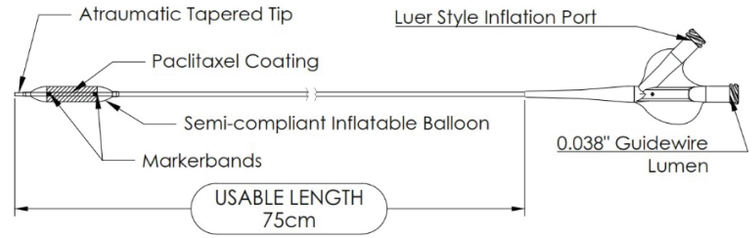
Instructions for Use

Table of Contents

1.0 DEVICE DESCRIPTION

1.1 Balloon Catheter

The Optilume Urethral Drug Coated Balloon (DCB) Catheter is a 0.038” (0.97 mm) guidewire and flexible cystoscope compatible over-the-wire (OTW) catheter with a dual lumen design and a tapered atraumatic tip. The DCB is used to exert radial force to dilate narrow urethral segments (strictures). The distal end of the catheter has a semi-compliant inflatable balloon that is coated with a proprietary coating containing the active pharmaceutical paclitaxel. The drug coating covers the working length of the balloon body. The device has two radiopaque marker bands that indicate the working length of the balloon.



The device is sterilized using ethylene oxide in a Tyvek pouch. Post sterilization the pouched catheter is sealed in a foil pouch with desiccant and contained within a single unit carton. Each DCB is supplied with a protective sheath that covers the drug-coated balloon portion of the catheter. A balloon compliance chart is located on the Tyvek pouch label.

ENGLISH

1.2 Drug Coating

The drug coating consists of the active pharmaceutical ingredient paclitaxel and excipients. The drug coating covers the working length of the balloon component of the catheter. The drug coating is evenly distributed across the balloon surface at a concentration of 3.5 µg/mm^2. The key functional characteristic of the drug coating is to allow for release of the paclitaxel to the urothelium during balloon inflation.

DCB Dosing Matrix

Catalog Number	Diameter (Fr/mm)	Length (mm)	Paclitaxel Dose (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

2.0 INTENDED USE

The Optilume Urethral Drug Coated Balloon (DCB) Catheter is intended for the treatment of strictures in the anterior urethra in adult males.

3.0 INDICATIONS FOR USE

The Optilume Urethral DCB Catheter is used to treat men ≥18 years of age with bothersome urinary symptoms associated with recurrent anterior urethral stricture. It is designed to be used as a dilation balloon for a single, tandem or diffuse anterior urethral stricture of ≤3 cm in length or used as an adjunctive therapy with other dilation devices and/or procedures.

4.0 CONTRAINDICATIONS

The Urethral Drug Coated Balloon (DCB) Dilation Catheter is contraindicated for use in:

- Patients with known hypersensitivity to paclitaxel or structurally related compounds.
- Patients with lesions that cannot be crossed with a 0.038" guidewire.

5.0 WARNINGS

- The urethral DCB is supplied STERILE for single use only. Do not reprocess or resterilize. Reprocessing and resterilizing could increase the risk of patient infection and risk of compromised device performance.
- The foil pouch and the outer surface of the inner pouch are NON-STERILE. The CONTENTS of the inner pouch are STERILE. Use Immediately once the foil pouch has been opened.
- Do not use this device if there is infection in the Urethra (UTI) or Bladder. Infection must be cleared before treating the stricture with the Optilume DCB.
- The DCB should be used only by physicians who are experienced and knowledgeable of the clinical and technical aspects of urethral balloon dilatation.
- Prior to use of the DCB, physicians should read and understand the instructions for use. Failure to follow the indications, contraindications, restrictions, warnings and precautions may result in complications.
- Do not use after the "Use By" date.
- The DCB contains paclitaxel, a known genotoxin. Men should have protected sex (wear a condom) for 30 days post treatment.
- Monitor for signs of anaphylaxis or hypersensitivity to Paclitaxel
- Never use air or any gaseous medium to inflate the DCB.
- When in use the DCB should be manipulated under direct visualization via cystoscopy or high quality fluoroscopic observation.
- Do not manipulate the DCB in an inflated state.
- If resistance is encountered at any time during the insertion procedure, do not force passage. Resistance may cause damage to device or lumen. Carefully withdraw the catheter.
- Men with sexual partners of childbearing potential should use condom for at least 90 days post-treatment.
- Adverse reaction to the paclitaxel and symptoms observed derived primarily from IV infusion studies of the drug in treating cancer subjects include
    - Chromosomal abnormalities and the risk of cancer
    - Fetal harm when a pregnant woman is exposed
    - Anaphylaxis and hypersensitivity with paclitaxel
    - Inhibition of the healing of the urethra post procedure
    - Myelosuppression including: neutropenia, leukopenia, thrombocytopenia, anemia
    - Arrhythmia
    - Peripheral neuropathy
    - Myalgia or Arthralgia
    - Alopecia
    - Hypotension
    - Nausea, vomiting or diarrhea
    - Elevated bilirubin, ALP and AST
    - Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered locally during the Optilume DCB procedure is much lower than a single dose of systemic chemotherapy provided to cancer patients and the drug appears to be essentially remain localized in the urethra.

6.0 PRECAUTIONS

- Always inflate with a sterile liquid (Sterile Saline or 50% contrast mixture). Never inflate with air, carbon dioxide or any other gas. The DCB should not be inflated beyond the rated burst pressure (RBP). Do not overinflate the balloon.
- Balloon catheters are intended for use by physicians trained and experienced in techniques for balloon catheter dilation.
- To ensure proper regulation of balloon pressure, use of a balloon inflation device with pressure gauge is recommended.
- Aspirate the balloon completely before gently removing the device from the urethra. Using excessive force to withdraw the balloon can inflict trauma to tissue.
- Carefully inspect the DCB and package prior to use. Do not use the catheter if it is damaged or if the size, shape or condition is unsuitable for the intended procedure.
- Do not immerse or wipe the balloon section of the DCB with any fluid as the integrity of the drug coating may be damaged or compromised. Replace any DCB where the balloon has come in contact with fluids prior to use.
- Use dry sterile gloves or dry gauze pads to handle the DCB prior to use. Care should be taken to minimize contact with the coated balloon portion of the device.
- Never inflate the DCB outside the body or prior to reaching the target stricture as it may disrupt the coating integrity.
- Do not attempt to pass the DCB through a smaller French size cystoscope than indicated on the label.
- The DCB working length must cover the entire target stricture length.
- For proper drug delivery to the target stricture, allow the coating to hydrate in the urethra for a minimum of 60 seconds prior to inflation and maintain inflation of the DCB for a minimum of 5 minutes. To optimize stricture dilatation, longer inflation times > 5 minutes may be performed at the discretion of the operator.

- If the product has a failure prior to, or during inflation replace DCB and inflate per procedure. If failure is after inflation to RBP do not repeat DCB procedure.
- After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local regulations.
- Healthcare practitioners should avoid using latex gloves to prevent possible allergic reactions by patients who are allergic to latex.
- Urethral lumen preparation of the target lesion, using the appropriate lumen preparation method as determined by the treating physician, is required prior to the use of the Optilume DCB.
- Lumen preparation using only pre-dilatation with an uncoated balloon catheter or DVIU was studied in the Robust I clinical study.
- In clinical studies, visual confirmation of significant stricture (≤12F urethral diameter) via cystoscopy or urethrogram was required and enrollment was restricted to patients exhibiting subjective and objective symptoms of urethral stricture (International Prostate Symptom Score [IPSS] >13, peak urinary flow rate <15 mL/sec). Subjects had undergone at least one prior endoscopic treatment before enrolling in the clinical studies.
- Safety and effectiveness data have not been established during the clinical study to support the treatment of strictures in patients with:
  - BPH
  - Radical prostatectomy
  - Pelvic radiation
  - Botox treatment
  - More than 1 stricture
  - Previous urethroplasty within the anterior urethra
  - Bacterial urethritis or gonorrhea
  - Presence of a penile implant artificial sphincter or urethra/prostatic stent
  - Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function.
  - Diagnosed with Lichen Sclerosis, or previous hypospadias repair.
  - History within the last 5 years of carcinoma of the bladder or prostate
  - Stricture due to balanitis xerotica obliterans (BXO)
  - Urethral tumors or penile cancer

7.0 USE IN SPECIAL POPULATIONS

The safety and effectiveness of the Urethral DCB has not been established in pediatric patients (< 18 years of age) or in women. Use of the Urethral DCB in patients ≥ 18 years of age and older is at the discretion of the physician.

8.0 POSSIBLE COMPLICATIONS

Possible complications associated with the use of the Optilume DCB Catheter are similar to the ones associated with standard urethra dilation procedures. Possible complications may include, but are not limited to:

- Pain and tenderness
- Bladder spasm from Foley catheter placement
- Tissue Trauma in surrounding structures, including urethral damage
- Hematuria
- Drug reactions, allergic reaction to contrast medium used during diagnostic urethrogram
- Urinary Tract Infection
- Tissue perforation
- Stricture recurrence requiring further surgery
- Incontinence
- Dysuria
- Fever
- Urinary retention

9.0 DRUG INFORMATION

○ MECHANISM OF ACTION

The Urethral DCB coating contains paclitaxel, an anti-mitotic pharmaceutical agent that specifically binds to and stabilizes microtubules. Paclitaxel has been reported to inhibit smooth muscle cell and fibroblast proliferation and migration as well as secretion of extracellular matrix. The combination of these effects may result in the inhibition of urothelium hyperplasia and therefore stricture recurrence.

ENGLISH

○ DRUG INTERACTIONS

Formal drug interaction studies have not been conducted for the Urethral DCB. The respective instructions for use for all drugs used in conjunction with the DCB should be consulted for interactions with paclitaxel.

Consideration should be given to the potential for systemic and local drug interactions in the urethra in a patient who is taking a drug with known interactions to paclitaxel or when deciding to initiate drug therapy in a patient who has been treated with the DCB. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 and it is a substrate of P-glycoprotein. Potential drug interactions may occur with any drug that affects these isoenzymes. In the absence of formal drug interaction studies, caution should be exercised when administering paclitaxel.

○ CARCINOGENICITY, GENOTOXICITY AND REPRODUCTIVE TOXICOLOGY

No long-term studies have been performed to evaluate the carcinogenic potential of the drug paclitaxel or of the Optilume DCB, and there are no adequate and well-controlled studies published in pregnant women or in men intending to father children. Paclitaxel inhibits cell proliferation by interacting with microtubules, and one consequence is the loss of whole chromosomes during cell division. This indirect action is consistent with positive responses in vitro and in vivo micronucleus genotoxicity assays, which detect DNA fragments. Positive results have also been reported for chromosomal aberrations in primary human lymphocytes. It is not known whether paclitaxel has a separate direct action on DNA in the generation of DNA strand breaks or fragments. It is negative in assays for gene mutation, including salmonella and CHO/HPRT.

Studies performed in rats and rabbits receiving IV paclitaxel during organogenesis revealed evidence of maternal toxicity, embryotoxicity, and fetotoxicity at dosages of 1 and 3 mg/kg, respectively (approximately 13 and 39 times the dose provided by the Optilume DCB coated with 5.5 mg paclitaxel (10mm x 50mm balloon) adjusted for body weight). No teratogenicity was observed in gravid rats receiving daily IV paclitaxel doses of 1 mg/kg (a daily dose of approximately 13 times the dose of the Optilume DCB (10mm x 50mm), adjusted for bodyweight).

The treating physician should balance the potential medical benefits of the Optilume DCB Catheter against these genotoxic and reproductive risks.

WARNING: The Urethral DCB contains paclitaxel, a known genotoxin. Men should have protected sex (wear a condom) for 30 days' post treatment.

10.0 HOW SUPPLIED

The Optilume DCB catheter is supplied STERILE for single use only (ethylene oxide sterilization). The DCB is in a double pouch packaging system (foil and Tyvek pouches) contained within a single unit box.

11.0 STORAGE

The Urethral DCB should be stored at room temperature in a dry location in its original packaging. The device should be used prior to the "Use by" date on the packaging.

12.0 RECOMMENDED ITEMS

Prepare the following items using sterile technique:

- Appropriately sized guidewire with flexible tip (refer to product labeling)
- Cystoscope (flexible preferred)
- Sterile saline
- 10 cc syringe
- Two-way stopcock
- Inflation device with manometer
- Contrast media – Note: Optional for use with fluoroscopic guided procedures

13.0 DIRECTIONS FOR USE

13.1 PRIOR TO USE

Peri Procedural Medication

It is recommended that physicians follow guidelines for pre-procedure medications and preparation for an endoscopic procedure, including the administration of a pre-procedure antibiotic as appropriate. Oral NSAIDs are also recommended to be given prior to the procedure.

If a urinary tract infection (UTI) is present at the time of treatment, the patient must be treated until the infection is cured before the treatment procedure can take place.

13.2 TARGET STRICTURE PREPARATION

Urethral pre-dilation of the target stricture, using the appropriate preparation method as determined by the treating physician (Uncoated dilation balloon or DVIU), is recommended for highly stenosed and difficult to cross strictures prior to the use of the Optilume DCB. Conduct a pre-dilation to "yield" the stricture. This is defined as the dilated stricture lumen diameter >20F or >50% larger than the non-dilated stricture lumen.

13.3 DEVICE SIZING

Verify the selected DCB balloon diameter at nominal pressure is the same or slightly greater than the diameter of the healthy urethra adjacent to the distal edge of the stricture. The balloon diameter divided by the distal healthy adjacent urethra is defined as the stretch ratio.

Bulbar Urethra Sizing
For Bulbar strictures do not exceed a 1.3 stretch ratio of balloon diameter to distal heathy urethra. If the size of the urethra falls between available device sizes, use the larger size provided that the stretch ratio is less than or equal to 1.3. If the next larger size produces a stretch ratio greater than 1.3, use the smaller device.

Penile Urethral Sizing
For Penile urethral strictures select the balloon diameter that best matches the distal healthy urethra. The stretch ratio of the penile urethra must not exceed 1:1. If the size of the urethra falls in-between available balloon sizes, select the smaller balloon size. DO NOT EXCEED 1:1 stretch ratio.

For both the penile urethra and the bulbar urethra the DCB balloon length should be longer than the stricture length to be treated. The balloon length must extend approximately 0.5-1 cm beyond the stricture on both sides.
For example, if the stricture length is 2 cm, choose a DCB balloon that is 3 cm.

13.4 BALLOON CATHETER PREPARATION

Evacuate Air from DCB Catheter. The balloon lumen of the catheter contains air and the air must be displaced to make certain that only liquid fills the balloon while the catheter is in the urethra.

1. Attach stopcock in the open position to the balloon inflation connector.
2. Attach half saline filled syringe to the stopcock.
3. With syringe tip down draw back plunger to full volume of syringe (this creates maximum negative pressure) and hold until no air bubbles can be seen coming out of the saline in the syringe. Repeat as needed to purge the air from the catheter and replace it with saline. Keep plunger back, turn stopcock to maintain vacuum and remove syringe. Half fill an inflation device with normal saline or 1:1 contrast: saline if using fluoroscopy, and purge air from the line.
4. Attach inflation device to the stopcock on the balloon catheter, turn stopcock and pull vacuum on the inflation device.

13.5 OPTILUME DCB INSERTION

1. Position a 0.038" guidewire with the flexible tip coiled in the bladder with the aid of a cystoscope.

2. Remove the balloon protector from the tip of the DCB catheter.

   Caution: *Care should be exercised when passing a balloon coated with paclitaxel through any cystoscope system. Minimize excessive handling and do not touch the balloon. Do not wipe the balloon with dry, wet or lubricated gauze, or any solvent which could damage the integrity of the drug coated balloon.*
3. Advance the DCB catheter within the working channel of the cystoscope. Alternately, place the guidewire and balloon catheter separate from the cystoscope working channel for side by side placement.
4. Use the cystoscope to guide the placement of the DCB. Alternatively position the DCB with fluoroscopy by using the radiopaque markers located under the balloon body/cone transition.

   Caution: *Do not advance the guidewire or the balloon dilation catheter if resistance is met without first determining the cause of resistance and taking remedial action.*

13.6 OPTILUME DCB INFLATION

Caution: *Inflation devices are capable of attaining very high pressures with minimal effort. The use of an inflation device with a high-pressure gauge is strongly recommended to optimize dilatation force to yield the urethral stricture and allow drug penetration into the yielded urothelium.*

1. Ensure that the urethra is flushed with saline.
2. Position the DCB across the stricture with the cystoscope distal to the balloon (away from the bladder) to visualize the proper placement of the balloon across the stricture. Leave the balloon in position uninflated for a minimum of 1 minute prior to inflation. Check that the balloon radiopaque markers are in the correct position using fluoroscopy.
3. Inflate the balloon to the rated burst pressure using the inflation device. Do not exceed rated burst pressure (RBP) of the balloon. Maintain pressure for a minimum of 5 minutes, or until desired dilation is achieved.
4. Deflate balloon by applying vacuum to the balloon with the inflation device. When the balloon is completely deflated, withdraw guidewire and DCB slowly. If slight resistance is felt when the balloon is being removed gently rotate the catheter to help the balloon fold around the catheter shaft and facilitate withdrawal.

   Caution: *If resistance is encountered when removing a guidewire through a catheter through a cystoscope, STOP and remove them together at the same time as a complete unit to prevent damage to the guidewire, catheter or patient anatomy.*
5. If the product has a failure prior to, or during inflation (but less than RBP) replace DCB and inflate per procedure. If failure is after inflation to RBP do not repeat DCB procedure.
6. Insert a 12-14 Fr lubricious Foley catheter and leave in place for a minimum of 2 days or per standard of care, whichever is greater.

13.7 COMPLIANCE CHART

18Fr (6mm) x 30mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	6.11 (18Fr)
8.0	800		6.23
10.0	1000		6.34
12.0	1200	**RBP**	6.45

18Fr (6mm) x 50mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	5.87 (18Fr)
8.0	800		6.03
10.0	1000		6.16
12.0	1200	**RBP**	6.25

24 Fr (8mm) x 30mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	7.98 (24Fr)
8.0	800		8.16
10.0	1000		8.32
12.0	1200	**RBP**	8.46

24 Fr (8mm) x 50mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	8.00 (24Fr)
8.0	800		8.20
10.0	1000		8.37
12.0	1200	**RBP**	8.54

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30 Fr (10mm) x 30mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	9.83 (30 Fr)
8.0	800		10.09
10.0	1000	**RBP**	10.29

30 Fr (10mm) x 50mm

(ATM) Pressure	kPa		(mm) Balloon
6.0	600	**Nominal**	9.98 (30 Fr)
8.0	800		10.23
10.0	1000	**RBP**	10.44

Caution: *The rated burst pressure should not be exceeded. Refer to product label for rated burst pressures. Inflation beyond the rated burst pressure may cause the balloon to rupture. If loss of pressure within the balloon occurs during inflation or if balloon ruptures during dilation, immediately discontinue the procedure. Deflate the balloon carefully and remove from urethra. Do not re-inflate.*

14.0 WARRANTY

Urotronic warrants that reasonable care has been used in the design and manufacture of this product. This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties for a particular purpose. Handling, storage, cleaning and sterilization of this device as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond Urotronic's control directly affect the device and the results obtained from its use. Urotronic's obligation under this warranty is limited to the repair or replacement of this device and Urotronic shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this device. Urotronic assumes no liability with respect to devices reused, reprocessed or re-sterilized and makes no warranties, express or implied, including but not limited for a particular purpose, with respect to such devices.

15.0 SYMBOLS USED IN THE DEVICE LABELS

1	Quantity of 1 per box
Rx only	Caution: Federal law restricts this device to sale by or on the order of a physician.
	Indicates the date when the medical device was manufactured.
	Do not resterilize
	Do not re-use
	Do not use if package is damaged
	Fragile
	Use-by date
	Keep away from sunlight
	Keep Dry
	Manufacturer
LATEX	Does not contain latex
	Temperature limit 15°C - 30°C
	Caution: Consult instructions for use
STERILE EO	Sterilized using ethylene oxide
REF	Catalog number
LOT	Lot number
CE 1434	CE Marked per the Medical Device Directive 93/42/EEC of the European Union (Notified Body #1434)
EC REP	European Union Authorized Representative

Urotronic, Inc.
2495 Xenium Lane North
Minneapolis, MN 55441
USA

CE 1434

EC REP

MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany

OPTILUME®

CATHÉTER URÉTRAL À BALLONNET À ÉLUTION MÉDICAMENTEUSE

Mode d’emploi

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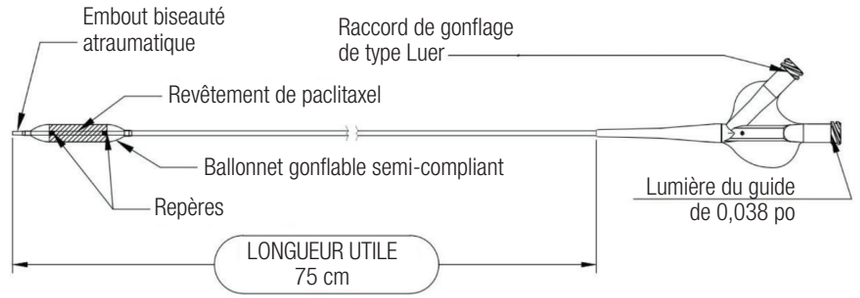
1.0 DESCRIPTION DU DISPOSITIF

1.1 Cathéter à ballonnet

Le cathéter urétral à ballonnet à élution médicamenteuse Optilume est un cathéter coaxial, compatible avec un guide de 0,038 po (0,97 mm) et un cystoscope souple, avec deux lumières et un embout biseauté atraumatique. Le cathéter à ballonnet à élution médicamenteuse est utilisé pour exercer une force radiale visant à diluer les parties rétrécies de l'urètre (sténoses). L'extrémité distale du cathéter est munie d'un ballonnet gonflable semi-compliant qui est enduit d'un revêtement exclusif contenant la substance active, le paclitaxel. Le revêtement médicamenteux couvre la longueur utile du corps du ballonnet. Le dispositif comporte deux repères radio-opaques qui indiquent la longueur utile du ballonnet.



Le dispositif est stérilisé à l'oxyde d'éthylène à l'intérieur d'une poche Tyvek. Après la stérilisation, le cathéter ensaché est scellé à l'intérieur d'une poche en aluminium avec un produit déshydratant et placé dans une boîte unitaire. Chaque cathéter est livré avec une gaine protectrice qui recouvre la partie ballonnet à élution médicamenteuse du cathéter. Un tableau de conformité du ballonnet figure sur l'étiquette de la poche Tyvek.

1.2 Revêtement médicamenteux

Le revêtement médicamenteux est composé de la substance active, le paclitaxel, et d'excipients. Le revêtement médicamenteux couvre la longueur utile du ballonnet du cathéter. Le revêtement médicamenteux est réparti de manière uniforme sur la surface du ballonnet, à une concentration de 3,5 µg/mm^2. La principale caractéristique fonctionnelle du revêtement médicamenteux est de permettre la libération du paclitaxel dans l'urothélium pendant le gonflage du ballonnet.

Matrice de dosage du cathéter à ballonnet à élution médicamenteuse

Référence catalogue	Diamètre (Fr/mm)	Longueur (mm)	Dose de paclitaxel (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

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2.0 USAGE PRÉVU

Le cathéter urétral à ballonnet à élution médicamenteuse Optilume est destiné au traitement des sténoses de l'urètre antérieur chez l'homme adulte.

3.0 INDICATIONS THÉRAPEUTIQUES

Le cathéter urétral à ballonnet à élution médicamenteuse Optilume est utilisé pour traiter des hommes âgés de 18 ans et plus souffrant de symptômes urinaires gênants associés à une sténose urétrale antérieure récurrente. Il est conçu pour être utilisé comme ballonnet de dilatation pour une sténose urétrale antérieure unique, tandem ou diffuse d'une longueur de ≤3 cm ou comme traitement d'appoint avec d'autres dispositifs et/ou procédures.

4.0 CONTRE-INDICATIONS

L'utilisation du cathéter de dilatation urétrale à élution médicamenteuse est contre-indiquée :

- Chez les patients qui présentent une hypersensibilité connue au paclitaxel ou à des composés ayant une affinité structurelle.
- Patients présentant des lésions qui ne peuvent traversées avec un guide de 0,038 po.

5.0 AVERTISSEMENTS

- Réservé à un usage unique, le cathéter urétral à ballonnet à élution médicamenteuse est fourni STÉRILE. Ne pas retraiter ni restériliser. Le retraitement et la restérilisation pourraient accroître le risque d'infection pour le patient et compromettre les performances du dispositif.
- La poche en aluminium et la surface extérieure de la poche interne NE sont PAS STÉRILES. Le CONTENU de la poche interne est STÉRILE. Utiliser immédiatement après l'ouverture de la poche en aluminium.
- Ne pas utiliser ce dispositif en présence d'une infection de l'urètre (infection urinaire) ou de la vessie. L'infection doit être éliminée avant de traiter la sténose à l'aide du cathéter à ballonnet à élution médicamenteuse Optilume.
- Le cathéter à ballonnet à élution médicamenteuse doit être utilisé uniquement par des médecins expérimentés qui maîtrisent les aspects aussi bien cliniques que techniques de la dilatation urétrale par ballonnet.
- Avant d'utiliser le cathéter à ballonnet à élution médicamenteuse, les médecins doivent lire le mode d'emploi et s'assurer de l'avoir compris. Le non-respect des indications, contreindications, limitations, avertissements et précautions peut entraîner des complications.
- Ne pas utiliser après la date de péremption.
- Le cathéter à ballonnet à élution médicamenteuse contient du paclitaxel, une génotoxine connue. Les hommes doivent avoir des rapports sexuels protégés (port d'un préservatif) pendant les 30 jours suivant le traitement.
- Surveiller l'apparition de signes d'anaphylaxie ou d'hypersensibilité au paclitaxel
- Ne jamais utiliser d'air ou de gaz pour gonfler le ballonnet à élution médicamenteuse.
- Pendant son utilisation, le ballonnet à élution médicamenteuse doit être manipulé sous visualisation directe, soit par cystoscopie, soit sous guidage radiographique de grande qualité.
- Ne pas manipuler le ballonnet à élution médicamenteuse une fois qu'il est gonflé.
- Si une résistance se fait sentir à un moment ou à un autre durant la procédure d'insertion, ne pas forcer le passage. Toute résistance risque d'endommager le dispositif ou la lumière. Retirer délicatement le cathéter.
- Les hommes dont les partenaires sexuelles présentent un risque de grossesse doivent utiliser des préservatifs pendant au moins 90 jours après le traitement.
- Les réactions indésirables au paclitaxel et les symptômes observés principalement dans le cadre d'études impliquant une perfusion IV de ce médicament pour traiter des sujets atteints de cancer incluent :
    - Aberrations chromosomiques et risque de cancer
    - Atteinte fœtale en cas d'exposition d'une femme enceinte
    - Anaphylaxie et hypersensibilité au paclitaxel
    - Inhibition de la cicatrisation de l'urètre après la procédure Myélosuppression, notamment : neutropénie, leucopénie, thrombopénie, anémie
    - Arythmie
    - Neuropathie périphérique
    - Myalgie ou arthralgie
    - Alopécie
    - Hypotension
    - Nausées, vomissements ou diarrhée
    - Taux élevé de bilirubine, ALP et AST
    - L'effet potentiel sur le foie et les reins reste inconnu et n'a pas été étudié.

La quantité de paclitaxel administré localement pendant la procédure à l'aide du cathéter à ballonnet à élution médicamenteuse Optilume est largement inférieure à une seule dose de chimiothérapie systémique administrée aux patients atteints de cancer, et le médicament semble rester principalement localisé dans l'urètre.

6.0 PRÉCAUTIONS

- Gonfler systématiquement le ballonnet avec un liquide stérile (sérum physiologique stérile ou mélange à 50 % de sérum physiologique et de produit de contraste). Ne jamais gonfler le ballonnet avec de l'air, du dioxyde de carbone ou tout autre gaz. Le ballonnet à élution médicamenteuse ne doit pas être gonflé au-delà de la pression de rupture nominale (PRN). Ne pas gonfler excessivement le ballonnet.
- L'utilisation des cathéters à ballonnet est réservée aux médecins formés aux techniques de dilatation par cathéter à ballonnet et ayant une solide expérience en la matière.
- L'utilisation d'un dispositif de gonflage du ballonnet avec manomètre est recommandée afin de garantir le réglage adéquat de la pression du ballonnet.
- Aspirer complètement le ballonnet avant de retirer délicatement le dispositif de l'urètre. L'usage d'une force excessive pour retirer le ballonnet peut provoquer des lésions tissulaires.
- Inspecter soigneusement le ballonnet à élution médicamenteuse et l'emballage avant utilisation. Ne pas utiliser le cathéter s'il est endommagé ou si ses dimensions, sa forme ou son état sont inadaptés à la procédure envisagée.
- Ne pas immerger la partie ballonnet du cathéter dans du liquide et ne pas l'essuyer afin de ne pas endommager ni altérer l'intégrité du revêtement médicamenteux. Remplacer tout cathéter dont le ballonnet est entré en contact avec des liquides avant utilisation.
- Utiliser des gants stériles secs ou des compresses de gaze sèches pour manipuler le cathéter à ballonnet à élution médicamenteuse avant utilisation. Veiller à limiter les contacts avec la partie ballonnet enduite de médicament du dispositif.

- Ne jamais gonfler le ballonnet à élution médicamenteuse en dehors du corps ou avant d'avoir atteint la sténose cible, car ceci risquerait d'altérer l'intégrité du revêtement.
- Ne pas tenter d'introduire le cathéter à ballonnet à élution médicamenteuse dans un cystoscope présentant un calibre French inférieur à celui indiqué sur l'étiquette.
- La longueur utile du ballonnet à élution médicamenteuse doit recouvrir la sténose cible sur toute sa longueur.
- Pour une diffusion adéquate du médicament vers la sténose cible, laisser le revêtement s'hydrater dans l'urètre pendant au moins 60 secondes avant le gonflage et laisser gonfler le ballonnet à élution médicamenteuse pendant au moins 5 minutes. Afin d'optimiser la dilatation de la sténose, l'opérateur peut opter pour une durée de gonflage supérieure à 5 minutes.
- Si le produit affiche un dysfonctionnement avant ou pendant le gonflage, remplacer le ballonnet à élution médicamenteuse et gonfler ce dernier selon la procédure. Si le dysfonctionnement se produit après le gonflage à la pression de rupture nominale, ne pas recommencer la procédure avec le ballonnet.
- Après utilisation, ce produit peut présenter un risque biologique. La manipulation et la mise au rebut du produit doivent s'effectuer conformément aux pratiques médicales validées et aux réglementations locales en vigueur.
- Les professionnels de santé doivent éviter de porter des gants en latex afin de prévenir d'éventuelles réactions allergiques chez les patients allergiques au latex.
- Une préparation de la lumière urétrale de la lésion cible, au moyen de la méthode de préparation de lumière appropriée et déterminée par le médecin traitant, s'impose avant l'utilisation du cathéter à ballonnet à élution médicamenteuse Optilume.
- Une préparation de lumière limitée à une prédilatation avec un cathéter à ballonnet non enduit ou une urétrotomie interne sous contrôle visuel a été étudiée lors de l'étude clinique Robust I.
- Dans les études cliniques, la confirmation visuelle d'une sténose significative (diamètre urétral ≤12F) par cystoscopie ou urétrogramme était nécessaire et le recrutement était limité aux patients présentant des symptômes subjectifs et objectifs de sténose urétrale (International Prostate Symptom Score [IPSS]>13, débit urinaire maximal <15 ml/s). Les sujets avaient déjà subi au moins un traitement endoscopique avant de participer aux études cliniques.
- Les données de sécurité et d'efficacité n'ont pas été établies au cours de l'étude clinique pour soutenir le traitement des sténoses chez les patients présentant les conditions suivantes :
    - HBP
    - Prostatectomie radicale
    - Rayonnement pelvien
    - Traitement à base de botox
    - Plus d'1 sténose
    - Urétroplastie précédente dans l'urètre antérieur
    - Urétrite ou gonorrhée bactérienne
    - Présence d'une prothèse pénienne, d'un sphincter artificiel ou d'un stent urétral/prostatique
    - Vessie neurogène, aberrations sphinctériennes ou dysfonctionnement du détrusor connu(es)
    - Diagnostic de lichen scléreux ou réparation d'hypospadias antérieur
    - Antécédents de cancer de la vessie ou de la prostate au cours des 5 dernières années
    - Sténose provoquée par un kraurosis penis
    - Tumeurs urétrales ou cancer pénien

7.0 UTILISATION CHEZ DES POPULATIONS PARTICULIÈRES

L'innocuité et l'efficacité du cathéter urétral à ballonnet à élution médicamenteuse n'ont pas été établies chez les patients pédiatriques (âgés de moins de 18 ans) ni chez les femmes. L'utilisation du cathéter urétral à ballonnet à élution médicamenteuse chez des patients âgés de 18 ans et plus est laissée à la discrétion du médecin.

8.0 COMPLICATIONS POSSIBLES

Les complications possibles associées à l'utilisation du cathéter à ballonnet à élution médicamenteuse Optilume sont similaires à celles associées aux procédures de dilatation urétrale standard. Les complications possibles peuvent inclure, sans toutefois s'y limiter :

- Douleur et sensibilité
- Spasmes de la vessie provoqués par la mise en place de la sonde de Foley
- Lésions tissulaires des structures avoisinantes, notamment des lésions urétrales
- Hématurie
- Réactions médicamenteuses, réaction allergique au produit de contraste injecté durant l'urétrographie à visée diagnostique
- Infection urinaire
- Perforation tissulaire
- Resténose nécessitant une intervention chirurgicale ultérieure
- Incontinence
- Dysurie
- Fièvre
- Rétention urinaire

9.0 INFORMATIONS CONCERNANT LE MÉDICAMENT

- **MÉCANISME D'ACTION**
  Le revêtement du cathéter urétral à ballonnet à élution médicamenteuse contient du paclitaxel, une substance active antimitotique qui se lie spécifiquement aux microtubules et les stabilise. Il a été démontré que le paclitaxel inhibe la prolifération et la migration des cellules du muscle lisse et des fibroblastes ainsi que la sécrétion de la matrice extracellulaire. L'association de ces effets peut induire l'inhibition de l'hyperplasie de l'urothélium et évite ainsi la resténose.

- **INTERACTIONS MÉDICAMENTEUSES**
  Aucune étude officielle sur les interactions médicamenteuses n'a été menée avec le cathéter urétral à ballonnet à élution médicamenteuse. Les notices respectives de tous les médicaments administrés en concomitance avec le cathéter à ballonnet à élution médicamenteuse doivent être consultées pour connaître les interactions avec le paclitaxel.

  Il convient de prendre en considération le risque d'interactions médicamenteuses systémiques et locales sur l'urètre chez un patient à qui l'on administre un médicament qui présente des interactions connues avec le paclitaxel ou lorsque l'on décide de commencer un traitement médicamenteux chez un patient qui a été traité avec le cathéter à ballonnet à élution médicamenteuse. Le métabolisme du paclitaxel est catalysé par les isoenzymes CYP2C8 et CYP3A4 du cytochrome P450 et

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il s'agit d'un substrat de la glycoprotéine P. Il existe un risque d'interaction médicamenteuse avec tout médicament qui affecte ces isoenzymes. En l'absence d'études officielles sur les interactions médicamenteuses, il convient de faire preuve de prudence lors de l'administration de paclitaxel.

- **CANCÉROGÉNICITÉ, GÉNOTOXICITÉ ET TOXICOLOGIE DE LA REPRODUCTION**

  Aucune étude n'a été menée sur le long terme pour évaluer le potentiel cancérogène du médicament paclitaxel ou du cathéter à ballonnet à élution médicamenteuse Optilume, et aucune étude adéquate et bien contrôlée concernant des femmes enceintes ou des hommes envisageant une paternité prochaine n'a été publiée. Le paclitaxel inhibe la prolifération des cellules en interagissant avec les microtubules. Il en résulte, entre autres, la perte de chromosomes entiers pendant la division cellulaire. Cette action indirecte concorde avec les réponses positives des dosages de génotoxicité in vitro et in vivo, qui détectent les fragments d'ADN. Des résultats positifs ont également été signalés pour les aberrations chromosomiques de lymphocytes humains primaires. Il n'est pas déterminé si le paclitaxel a une action directe isolée sur l'ADN lors de la génération de ruptures de brins ou de fragments d'ADN. Le résultat est négatif lors des dosages de mutation génique, notamment salmonelle et CHO/HPRT.

  Des études réalisées sur des rats et des lapins ayant absorbé du paclitaxel par intraveineuse pendant leur organogénèse ont révélé des signes de toxicité maternelle, d'embryotoxicité et de fœtotoxicité à des dosages de 1 et 3 mg/kg, respectivement (environ 13 et 39 fois la dose administrée par le cathéter à ballonnet à élution médicamenteuse Optilume enduit de 5,5 mg de paclitaxel (ballonnet de 10 mm x 50 mm) et ajustée en fonction du poids corporel). Aucune tératogénicité n'a été observée chez des rates gravides ayant absorbé des doses de paclitaxel par intraveineuse de 1 mg/kg (dose quotidienne correspondant à environ 13 fois la dose du cathéter à ballonnet à élution médicamenteuse Optilume (10 mm x 50 mm), ajustée en fonction du poids corporel).

  Le médecin traitant doit mettre en balance les avantages médicaux potentiels du cathéter à ballonnet à élution médicamenteuse Optilume et ces risques génotoxiques et pour la reproduction. AVERTISSEMENT : le cathéter urétral à ballonnet à élution médicamenteuse contient du paclitaxel, une génotoxine connue. Les hommes doivent avoir des rapports sexuels protégés (port d'un préservatif) pendant les 30 jours suivant le traitement.

10.0 PRÉSENTATION

Réservé à un usage unique, le cathéter à ballonnet à élution médicamenteuse Optilume est fourni STÉRILE (stérilisation à l'oxyde d'éthylène). Le cathéter à ballonnet à élution médicamenteuse est livré dans un emballage à deux poches (poches en aluminium et Tyvek) placé dans une boîte unitaire.

11.0 CONSERVATION

Le cathéter urétral à ballonnet à élution médicamenteuse doit être conservé à température ambiante, dans un endroit sec, dans son emballage d'origine. Le dispositif doit être utilisé avant la date de péremption imprimée sur l'emballage.

12.0 MATÉRIEL RECOMMANDÉ

Préparer le matériel suivant en adoptant une technique stérile :

- Guide de taille appropriée à embout souple (consulter l'étiquette de produit)
- Cystoscope (de préférence souple)
- Sérum physiologique stérile
- Seringue 10 ml
- Robinet deux voies
- Dispositif de gonflage avec manomètre
- Produit de contraste – Remarque : facultatif, à utiliser pour les procédures sous guidage radioscopique

13.0 INSTRUCTIONS D'UTILISATION

13.1 AVANT L'UTILISATION

Traitement périprocédural
Il est recommandé au médecins de respecter les directives applicables aux traitements périprocéduraux et à la préparation d'une intervention sous endoscopie, notamment l'administration d'un antibiotique avant l'intervention, s'il y a lieu. Il est également recommandé d'administrer des AINS avant la procédure.

En présence d'une infection urinaire (IU) au moment du traitement, le patient doit être traité jusqu'à guérison totale de l'infection pour que l'intervention puisse avoir lieu.

13.2 PRÉPARATION DE LA STÉNOSE CIBLE

Il est recommandé de procéder à une prédilatation urétrale de la sténose cible, au moyen de la méthode de préparation appropriée et déterminée par le médecin traitant (ballonnet de dilatation non enduit ou urétrotomie interne sous contrôle visuel) pour les sténoses conséquentes ou difficiles à traverser avant l'utilisation du cathéter à ballonnet à élution médicamenteuse Optilume. Réaliser une prédilatation pour « ouvrir » la sténose. Il s'agit là du diamètre de la lumière de sténose dilatée >20 F ou >50 % plus grande que la lumière de sténose non dilatée.

13.3 DIMENSIONS DU DISPOSITIF

Vérifier que le diamètre du ballonnet à élution médicamenteuse sélectionné, lorsqu'il est à une pression nominale, a une taille identique ou légèrement supérieure au diamètre de l'urètre sain adjacent au bord distal de la sténose. Le diamètre du ballonnet divisé par celui de l'urètre sain adjacent au bord distal se définit comme le rapport d'étirement.

Dimension pour l'urètre bulbaire
Pour les sténoses bulbaires, ne pas dépasser un rapport d'étirement de 1,3 entre le diamètre du ballonnet et celui de l'urètre sain distal. Si la dimension de l'urètre se situe entre deux tailles de dispositif disponibles, utiliser la plus grande taille à condition que le rapport d'étirement soit inférieur ou égal à 1,3. Si la taille supérieure du produit donne un rapport d'étirement supérieur à 1,3, utiliser le dispositif le plus petit.

Dimension pour l'urètre pénien
Pour les sténoses de l'urètre pénien, sélectionner le diamètre de ballonnet qui correspond le mieux à l'urètre sain distal. Le rapport d'étirement de l'urètre pénien ne doit pas dépasser 1:1. Si la dimension de l'urètre se situe entre deux tailles de ballonnet disponibles, sélectionner la plus petite taille de ballonnet. NE PAS DÉPASSER un rapport d'étirement de 1:1.

Tant pour l'urètre pénien que pour l'urètre bulbaire, la longueur du ballonnet à élution médicamenteuse doit être supérieure à la longueur de la sténose à traiter. La longueur du ballonnet doit dépasser d'environ 0,5 à 1 cm des deux côtés de la sténose. À titre

d'exemple, si la sténose mesure 2 cm, choisir un ballonnet à élution médicamenteuse de 3 cm.

13.4 PRÉPARATION DU CATHÉTER À BALLONNET

Évacuer l'air du cathéter à ballonnet à élution médicamenteuse. La lumière du ballonnet du cathéter contient de l'air qui doit être évacué afin de s'assurer que le ballonnet est uniquement rempli de liquide lorsque le cathéter se trouve dans l'urètre.

1. Fixer le robinet en position ouverte sur le raccord de gonflage du ballonnet
2. Raccorder une seringue remplie à moitié de sérum physiologique au robinet
3. Avec l'embout de la seringue vers le bas, tirer le piston jusqu'à atteindre le plein volume de la seringue (ce qui crée une dépression maximale) et maintenir en position jusqu'à ce que plus aucune bulle d'air ne sorte du sérum physiologique dans la seringue. Répéter cette opération si nécessaire pour p ger l'air du cathéter et le remplacer par le sérum physiologique. Maintenir le piston en arrière, tourner le robinet pour maintenir la dépression et retirer la seringue. Remplir à moitié un dispositif de gonflage avec du sérum physiologique normal, ou avec un mélange de produit de contraste et de sérum physiologique à parts égales en cas d'utilisation du guidage radioscopique, et purger l'air de la ligne.
4. Fixer le dispositif de gonflage sur le robinet du cathéter à ballonnet, tourner le robinet et appliquer une dépression sur le dispositif de gonflage.

13.5 INSERTION DU BALLONNET À ÉLUTION MÉDICAMENTEUSE OPTILUME

1. Introduire un guide de 0,038 po avec l'embout souple enroulé dans la vessie sous guidage cystoscopique.
2. Retirer la gaine de protection du ballonnet de l'extrémité du cathéter à ballon net à élution médicamenteuse.

   Mise en garde : *faire preuve de prudence lors du passage d'un ballonnet enduit de paclitaxel dans un cystoscope. Réduire au minimum toute manipulation excessive et ne pas toucher le ballonnet. Ne pas essuyer le ballonnet avec de la gaze sèche, humide ou lubrifiée ou avec n'importe quel solvant susceptible de détériorer l'intégrité du ballonnet à élution médicamenteuse.*

3. Faire progresser le cathéter à ballonnet à élution médicamenteuse à l'intérieur du canal opératoire du cystoscope. Le cas échéant, placer le guide et le cathéter à ballonnet séparément du canal opératoire du cystoscope pour une mise e place côte à côte.
4. Utiliser le cystoscope pour guider le positionnement du cathéter à ballonnet à élution médicamenteuse. Il est également possible de positionner le cathéter à ballonnet à élution médicamenteuse par guidage radioscopique à l'aide des marqueurs radio-opaques situés sous la zone entre le corps et le cône du ballonnet

   Mise en garde : *ne pas faire progresser le guide ou le cathéter de dilatation à ballonnet si une résistance se fait sentir sans avoir tout d'abord déterminé la cause de la résistance et y avoir remédié.*

13.6 GONFLAGE DU BALLONNET À ÉLUTION MÉDICAMENTEUSE OPTILUME

Mise en garde : *les dispositifs de gonflage peuvent atteindre des pressions très élevées sans déployer d'effort particulier. L'utilisation d'un ballonnet de gonflage avec un manomètre haute pression est fortement recommandée pour optimiser la force de dilatation nécessaire à l'ouverture de la sténose urétrale et permettre la pénétration du médicament dans l'urothélium ouvert.*

1. Veiller à rincer l'urètre avec du sérum physiologique.
2. Positionner le cathéter à ballonnet à élution médicamenteuse sur la sténose avec le cystoscope en position distale par rapport au ballonnet (à distance de la vessie) pour visualiser le bon positionnement du ballonnet sur la sténose. Laisser le ballonnet en position dégonflée pendant au moins 1 m nute avant le gonflage. Vérifier que les marqueurs radio-opaques du ballonnet sont correctement positionnés sous guidage radioscopique.
3. Gonfler le ballonnet à la pression de rupture nominale à l'aide du dispositif de gonflage. Ne pas dépasser la pression de rupture nominale (PRN) du ballonnet. Maintenir la pression pendant au moins 5 minutes ou jusqu'à l'obtention de la dilatation souhaitée.
4. Dégonfler le ballonnet en appliquant une dépression sur le ballonnet à l'aide du dispositif de gonflage. Une fois le ballonnet complètement dégonflé, retirer lentement le guide et le cathéter à ballonnet à élution médicamenteuse. Si une légère résistance se fait sentir lorsque le ballonnet est retiré, tourner délicatement le cathéter pour mieux enrouler le ballonnet autour du corps du cathéter et faciliter le retrait.

   Mise en garde : *si une résistance se fait sentir durant le retrait du guide à travers le cathéter et à travers le cystoscope, ARRÊTER et retirer simultanément les deux d'un seul tenant pour éviter d'endommager le guide, le cathéter ou de* provoquer des lésions anatomiques sur le patient.

5. Si le produit affiche un dysfonctionnement avant ou pendant le gonflage, remplacer le ballonnet à élution médicamenteuse et gonfler ce dernier selon la procédure. Si le dysfonctionnement se produit après le gonflage à la pression de rupture nominale, ne pas recommencer la procédure avec le ballonnet.
6. Insérer une sonde de Foley lubrifiée 12-14 Fr et la laisser en place pendant au moins 2 jours ou selon ce que la norme de prudence recommande, le délai le plus long prévalant.

13.7 TABLEAU DE CONFORMITÉ

18Fr (6mm) x 30mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**PRN**	6,45

18Fr (6mm) x 50mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**PRN**	6,25

24Fr (8mm) x 30mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**PRN**	8,46

24Fr (8mm) x 50mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**PRN**	8,54

30Fr (10mm) x 30mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**PRN**	10,29

30Fr (10mm) x 50mm

(ATM) Pression	kPa		(mm) Ballonnet
6,0	600	**Nominale**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**PRN**	10,44

Mise en garde : *la pression de rupture nominale ne doit pas être dépassée. Consulter l'étiquette du produit pour connaître les pressions de rupture nominales. Tout gonflage au-delà de la pression de rupture nominale peut provoquer la rupture du ballonnet. Si une chute de pression se produit à l'intérieur du ballonnet pendant le gonflage ou que le ballonnet se rompt pendant la dilatation, arrêter immédiatement la procédure. Dégonfler soigneusement le ballonnet et le retirer de l'urètre. Ne pas regonfler.*

14.0 GARANTIE

Urotronic garantit que la conception et la fabrication de ce produit ont fait l'objet d'une diligence raisonnable. Cette garantie remplace et exclut toute autre garantie non expressément énoncée aux présentes, expresse ou implicite en vertu de la loi ou non, y compris, sans toutefois s'y limiter, toute garantie implicite d'adéquation à un usage particulier. La manipulation, la conservation, le nettoyage et la stérilisation de ce dispositif ainsi que d'autres facteurs ayant trait au patient, comme le diagnostic, le traitement, les interventions chirurgicales et autres éléments indépendants du contrôle d'Urotronic, se répercutent directement sur le dispositif et sur les résultats découlant de son utilisation. Les obligations d'Urotronic aux termes de cette garantie se limitent à la réparation ou au remplacement de ce dispositif et Urotronic décline toute responsabilité en cas de perte, de dommages ou de frais accessoires ou indirects découlant, directement ou indirectement, de l'utilisation de ce dispositif. Urotronic décline toute responsabilité en cas de réutilisation, retraitement ou restérilisation des dispositifs et n'offre aucune garantie, expresse ou implicite, y compris, sans toutefois s'y limiter, d'adéquation à un usage particulier, en rapport avec lesdits dispositifs.

15.0 SYMBOLES UTILISÉS SUR LES ÉTIQUETTES DU DISPOSITIF

	Un dispositif par boîte
	Mise en garde : la loi fédérale limite la vente de ce dispositif par un médecin ou sur ordonnance médicale.
	Indique la date à laquelle le dispositif médical a été fabriqué.
	Ne pas restériliser
	Ne pas réutiliser
	Ne pas utiliser si l'emballage est endommagé
	Fragile
	À utiliser avant le
	Tenir à l'abri de la lumière du soleil
	Conserver au sec
	Fabricant
	Ne contient pas de latex
	Limite de température entre 15 °C et 30 °C
	Mise en garde : consulter le mode d'emploi
	Stérilisé à l'oxyde d'éthylène
	Référence catalogue
	Numéro de lot
	Marqué CE selon la directive 93/42/CEE relative aux dispositifs médicaux de l'Union européenne (organisme notifié n°1434)
	Représentant autorisé de l'Union européenne


Urotronic, Inc.
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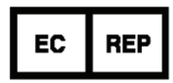
Minneapolis, MN 55441
USA

CE 1434



MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany

OPTILUME®

MEDIKAMENTENBESCHICHTETER HARNRÖHREN-BALLONKATHETER

Gebrauchsanweisung

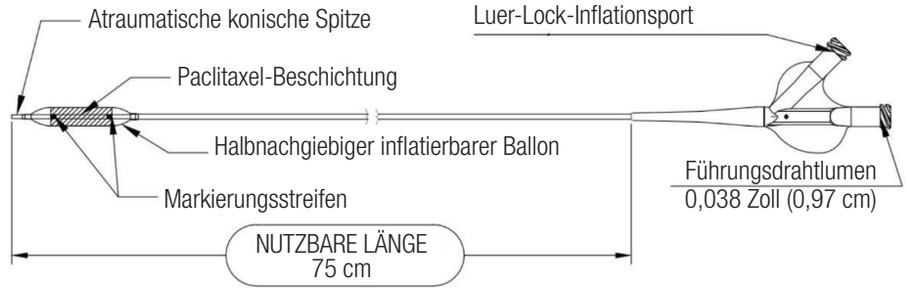
DEUTSCHE

Inhaltsverzeichnis

1.0 PRODUKTBESCHREIBUNG

1.1 Ballonkatheter

Der Optilume medikamentenbeschichtete Harnröhren-Ballonkatheter (Drug Coated Balloon, DCB) besteht aus einem 0,038-Zoll-Führungsdraht (0,97 mm) und einem flexiblen, mit einem Zystoskop kompatiblen Over-the-Wire-Katheter (OTW) mit einem doppellumigen Design und einer konischen atraumatischen Spitze. Der DCB wird zur Ausübung radialer Kraft zur Dilatation enger Harnröhrenbereiche (Strikturen) verwendet. Das distale Ende des Katheters verfügt über einen inflatierbaren halbnachgiebigen Ballon, der mit einer firmeneigenen Beschichtung versehen ist, die den aktiven Wirkstoff Paclitaxel enthält. Die Medikamentenschicht bedeckt die gesamte Arbeitslänge des Ballonkörpers. Das Produkt verfügt über zwei röntgendichte Markierungsstreifen, die die Arbeitslänge des Ballons markieren.



Das Produkt wird mit Ethylenoxid in einem Tyvek-Beutel sterilisiert. Nach der Sterilisation wird der Katheter noch im Beutel in einem Folienbeutel mit einem Trocknungsmittel versiegelt und als Einzeleinheit in einen Karton verpackt. Jeder DCB wird mit einer Schutzhülle geliefert, die den Bereich des medikamentenbeschichteten Ballons des Katheters bedeckt. Eine Übersicht zur Ballon-Compliance befindet sich auf dem Etikett des Tyvek-Beutels.

DEUTSCHE

1.2 Medikamentenbeschichtung

Die Medikamentenbeschichtung besteht aus dem aktiven Arzneimittelwirkstoff Paclitaxel. Die Medikamentenschicht bedeckt die gesamte Arbeitslänge der Ballonkomponente des Katheters. Die Medikamentenschicht ist gleichmäßig mit einer Konzentration von 3,5 µg/mm^2 über die Ballonoberfläche hinweg verteilt. Das wesentliche Funktionsmerkmal der Medikamentenbeschichtung ist die Abgabe von Paclitaxel an das Urothel während der Balloninflation.

DCB-Dosiertabelle

Bestellnummer	Durchmesser (Fr/mm)	Länge (mm)	Paclitaxel-Dosis (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

2.0 VERWENDUNGSZWECK
Der Optilume medikamentenbeschichtete Harnröhren-Ballonkatheter (DCB) dient zur Behandlung von Strikturen in der anterioren Harnröhre bei erwachsenen Männern.

3.0 INDIKATIONEN
Der Optilume Harnröhren-DCB-Katheter wird zur Behandlung von Männern ≥18 Jahren mit störenden Harnwegssymptomen mit Rezidivstrikturen der anterioren Harnröhre verwendet. Er dient zur Verwendung als Dilatationsballon für Einzel-, Tandem- oder diffuse Harnröhrenstrikturen mit einer Länge von ≤3 cm oder als Ergänzungstherapie mit anderen Dilatationsprodukten und/oder -verfahren.

4.0 KONTRAINDIKATIONEN
Der medikamentenbeschichtete Harnröhren-Ballondilatationskatheter (Drug Coated Balloon, DCB) ist in folgenden Fällen kontraindiziert:
- Patienten mit bekannter Überempfindlichkeit gegenüber Paclitaxel oder strukturell verwandten Verbindungen.
- Patienten mit Läsionen, die nicht mit einem 0,038-Zoll-Führungsdraht (0,97 mm) durchdrungen werden können.

5.0 WARNHINWEISE
- Der Harnröhren-DCB wird STERIL zur Einmalverwendung geliefert. Nicht wiederaufbereiten oder erneut sterilisieren. Das Wiederaufbereiten oder erneute Sterilisieren kann das Risiko einer Patienteninfektion und das Risiko einer beeinträchtigten Produktleistung erhöhen.
- Der Folienbeutel und die Außenfläche des Innenbeutels sind UNSTERIL. Der INHALT des Innenbeutels ist STERIL. Nach dem Öffnen des Folienbeutels sofort verwenden.
- Liegt eine Harnwegs- oder Blaseninfektion vor, dieses Produkt nicht verwenden. Vor der Behandlung der Striktur mit dem Optilume DCB müssen Infektionen ab geklärt werden.
- Der DCB darf nur von Ärzten verwendet werden, die hinsichtlich der klinischen und technischen Aspekte der Ballondilatation der Harnröhre über Erfahrung und Kenntnis verfügen.
- Vor der Verwendung des DCB müssen Ärzte die Gebrauchsanweisung gelesen und verstanden haben. Werden die Indikationen, Kontraindikationen, Einschrän kungen, Warnungen und Vorsichtsmaßnahmen nicht beachtet, so kann dies zu Komplikationen führen.
- Nicht nach dem Verfallsdatum verwenden.
- Der DCB enthält Paclitaxel, einen bekanntermaßen genotoxischen Wirkstoff. Männer sollten innerhalb von 30 Tagen nach der Behandlung nur geschützten Geschlechtsverkehr (mit Kondom) haben.
- Auf Anzeichen von Anaphylaxie oder Überempfindlichkeit gegenüber Paclitaxel achten.
- Den DCB keinesfalls mit Luft oder Gas inflatieren.
- Während der Verwendung darf der DCB nur unter direkter Visualisierung mittels Zystoskopie oder hochqualitativer röntgenologischer Bildgebung bedient werden.
- Den DCB nicht im inflatierten Zustand bedienen.
- Ist beim Einführen zu irgendeinem Zeitpunkt Widerstand spürbar, darf keine übermäßige Kraft angewendet werden. Der Widerstand kann zur Beschädigung des Produkts oder des Lumens führen. Den Katheter vorsichtig herausziehen.
- Männer, deren Sexualpartnerinnen empfängnisbereit sind, sollten für mindestens 90 Tage nach der Behandlung Kondome benutzen..
- Unerwünschte Reaktionen auf Paclitaxel sowie Symptome, die vorwiegend aus IV-Infusionsstudien für das Medikament zur Behandlung von Probanden mit Krebs gewonnen wurden, sind u. a.
    - Chromosomale Anomalien und Krebsrisiko
    - Fruchtschäden bei Kontakt mit schwangeren Frauen
    - Anaphylaxie und Überempfindlichkeit gegen Paclitaxel
    - Heilungsverzögerung der Harnröhre nach dem Eingriff
    - Myelosuppression u. a. mit Neutropenie, Leukopenie, Thrombozytopenie, Anämie
    - Arrhythmie
    - Periphere Neuropathie
    - Myalgie oder Arthralgie
    - Alopezie
    - Hypotonie
    - Übelkeit, Erbrechen oder Durchfall
    - Erhöhtes Bilirubin, ALP und AST
    - Eine potenzielle Wirkung auf Leber und Nieren ist unbekannt und wurde nicht untersucht.

Die Menge an während des Verfahrens mit dem Optilume DCB lokal verabreichtem Paclitaxel ist weit niedriger als eine Einzeldosis systemischer Chemotherapie für Krebspatienten. Zudem scheint das Medikament örtlich begrenzt in der Harnröhre zu verbleiben.

6.0 VORSICHTSMASSNAHMEN
- Stets mit steriler Flüssigkeit (sterile Kochsalzlösung oder 50%ige Kontrastmittel-Mischung) inflatieren. Keinesfalls mit Luft, Kohlenstoffdioxid oder einem anderem Gas inflatieren. Der DCB darf nicht über den Nennberstdruck hinweg inflatiert werden Den Ballon nicht übermäßig inflatieren.
- Ballonkatheter sind für die Verwendung von Ärzten bestimmt, die hinsichtlich der Techniken zur Ballonkatheterdilatation geschult wurden und entsprechende Erfahrung haben.
- Um eine korrekte Regelung des Ballondrucks zu gewährleisten, wird eine Balloninflationsvorrichtung mit Druckanzeige empfohlen.
- Die Flüssigkeit vollständig aus dem Ballon ablassen, bevor das Produkt vorsichtig aus der Harnröhre entfernt wird. Wird übermäßige Kraft beim Herausziehen des Ballons verwendet, kann dies zur Verletzung von Gewebe führen.
- Vor der Verwendung den DCB und die Verpackung sorgfältig überprüfen. Den Katheter nicht verwenden, wenn er beschädigt ist oder wenn Größe, Form oder Zustand nicht für den gewünschten Eingriff geeignet sind.
- Den Ballonteil des DCB nicht in Flüssigkeit tauchen oder abwischen, da dadurch die Unversehrtheit der Medikamentenbeschichtung beschädigt oder beeinträchtigt werden kann. Kommt der Ballon vor der Verwendung mit Flüssigkeit in Kontakt, den DCB austauschen.

- Zur Handhabung des DCB vor der Verwendung trockene, sterile Handschuhe und trockene Tupfer verwenden. Der Kontakt mit dem beschichteten Ballonteil des Produkts sollte nach Möglichkeit minimiert werden.
- Den DCB keinesfalls außerhalb des Körpers oder vor dem Erreichen der Zielstriktur inflatieren, da andernfalls die Unversehrtheit der Beschichtung beeinträchtigt werden kann.
- Nicht versuchen, den DCB durch ein Zystoskop einer geringeren French-Größe zu schieben, als auf dem Etikett angegeben ist.
- Die Arbeitslänge des DCB muss der Gesamtlänge der Zielstriktur entsprechen.
- Um eine ausreichende Medikamentenabgabe an die Zielstriktur zu gewährleisten, muss die Beschichtung in der Harnröhre mindestens 60 Sekunden befeuchtet werden, bevor der DCB für mindestens 5 Minuten inflatiert wird. Um die Dilatation der Striktur zur optimieren, können nach Ermessen des Anwenders Inflationszeiten >5 Minuten zum Einsatz kommen.
- Tritt vor oder nach dem Inflatieren ein Produktversagen auf, den DCB ersetzen und gemäß Anweisung inflatieren. Tritt das Versagen nach dem Inflatieren bis zum Nennberstdruck auf, das DCB-Verfahren nicht wiederholen.
- Nach der Verwendung kann das Produkt biogefährlich sein. In Übereinstimmung mit der anerkannten medizinischen Praxis und den anwendbaren Richtlinien vor Ort handhaben und entsorgen.
- Medizinische Fachkräfte sollten keine Latexhandschuhe verwenden, um möglichen allergischen Reaktionen von Patienten mit Latexallergie vorzubeugen.
- Vor dem Gebrauch des Optilume DCB muss das Harnröhrenlumen der Zielläsion vorbereitet werden. Hierbei ist das entsprechende Verfahren des behandelnden Arztes zur Lumenvorbereitung anzuwenden.
- In der medizinischen Studie Robust I wurde die Lumenvorbereitung mit einem unbeschichteten Ballonkatheter oder direkter visueller interner Urethrotomie untersucht.
- In klinischen Studien war eine visuelle Bestätigung einer signifikanten Striktur (≤12 F Harnröhrendurchmesser) mittels Zystoskopie oder Urethrogramm erforderlich und die Aufnahme war auf Patienten beschränkt, die subjektive und objektive Symptome einer Harnröhrenstriktur aufwiesen (International Prostate Symptom Score [IPSS] >13, Spitzenharnflussrate <15 ml/sec). Die Patienten hatten sich vor der Aufnahme in die klinischen Studien mindestens einer vorherigen endoskopischen Behandlung unterzogen.
- Über die Sicherheit und Wirksamkeit bei der Behandlung von Strikturen bei Patienten mit folgenden Zuständen wurden in der klinischen Studie keine Daten erhoben:
    - Prostatahypertrophie (BPH)
    - Radikale Prostatektomie
    - Strahlentherapie des Beckens
    - Botox-Behandlung
    - Mehr als 1 Striktur
    - Vorherige Urethroplastie innerhalb der anterioren Harnröhre
    - Bakterielle Urethritis oder Gonorrhoe
    - Penisimplantat, künstlicher Ringmuskel oder Harnröhren-/Prostata-Stent
    - Neurogene Blase, Anomalien des Ringmuskels oder mangelhafte Funktion des Entleerungsmuskels.
    - Diagnose einer Lichen-Sklerose oder vorherige Hypospadie-Rekonstruktion
    - Innerhalb der letzten 5 Jahre Karzinom der Blase oder Prostata
    - Striktur aufgrund von Balanitis xerotica obliterans (BXO)
    - Tumoren der Harnröhre oder Peniskrebs

7.0 VERWENDUNG BEI SPEZIELLEN POPULATIONEN

Die Sicherheit und Wirksamkeit des Harnröhren-DCB wurde für pädiatrische Patienten (<18 Jahre) oder Frauen nicht nachgewiesen. Die Anwendung des Harnröhre-DCB bei Patienten ≥18 Jahre erfolgt im Ermessen des Arztes.

8.0 MÖGLICHE KOMPLIKATIONEN

Mögliche Komplikationen in Zusammenhang mit der Verwendung des Optilume DCB-Katheters ähneln denen in Zusammenhang mit standardmäßigen Dilatationsverfahren der Harnröhre. Mögliche Komplikationen können unter anderem Folgendes beinhalten:

- Schmerzen und Druckempfindlichkeit
- Blasenkrämpfe durch Legung eines Foley-Katheters
- Gewebetrauma in umgebenden Strukturen inkl. Schäden an der Harnröhre
- Hämaturie
- Medikamentenreaktionen, allergische Reaktion auf das während des diagnostischen Urethrogramms verwendete Kontrastmittel
- Harnwegsinfektion
- Gewebeperforation
- Rezidivstriktur, wodurch ein weiterer Eingriff erforderlich ist
- Inkontinenz
- Dysurie
- Fieber
- Harnverhalt

DEUTSCHE

9.0 INFORMATIONEN ZUM WIRKSTOFF

- **WIRKMECHANISMUS**
  Die Beschichtung des Harnröhren-DCB enthält Paclitaxel, einen antimitotischen Arzneimittelwirkstoff, der spezifisch an Mikrotubuli bindet und diese stabilisiert. Berichten zufolge hemmt Paclitaxel die Proliferation und Migration von Fibroblasten und glatten Muskelzellen sowie die Sekretion extrazellulärer Matrix. Die Kombination dieser Wirkweisen kann zur Hemmung einer Hyperplasie des Urothels und damit zur Hemmung einer Rezidivstriktur führen.

- **WECHSELWIRKUNGEN MIT ANDEREN MEDIKAMENTEN**
  Für den Harnröhren-DCB wurden bislang keine formellen Wechselwirkungsstudien durchgeführt. Hinsichtlich Wechselwirkungen mit Paclitaxel sollten die entsprechenden Gebrauchsanweisungen für alle in Verbindung mit dem DCB verwendeten Medikamente zurate gezogen werden.

  Dabei müssen auch mögliche systemische oder lokale Wechselwirkungen mit Medikamenten in der Harnröhre von Patienten beachtet werden, die ein Medikament mit bekannten Wechselwirkungen mit Paclitaxel einnehmen,

oder wenn entschieden wird, eine Medikamententherapie bei einem Patienten einzuleiten, der mit dem DCB behandelt wurde. Die Verstoffwechselung von Paclitaxel wird von den Isoenzymen CYP2C8 und CYP3A4 der Cytochrom-P450-Familie katalysiert. Es ist ein Substrat des P-Glykoproteins. Mögliche Medikamentenwechselwirkungen können mit jedem Medikament auftreten, das einen Einfluss auf diese Isoenzyme hat. Da keine formalen Studien zu Medikamentenwechselwirkungen vorliegen, sollte bei der Anwendung von Paclitaxel umsichtig vorgegangen werden.

- **KARZINOGENITÄT, GENOTOXIZITÄT UND REPRODUKTIONSTOXIKOLOGIE**
  Es gibt keine langfristigen Studien über das krebserzeugende Potenzial des Medikaments Paclitaxel oder des Optilume DCB, und es wurden keine angemessenen und kontrollierten Studien an schwangeren Frauen oder Männern mit Zeugungswunsch veröffentlicht. Paclitaxel hemmt die Zellproliferation durch Wechselwirkung mit Mikrotubuli. Eine Folge davon ist der Verlust ganzer Chromosomen bei der Zellteilung. Diese indirekte Wirkweise entspricht dem positiven Ansprechen auf Gentoxizitäts-Tests des Mikronukleus in vitro und in vivo zum Erkennen von DNA-Fragmenten. Auch bei Chromosomenaberrationen in primären menschlichen Lymphozyten wurden positive Ergebnisse gemeldet. Es ist nicht bekannt, ob Paclitaxel eine separate Direktwirkung auf die DNA bei der Entstehung von DNA-Strangbrüchen oder -fragmenten hat. Es testet negativ auf Genmutationen, u. a. Salmonellen und CHO/HPRT.

  Studien an Ratten und Kaninchen, denen während der Organbildung Paclitaxel intravenös verabreicht wurde, ergaben Hinweise auf maternale Toxizität, Embryotoxizität und Fetotoxizität bei Dosierungen von 1 bzw. 3 mg/kg (ca. das 13- bzw. 39-Fache der durch den Optilume DCB mit 5,5 mg Paclitaxel-Beschichtung verabreichten Dosis (10 x 50 mm Ballon) an Körpergewicht angepasst). Bei trächtigen Ratten, die täglich intravenös Paclitaxel-Dosierungen von 1 mg/kg erhielten (eine Tagesdosis von dem rund 13-Fachen der Dosis des Optilume DCB (10 x 50 mm) an Körpergewicht angepasst), wurde keine Teratogenizität beobachtet.

  Der behandelnde Arzt muss die möglichen medizinischen Vorteile des Optilume DCB-Katheters gegen diese genotoxischen und Fortpflanzungsrisiken abwägen. WARNHINWEIS: Der Harnröhren-DCB enthält Paclitaxel, einen bekanntermaßen genotoxischen Wirkstoff. Männer sollten innerhalb von 30 Tagen nach der Behandlung nur geschützten Geschlechtsverkehr (mit Kondom) haben.

10.0 LIEFERUMFANG

Der Optilume DCB-Katheter wird STERIL und nur zur Einmalverwendung geliefert (Sterilisation mit Ethylenoxid). Der DCB befindet sich in einer Doppelbeutel-Verpackung (Folien- und Tyvek-Beutel), die in einer Einzelbox verpackt ist.

11.0 LAGERUNG

Der Harnröhren-DCB muss bei Raumtemperatur an einem trockenen Ort in der Originalverpackung aufbewahrt werden. Das Produkt muss vor dem auf der Packung aufgebrachten Verfallsdatum verwendet werden.

12.0 EMPFOHLENE HILFSMITTEL

Die folgenden Hilfsmittel mit steriler Technik vorbereiten:

- Führungsdraht geeigneter Größe mit flexibler Spitze (siehe Produktetikettierung)
- Zystoskop (vorzugsweise flexibel)
- Sterile Kochsalzlösung
- 10-ml-Spritze
- Zweiwege-Absperrhahn
- Inflationsvorrichtung mit Manometer
- Kontrastmittel – Hinweis: Optional zur Verwendung mit röntgenologisch geführten Verfahren

13.0 GEBRAUCHSANLEITUNG

13.1 VOR DEM GEBRAUCH

Verfahrenstechnische Medikamente
Ärzten wird die Beachtung der Richtlinien für Arzneimittel vor dem Eingriff und für endoskopische Verfahren empfohlen. Dazu gehört bei Bedarf auch die Gabe eines Antibiotikums vor dem Eingriff. Auch die Gabe von NSAID vor dem Eingriff wird empfohlen.

Liegt zum Zeitpunkt der Behandlung eine Harnwegsinfektion vor, muss der Patient behandelt werden, bis die Infektion auskuriert ist, bevor das Verfahren durchgeführt werden kann.

13.2 VORBEREITUNG DER ZIELSTRIKTUR

Bei stark stenotischen und schwierig zu durchdringenden Strikturen wird dringend empfohlen, vor dem Gebrauch des Optilume DCB die Zielstriktur in der Harnröhre vorzudilatieren (entsprechend dem vom behandelnden Arzt bestimmten Vorbereitungsverfahren, z. B. unbeschichteter Dilatationsballon oder DVIU). Eine Vordilatation durchführen, um die Striktur aufzudehnen. Dies ist definiert als ein Lumendurchmesser der dilatierten Striktur, der um >20 F oder >50 % größer als das nicht dilatierte Lumen der Striktur ist.

13.3 AUSWAHL DER PRODUKTGRÖSSE
Überprüfen, ob der ausgewählte Durchmesser des DCB-Ballons bei Nenndruck gleich groß wie oder etwas größer als der Durchmesser der an das distale Ende der Striktur angrenzenden gesunden Harnröhre ist. Der Ballondurchmesser geteilt durch die distal angrenzende gesunde Harnröhre ist als Dehnungsverhältnis definiert.

Auswahl der Größe der bulbären Harnröhre
Für bulbäre Strikturen darf das Dehnungsverhältnis von Ballondurchmesser zu distaler gesunder Harnröhre 1,3 nicht überschreiten. Wenn die Größe der Harnröhre zwischen den Größen verfügbarer Produkte liegt, die nächstgrößere Größe verwenden, vorausgesetzt, dass das Dehnungsverhältnis kleiner als oder gleich 1,3 ist. Wenn die nächstgrößere Größe ein Dehnungsverhältnis von mehr als 1,3 ergibt, das nächstkleinere Produkt verwenden.

Auswahl der Größe der penilen Harnröhre
Für penile Harnröhrenstrikturen den Ballondurchmesser wählen, der für die distale gesunde Harnröhre am besten geeignet ist. Das Dehnungsverhältnis der penilen Harnröhre darf 1:1 nicht überschreiten. Wenn die Größe der Harnröhre zwischen den

Größen verfügbarer Ballons liegt, die nächstkleinere Ballongröße wählen. Das Dehnungsverhältnis von 1:1 NICHT ÜBERSCHREITEN.

Sowohl für die penile als auch die bulbäre Harnröhre sollte der DCB-Ballon länger als die zu behandelnde Striktur sein. Die Ballonlänge muss an beiden Seiten um ca. 0,5–1 cm über die Striktur hinausragen. Wenn die Strikturlänge beispielsweise 2 cm beträgt, einen 3 cm langen DCB-Ballon wählen.

13.4 VORBEREITUNG DES BALLONKATHETERS

Luft aus dem DCB-Katheter entfernen. Das Ballonlumen des Katheters enthält Luft, die entfernt werden muss, damit der Ballon ausschließlich mit Flüssigkeit gefüllt wird, während sich der Katheter in der Harnröhre befindet.

1. Absperrhahn in offener Position mit dem Balloninflatationsanschluss verbinden.
2. Eine zur Hälfte mit Kochsalzlösung gefüllte Spritze an den Absperrhahn anschließen.
3. Spritze nach unten halten und den Kolben vollständig zurückziehen (für maximalen Unterdruck) und halten, bis keine Luftblasen mehr aus der Kochsalzlösung in der Spritze austreten. Nach Bedarf wiederholen, um die Luft aus dem Katheter zu entfernen und durch Kochsalzlösung zu ersetzen. Kolben zurückgezogen halten, Absperrhahn zum Beibehalten des Unterdrucks drehen und Spritze abziehen. Eine Inflationsvorrichtung zur Hälfte mit normaler Kochsalzlösung oder bei Verwendung von Fluoroskopie im Verhältnis 1:1 mit Kontrastmittel und Kochsalzlösung füllen und Luft aus der Leitung entfernen.
4. Die Inflationsvorrichtung mit dem Absperrhahn am Ballonkatheter verbinden, Absperrhahn drehen und Unterdruck auf die Inflationsvorrichtung ausüben.

13.5 EINFÜHREN DES OPTILUME DCB

1. Einen 0,038”-Führungsdraht mit flexibler Spitze aufgerollt in der Blase zysto skopisch positionieren.
2. Ballonschutz von der Spitze des DCB-Katheters entfernen.

   Vorsicht: *Bei der Passage eines mit Paclitaxel beschichteten Ballons durch ein Zystoskopsystem muss vorsichtig vorgegangen werden. Übermäßige Bewegung minimieren und den Ballon nicht berühren. Den Ballon nicht mit trockener, feuchter oder mit Gleitmittel versehener Gaze oder mit einem Lösungsmittel abwischen, das die Unversehrtheit des medikamentenbeschichteten Ballons beeinträchtigen könnte.*
3. DCB-Katheter im Arbeitskanal des Zystoskops vorschieben. Alternativ können der Führungsdraht und der Ballonkatheter nicht im Arbeitskanal des Zystos kops, sondern neben dem Zystoskop positioniert werden.
4. Die Positionierung des DCB mittels Zystoskop unterstützen. Andernfalls den DCB mittels Fluoroskopie anhand der röntgendichten Markierungen unter dem Übergang von Ballonteil/Konus positionieren.

   Vorsicht: *Den Führungsdraht oder den Ballondilatationskatheter bei Widerstand nicht vorschieben, bevor die Ursache des Widerstands bestimmt und beseitigt wurde.*

13.6 INFLATIEREN DES OPTILUME DCB

Vorsicht: *Inflationsvorrichtungen können bei minimalem Aufwand sehr hohe Drücke erzielen. Zur Optimierung der Inflationskraft wird dringend die Verwendung einer Inflationsvorrichtung mit einem Hochdruckmesser empfohlen, um die Harnröhrenstriktur aufzudehnen und das Eindringen des Medikaments in das aufgedehnte Urothel zu ermöglichen.*

1. Darauf achten, dass die Harnröhre mit Kochsalzlösung gespült wurde.
2. Den DCB mit dem Zystoskop distal zum Ballon (von der Blase abgewandt) über der Striktur positionieren, um die richtige Position des Ballons über der Striktur sichtbar zu machen. Den Ballon vor dem Inflatieren mindestens 1 Minute leer lassen. Mittels Fluoroskopie überprüfen, ob die Position der röntgendichten Ballonmarkierungen korrekt ist.
3. Den Ballon mit der Inflationsvorrichtung auf Nennberstdruck inflatieren. Den Nennberstdruck des Ballons nicht überschreiten. Den Druck mindestens 5 Minuten lang oder bis zur gewünschten Dilatation beibehalten.
4. Den Ballon entleeren, indem er mit der Inflationsvorrichtung leer gesaugt wird. Ist der Ballon vollständig entleert, den Führungsdraht und den DCB langsam herausziehen. Ist beim Zurückziehen des Ballons ein leichter Widerstand spürbar, den Katheter vorsichtig drehen, damit sich der Ballon um den Katheterschaft falten kann und das Herausziehen erleichtert wird.

   Vorsicht: *Ist beim Herausziehen eines Führungsdrahts durch den Katheter durch ein Zystoskop ein Widerstand spürbar, SOFORT ANHALTEN und die Instrumente gleichzeitig als Einheit herausziehen, um eine Beschädigung von Führungsdraht, Katheter oder Anatomie des Patienten zu vermeiden.*
5. Tritt vor oder während dem Inflatieren (aber unterhalb des Nennberstdrucks) ein Produktversagen auf, den DCB ersetzen und gemäß Anweisung inflatieren. Tritt das Versagen nach dem Inflatieren bis zum Nennberstdruck auf, das DCB-Verfahren nicht wiederholen.
6. Einen befeuchteten Foley-Katheter (12–14 Fr) einführen und mindestens 2 Tage oder gemäß Standardversorgung liegen lassen (längerer Zeitraum gilt).

13.7 COMPLIANCE-TABELLE

18Fr (6mm) x 30 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**Nennberstdruck**	6,45

18Fr (6mm) x 50 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**Nennberstdruck**	6,25

24Fr (8mm) x 30 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**Nennberstdruck**	8,46

24Fr (8mm) x 50 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**Nennberstdruck**	8,54

30Fr (10mm) x 30 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**Nennberstdruck**	10,29

30Fr (10mm) x 50 mm

(atmosphärischer) Druck	kPa		Ballon (mm)
6,0	600	**Nenndruck**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**Nennberstdruck**	10,44

Vorsicht: Der Nennberstdruck darf nicht überschritten werden. Die Nennberstdrücke sind dem Produktetikett zu entnehmen. Ein Inflatieren über den Nennberstdruck hinaus kann zum Reißen des Ballons führen. Sinkt der Druck im Ballon während des Inflatierens ab oder reißt der Ballon während der Dilatation, das Verfahren umgehend abbrechen. Die Luft vorsichtig aus dem Ballon ablassen und ihn aus der Harnröhre entfernen. Nicht erneut inflatieren.

14.0 GEWÄHRLEISTUNG

Urotronic gewährleistet, dass bei der Entwicklung und Herstellung dieses Produkts angemessene Sorgfalt angewendet wurde. Diese Gewährleistung ersetzt sämtliche anderen, hierin nicht ausdrücklich aufgeführten Gewährleistungen, ob ausdrücklich oder stillschweigend durch ein Rechtssystem oder anderweitig bestehend, einschließlich, jedoch nicht beschränkt auf, etwaige stillschweigenden Gewährleistungen über die Eignung zu einem bestimmten Zweck. Handhabung, Aufbewahrung, Reinigung und Sterilisation dieses Produkts sowie weitere Faktoren hinsichtlich Patient, Diagnose, Behandlung, chirurgischer Verfahren und anderer Sachverhalte außerhalb der Kontrolle von Urotronic können das Produkt und damit erzielten Ergebnisse unmittelbar beeinträchtigen. Die Verpflichtung von Urotronic im Rahmen dieser Gewährleistung beschränkt sich auf die Reparatur oder den Ersatz des Produkts und Urotronic ist nicht haftbar für jegliche zufälligen oder zwangsläufigen Verluste, Schäden oder Aufwendungen, die direkt oder indirekt aus der Verwendung dieses Produkts entstehen. Urotronic übernimmt keine Haftung für wiederverwendete, wiederaufbereitete oder erneut sterilisierte Produkte und übernimmt keine ausdrücklichen oder stillschweigenden Haftungen, einschließlich, jedoch nicht beschränkt auf, Gewährleistungen über die Eignung zu einem bestimmten Zweck hinsichtlich solcher Produkte.

15.0 SYMBOLE AUF DEN PRODUKTETIKETTEN

1	Anzahl: 1 pro Box
Rx only	Vorsicht: Laut US-Bundesgesetz darf dieses Produkt nur an Ärzte oder auf deren Anordnung verkauft werden.
	Verweist auf das Datum, an dem das Medizinprodukt hergestellt wurde.
2	Nicht erneut sterilisieren
	Nicht wiederverwenden
	Bei beschädigter Verpackung nicht verwenden
	Zerbrechlich
	Verfallsdatum
	Vor direkter Sonneneinstrahlung schützen
	Vor Nässe schützen
	Hersteller
LATEX	Latexfrei
	Temperaturgrenzwert: 15 °C – 30 °C
	Vorsicht: Gebrauchsanweisung beachten
STERILE EO	Mit Ethylenoxid sterilisiert
REF	Bestellnummer
LOT	Losnummer
CE 1434	CE-Kennzeichnung gemäß der Medizinprodukterichtlinie 93/42/EWG der Europäischen Union (Benannte Stelle Nr. 1434)
EC REP	Bevollmächtigter Vertreter in der Europäischen Union

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Minneapolis, MN 55441
USA

EC REP
MDSS GmbH
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CE 1434

OPTILUME®

CATÉTER URETRAL CON BALÓN RECUBIERTO DE FÁRMACO

Instrucciones de uso

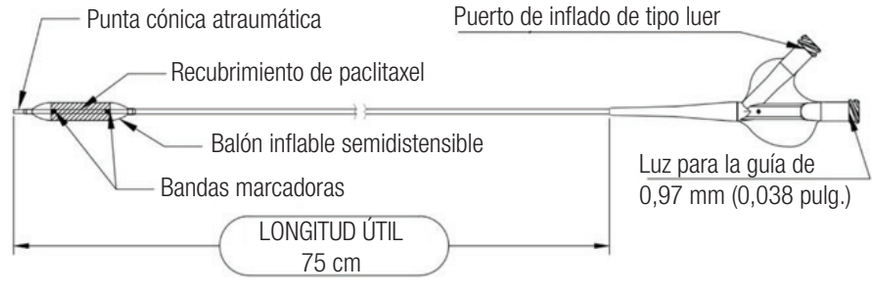
ESPAÑOL

Índice

1.0 DESCRIPCIÓN DEL DISPOSITIVO

1.1 Catéter con balón

El catéter uretral con balón recubierto de fármaco (DCB) Optilume es un catéter coaxial compatible con una guía de 0,97 mm (0,038 pulg.) y un cistoscopio flexible con un diseño de doble luz y una punta cónica atraumática. El DCB se emplea para ejercer una fuerza radial con el fin de dilatar segmentos uretrales estrechos (estenosis). El extremo distal del catéter dispone de un balón inflable semidistensible con un recubrimiento patentado que contiene el principio activo paclitaxel. El recubrimiento farmacológico abarca toda la longitud útil del cuerpo del balón. El dispositivo cuenta con dos bandas marcadoras radiopacas que indican la longitud útil del balón.



El dispositivo se esteriliza con óxido de etileno en una bolsa de Tyvek. Una vez esterilizado, el catéter embolsado se sella en una bolsa laminada con un desecante y se envasa en una caja de cartón individual. Cada DCB se suministra con una funda protectora que cubre la parte del catéter que aloja el balón recubierto de fármaco. La etiqueta de la bolsa de Tyvek incluye un gráfico de la distensibilidad del balón.

1.2 Recubrimiento farmacológico

El recubrimiento farmacológico se compone del principio activo paclitaxel y los excipientes, abarca la longitud útil del balón del catéter y se distribuye de manera uniforme por toda la superficie del balón con una concentración de 3,5 µg/mm^2. La principal característica funcional del recubrimiento farmacológico es que permite administrar el paclitaxel al urotelio mientras se infla el balón.

Tabla de dosificación de los DCB

Número de referencia	Diámetro (Fr/mm)	Longitud (mm)	Dosis de paclitaxel (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

ESPAÑOL

2.0 USO PREVISTO

El catéter uretral con balón recubierto de fármaco (DCB) Optilume está concebido para el tratamiento de la estenosis en la uretra anterior en hombres adultos.

3.0 INDICACIONES DE USO

El catéter uretral con DCB Optilume se usa para tratar a hombres mayores de 18 años con síntomas urinarios molestos asociados a estenosis uretral anterior recurrente. Está diseñado para su uso como balón de dilatación para una estenosis uretral única, en tándem o difusa de ≤3 cm de longitud o para su uso como tratamiento coadyuvante junto a otros dispositivos de dilatación o intervenciones.

4.0 CONTRAINDICACIONES

El catéter de dilatación uretral con balón recubierto de fármaco (DCB) está contraindicado para tratar a:

- Pacientes con hipersensibilidad conocida al paclitaxel o a otras sustancias con una estructura similar.
- Pacientes con lesiones que no se puedan atravesar con una guía de 0,97 mm (0,038 pulg.).

5.0 ADVERTENCIAS

- El DCB uretral se suministra ESTÉRIL para un solo uso. No reprocesar ni reesterilizar. El reprocesamiento y la reesterilización pueden aumentar el riesgo de infección del paciente y de que el dispositivo no funcione correctamente.
- La bolsa laminada y la superficie externa de la bolsa interna NO SON ESTÉRILES. El CONTENIDO de la bolsa interna es ESTÉRIL. Una vez abierta la bolsa laminada, usar inmediatamente.
- No emplear este dispositivo si existe infección en la uretra (IVU) o la vejiga. La infección se deberá resolver antes de tratar la estenosis con el DCB Optilume.
- El DCB solo debe ser manipulado por médicos con experiencia y conocimientos sobre los aspectos clínicos y técnicos de la dilatación uretral con balón.
- Antes de utilizar el DCB, el médico debe leer y comprender las instrucciones de uso. Si no se siguen las indicaciones, contraindicaciones, restricciones, advertencias y precauciones, pueden producirse complicaciones.
- No utilizar después de la fecha de caducidad.
- El DCB contiene paclitaxel, una genotoxina conocida. Los hombres deberán mantener relaciones sexuales con protección (con preservativo) durante los 30 días posteriores al tratamiento.
- Es preciso hacer un seguimiento para detectar posibles signos de anafilaxia o hipersensibilidad al paclitaxel.
- No emplear en ningún caso aire ni ningún otro medio gaseoso para inflar el DCB.
- Durante su uso, el DCB deberá manipularse con visualización directa por cistoscopia u observación fluoroscópica de alta calidad.
- No manipular el DCB cuando esté inflado.
- Si se advierte resistencia en cualquier momento durante el procedimiento de inserción, no se debe forzar el avance. La resistencia puede provocar daños en el dispositivo o en la luz. Retirar el catéter con mucho cuidado.
- Los hombres con pareja en edad fértil deben usar preservativo durante al menos 90 días después del tratamiento.
- Entre las reacciones adversas al paclitaxel y los síntomas observados, derivados principalmente de los estudios de infusión intravenosa del fármaco para el tratamiento de sujetos con cáncer, se encuentran los siguientes:
    - Aberraciones cromosómicas y riesgo de cáncer
    - Si se ve expuesta una mujer embarazada, daños al feto
    - Anafilaxis e hipersensibilidad al paclitaxel
    - Inhibición de la cicatrización de la uretra tras la intervención
    - Mielosupresión, por ejemplo: neutropenia, leucopenia, trombocitopenia, anemia
    - Arritmia
    - Neuropatía periférica
    - Mialgia o artralgia
    - Alopecia
    - Hipotensión
    - Náuseas, vómitos o diarrea
    - Elevación de la bilirrubina, fosfatasa alcalina y aspartato-aminotransferasa
    - Los posibles efectos sobre el hígado y los riñones se desconocen y no han sido estudiados.

La cantidad de paclitaxel administrada localmente durante la intervención del DCB Optilume es muy inferior a una única dosis de quimioterapia sistémica administrada a los pacientes de cáncer, y el fármaco parece permanecer esencialmente localizado en la uretra.

6.0 PRECAUCIONES

- Inflar el balón siempre con un líquido estéril (solución salina o una mezcla al 50 % con un medio de contraste). No inflar nunca con aire, dióxido de carbono ni ningún otro gas. No deberá inflarse el DCB por encima de la presión de estallido nominal (RBP). No inflar el balón en exceso.
- Los catéteres con balón están diseñados para ser manipulados por médicos con formación y experiencia en las técnicas de dilatación mediante catéter con balón.
- Para garantizar que se regule adecuadamente la presión del balón, se recomienda emplear un dispositivo de inflado con manómetro.
- Aspirar el balón por completo antes de retirar suavemente el dispositivo de la uretra. Un exceso de fuerza al retirar el balón puede provocar traumatismos en los tejidos.
- Inspeccionar atentamente el DCB y el embalaje antes de usarlo. No emplear el catéter si presenta daños o si su tamaño, forma o estado no resultan adecuados para la intervención prevista.
- No sumergir ni limpiar con ningún líquido la parte del DCB donde va alojado el balón, ya que puede verse afectada o dañada la integridad del recubrimiento farmacológico. Sustituir cualquier DCB cuyo balón haya entrado en contacto con líquidos antes de su uso.
- Emplear guantes estériles secos o apósitos de gasa secos para manipular el DCB antes de utilizarlo. Hay que procurar reducir al mínimo el contacto con la parte del dispositivo donde se aloja el balón recubierto.

- No inflar nunca el DCB fuera del cuerpo ni antes de alcanzar la estenosis que se vaya a tratar ya que se puede alterar la integridad del recubrimiento.
- No intentar introducir el DCB por un cistoscopio de un calibre French inferior al que se indica en la etiqueta.
- La longitud útil del DCB debe abarcar toda la longitud de la estenosis que se vaya a tratar.
- Para garantizar una liberación adecuada del fármaco en la estenosis que se vaya a tratar, dejar que el recubrimiento se hidrate en la uretra durante un mínimo de 60 segundos antes de inflar el DCB y mantenerlo inflado durante un mínimo de 5 minutos. Si el facultativo lo considera oportuno, para optimizar la dilatación de la estenosis puede mantenerse el balón inflado durante más de 5 minutos.
- Si el producto presenta algún fallo antes o durante el inflado, sustituir el DCB e inflarlo siguiendo el procedimiento. Si el fallo se produce después de inflar el balón a la RBP, no repetir la intervención con el DCB.
- Después de su uso, este producto puede constituir un riesgo biológico. Manipular y desechar siguiendo las prácticas médicas aceptadas y la legislación local vigente.
- Los profesionales sanitarios deberán evitar utilizar guantes de látex para prevenir posibles reacciones alérgicas de los pacientes con alergia al látex.
- Antes de utilizar el DCB Optilume, es necesario preparar la luz uretral de la lesión que se vaya a tratar, empleando un método adecuado de preparación de la luz, según lo determine el médico a cargo del paciente.
- La preparación de la luz empleando únicamente predilatación con un catéter con balón sin recubrimiento o UIVD ha sido analizada en el estudio Robust I.
- En los estudios clínicos, se requirió la confirmación visual de una estenosis significativa (diámetro uretral ≤12 F) mediante cistoscopia o uretrograma y la inscripción se restringió a los pacientes que presentaban síntomas subjetivos y objetivos de estenosis uretral (Puntuación internacional de síntomas prostáticos [IPSS] >13, índice de flujo urinario máximo <15 ml/s). Los sujetos se habían sometido al menos a un tratamiento endoscópico previo antes de inscribirse en los estudios clínicos.
- Los datos de seguridad y eficacia no han sido establecidos durante este estudio clínico para respaldar el tratamiento de las estenosis en pacientes con:
    - HBP
    - Prostatectomía radical
    - Irradiación pélvica
    - Tratamiento con bótox
    - Más de 1 estenosis
    - Uretroplastia previa en la uretra anterior
    - Uretritis bacteriana o gonorrea
    - Presencia de implante de pene/esfínter artificial o stent uretral/prostático
    - Vejiga neurogénica conocida, anomalías del esfínter o deficiencias funcionales del músculo detrusor.
    - Diagnóstico de liquen escleroso o reparación de hipospadias previa.
    - Antecedentes de carcinoma de vejiga o próstata en los 5 años anteriores
    - Estenosis debida a balanitis xerótica obliterante (BXO)
    - Tumores uretrales o cáncer de pene

7.0 USO EN POBLACIONES ESPECIALES

La seguridad y la eficacia del DCB uretral no han sido establecidas en pacientes pediátricos (<18 años de edad) ni en mujeres. El uso del DCB uretral en pacientes de ≥18 años de edad queda a discreción del médico.

8.0 POSIBLES COMPLICACIONES

Las posibles complicaciones asociadas al uso del catéter con DCB Optilume son similares a las que se asocian a las intervenciones habituales de dilatación uretral. Las posibles complicaciones pueden abarcar, entre otras:

- Dolor y sensibilidad a la palpación
- Espasmo vesical por la colocación de una sonda de Foley
- Traumatismo tisular en las estructuras circundantes, por ejemplo, daños uretrales
- Hematuria
- Reacciones adversas al medicamento, reacción alérgica al medio de contraste empleado durante la uretrografía diagnóstica
- Infección de las vías urinarias
- Perforación de los tejidos
- Recurrencia de la estenosis que obliga a realizar una nueva intervención quirúrgica
- Incontinencia
- Disuria
- Fiebre
- Retención urinaria

9.0 INFORMACIÓN SOBRE EL FÁRMACO

- **MECANISMO DE ACCIÓN**
  El recubrimiento del DCB uretral contiene paclitaxel, un agente antimitótico que se une específicamente a los microtúbulos y los estabiliza. Se ha notificado que el paclitaxel inhibe la proliferación y la migración de las células del músculo liso y los fibroblastos, así como las secreciones de la matriz extracelular. La combinación de estos efectos puede reducir la hiperplasia urotelial y, por tanto, evitar la recurrencia de las estenosis.

- **INTERACCIONES FARMACOLÓGICAS**
  No se han realizado estudios formales de interacciones farmacológicas con el DCB uretral. Deben consultarse las respectivas instrucciones de uso de todos los fár macos empleados junto con el DCB para conocer sus interacciones con el paclitaxel.

  Es preciso tener en cuenta las posibles interacciones farmacológicas sistémicas y locales en la uretra de un paciente que esté tomando un fármaco con interacciones conocidas con el paclitaxel o cuando se decide comenzar una farmacoterapia en un paciente que ha sido tratado con el DCB. El metabolismo del paclitaxel se cataliza por las isoenzimas CYP2C8 y CYP3A4 del citocromo P-450 y es un sustrato de la glicoproteína P. Pueden producirse interacciones farmacológicas con cualquier fármaco que afecte a estas isoenzimas. A falta de estudios formales de interacciones farmacológicas, es necesario administrar el paclitaxel con precaución.

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- **CARCINOGENICIDAD, GENOTOXICIDAD Y TOXICIDAD PARA LA REPRODUCCIÓN**
  No se han llevado a cabo estudios a largo plazo para evaluar el potencial carcinogénico del fármaco paclitaxel ni del DCB Optilume, y no se han publicado estudios adecuados y bien controlados en mujeres embarazadas o en hombres con intención de tener hijos. El paclitaxel inhibe la proliferación celular interactuando con los microtúbulos, y una consecuencia de ello es la pérdida de cromosomas completos durante la división celular. Esta acción indirecta es coherente con las respuestas positivas en los ensayos in vitro e in vivo de genotoxicidad de micronúcleos, en los que se detectan fragmentos de ADN. Estos resultados positivos también se han observado en lo referente a aberraciones cromosómicas en linfocitos humanos primarios. Se desconoce si el paclitaxel ejerce alguna acción directa por separado sobre el ADN en la generación de roturas o fragmentos de cadenas de ADN. Da negativo en los ensayos de mutación de genes, como el de la Salmonella o el de CHO/HPRT.

  Estudios realizados en ratas y conejos a los que se administró paclitaxel intravenoso durante la organogénesis, revelaron evidencias de toxicidad maternal, embriotoxicidad y fetotoxicidad a dosis de 1 y 3 mg/kg, respectivamente (aproximadamente 13 y 39 veces la dosis que administra el DCB Optilume con un revestimiento de 5,5 mg de paclitaxel [balón de 10 mm x 50 mm] ajustadas al peso corporal). No se observó teratogenicidad en ratas preñadas a las que se administró paclitaxel intravenosos en dosis diarias de 1 mg/kg (una dosis diaria de aproximadamente 13 veces la dosis del DCB Optilume [10 mm x 50 mm], ajustada al peso corporal).

  El médico a cargo del paciente deberá sopesar los posibles beneficios médicos del catéter con DCB Optilume frente a estos riesgos genotóxicos y reproductivos. ADVERTENCIA: El DCB uretral contiene paclitaxel, una genotoxina conocida. Los hombres deberán mantener relaciones sexuales con protección (con preservativo) durante los 30 días posteriores al tratamiento.

10.0 PRESENTACIÓN

El catéter con DCB Optilume se suministra ESTÉRIL para un solo uso (esterilización con óxido de etileno). El DCB se presenta en un sistema de envase de doble bolsa (una laminada y una de Tyvek) dentro de una caja de cartón individual.

11.0 CONSERVACIÓN

El DCB uretral debe conservarse a temperatura ambiente, en un lugar seco y en su envase original. El dispositivo debe usarse antes de la fecha de caducidad que figura en el envase.

12.0 ELEMENTOS RECOMENDADOS

Preparar los siguientes elementos mediante una técnica estéril:

- Una guía del tamaño adecuado con punta flexible (consultar el etiquetado del producto)
- Un cistoscopio (preferentemente uno flexible)
- Solución salina estéril
- Jeringa de 10 cc
- Llave de paso de dos vías
- Dispositivo de inflado con manómetro
- Medios de contraste. Nota: Opcionales para su uso en intervenciones guiadas con fluoroscopia

13.0 INSTRUCCIONES DE USO

13.1 ANTES DE SU UTILIZACIÓN

Medicación perioperatoria
Se recomienda a los médicos que sigan las pautas de medicación preoperatoria y de preparación de una intervención endoscópica, incluida la administración de algún antibiótico preoperatorio según proceda. También se recomienda administrar AINE orales antes de la intervención.

Si existe infección de las vías urinarias (IVU) en el momento del tratamiento, se debe tratar al paciente hasta curarle la infección, antes de poder llevar a cabo esta intervención.

13.2 PREPARACIÓN DE LA ESTENOSIS QUE SE VAYA A TRATAR

La predilatación uretral de la estenosis que se vaya a tratar, mediante un método de preparación adecuado según lo determine el médico a cargo del paciente (balón de dilatación sin revestimiento o UIVD), está recomendada para las estenosis muy pronunciadas y difíciles de atravesar, antes del uso del DCB Optilume. Lleve a cabo una predilatación para que la estenosis “ceda”. Estos casos se definen como aquellos con un diámetro de la luz de la estenosis dilatada >20 F o >50 % mayor que la luz de la estenosis no dilatada.

13.3 TAMAÑOS DEL DISPOSITVO

Verifique que el diámetro del balón DCB seleccionado a la presión nominal sea el mismo o ligeramente mayor que el diámetro de la uretra sana adyacente al borde distal de la estenosis. El diámetro del balón dividido por la uretra sana adyacente distal se define como la relación de estiramiento.

Dimensionamiento de la uretra bulbar
Para estenosis bulbares que no superan una relación de estiramiento de 1,3 entre el diámetro del balón y la uretra distal sana. Si el tamaño de la uretra se encuentra entre dos tamaños de dispositivo disponibles, utilice el tamaño más grande siempre que la relación de estiramiento sea menor o igual que 1,3. Si el siguiente tamaño más grande produce una relación de estiramiento superior a 1,3, utilice el dispositivo más pequeño.

Dimensionamiento de la uretra del pene
Para las estenosis uretrales del pene, seleccione el diámetro de balón que mejor se adapte a la uretra sana distal. La relación de estiramiento de la uretra del pene no debe exceder de 1:1. Si el tamaño de la uretra se encuentra entre dos tamaños de balón disponibles, seleccione el tamaño de balón más pequeño. NO SUPERE la relación de estiramiento de 1:1.

Tanto para la uretra del pene como la uretra bulbar, la longitud del balón DCB debe ser mayor que la de la estenosis que se vaya a tratar. La longitud del balón debe extenderse aproximadamente 0,5-1 cm más allá de la estenosis a ambos lados. Por ejemplo, si la longitud de la estenosis es de 2 cm, elija un balón DCB de 3 cm.

13.4 PREPARACIÓN DEL CATÉTER CON BALÓN

Evacue del catéter con DCB el aire. La luz del balón del catéter contiene aire y es necesario desplazarlo para asegurarse de que el balón se llene solo de líquido mientras el catéter se encuentre dentro de la uretra.

1. Fijar la llave de paso en posición abierta al conector de inflado del balón.
2. Conectar una jeringa medio llena de solución salina a la llave de paso.
3. Con la punta de la jeringa hacia abajo, tirar del émbolo hasta alcanzar el volumen total de la jeringa (creando así presión negativa máxima) y retenerlo hasta que dejen de verse burbujas de aire saliendo de la solución salina de la jeringa. Repetir según sea necesario para purgar el aire del catéter y sustituirlo con solución salina. Mantener el émbolo atrás, girar la llave de paso para mantener el vacío y retirar la jeringa. Llenar a medias un dispositivo de inflado con solución salina isotónica, o una proporción 1:1 de medio de contraste: solución salina en caso de que se emplee fluoroscopia, y purgar el aire de la vía.
4. Conectar el dispositivo de inflado a la llave de paso del catéter con balón, girar la llave de paso y hacer el vacío en el dispositivo de inflado.

13.5 INSERCIÓN DEL DCB OPTILUME

1. Colocar con un cistoscopio una guía de 0,97 mm (0,038 pulg.) con la punta flexible enrollada en la vejiga.
2. Retirar de la punta del catéter con DCB el protector del balón.

   Precaución: *Es necesario actuar con cuidado al pasar un balón recubierto de paclitaxel por cualquier cistoscopio. Minimizar la manipulación excesiva y no tocar el balón. No limpiar el balón con gasa seca, húmeda ni lubricada, ni con ningún disolvente que pudiera dañar la integridad del balón recubierto de fármaco.*

3. Empujar el catéter con DCB por el interior del canal de trabajo del cistoscopio. Otra posibilidad es colocar la guía y el catéter con balón fuera del canal de trabajo del cistoscopio para poder situarlos en paralelo.
4. Utilice el cistoscopio para guiar la colocación del DCB. También puede ajustar la posición del DCB mediante fluoroscopia, sirviéndose de los marcadores radi opacos ubicados debajo de la zona de transición entre el cuerpo del balón y el cono.

   Precaución: *No empujar la guía ni el catéter de dilatación con balón si se encuentra resistencia sin antes determinar su causa y tomar las medidas correctoras oportunas.*

13.6 INFLADO DEL DCB OPTILUME

Precaución: *Los dispositivos de inflado pueden alcanzar presiones muy altas con un mínimo esfuerzo. Es muy recomendable emplear un dispositivo de inflado con un manómetro de alta presión para optimizar la fuerza de dilatación de modo que la estenosis uretral ceda y permita la penetración del fármaco en el urotelio cedido.*

1. Asegúrese de lavar la uretra con solución salina.
2. Situar el DCB a lo largo de la estenosis con el cistoscopio distal al balón (alejado de la vejiga) para poder visualizar la correcta colocación del balón a lo largo de la estenosis. Dejar el balón en posición desinflado durante un mínimo de 1 minuto antes de inflarlo. Comprobar que los marcadores radiopacos del balón se encuentren en la posición correcta mediante fluoroscopia.
3. Inflar el balón a la presión de estallido nominal (RBP) empleando el dispositivo de inflado. No superar la presión de estallido nominal (RBP) del balón. Mantener la presión durante un mínimo de 5 minutos o hasta obtener la dilatación que se desee.
4. Desinflar el balón aplicando vacío al mismo con el dispositivo de inflado. Cuando el balón esté totalmente desinflado, retirar la guía y el DCB lentamente. Si se advierte una leve resistencia al retirar el balón, girar suavemente el catéter para permitir que el balón se pliegue alrededor del eje del catéter y facilitar así la retirada.

   Precaución: *Si se advierte resistencia al retirar una guía a través de un catéter introducido en un cistoscopio, DEJAR DE TIRAR y retirarlos juntos al mismo tiempo como si fuesen una unidad para evitar daños en la guía, el catéter o la anatomía del paciente.*

5. Si el producto presenta algún fallo antes o durante el inflado (por debajo de la RBP), sustituir el DCB e inflarlo siguiendo el procedimiento. Si el fallo se produce después de inflar el balón a la RBP, no repetir la intervención con el DCB.
6. Introducir una sonda de Foley de 12-14 Fr lubricada y dejarla en su sitio durante un mínimo de 2 días o lo que marque el protocolo estándar, eligiendo la duración mayor entre ambas.

13.7 GRÁFICO DE DISTENSIBILIDAD

18 Fr (6 mm) x 30 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**RBP**	6,25

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24 Fr (8 mm) x 30 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Presión	kPa		(mm) Balón
6,0	600	**Nominal**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**RBP**	10,44

Precaución: *No debe superarse la presión de estallido nominal. Consultar la etiqueta del producto para conocer las presiones de estallido nominales. Inflar el balón con una presión mayor que la presión de estallido nominal puede provocar su rotura. Si se produce una pérdida de presión en el balón durante el inflado o si este se rompe durante la dilatación, interrumpir inmediatamente la intervención. Desinflar el balón con cuidado y retirarlo de la uretra. No volver a inflarlo.*

14.0 GARANTÍA

Urotronic garantiza que se han tomado las precauciones oportunas en el diseño y la fabricación de este producto. Esta garantía sustituye y excluye cualquier otra garantía que no se haya indicado expresamente en el presente documento, ya sea prevista por la ley explícita o implícitamente o de cualquier otro modo, entre otras, toda garantía implícita para un fin particular. La manipulación, conservación, limpieza y esterilización de este dispositivo, además de otros factores relacionados con el paciente, el diagnóstico, el tratamiento, las intervenciones quirúrgicas y otros aspectos que escapen al control directo de Urotronic afectan directamente al dispositivo y los resultados obtenidos de su uso. La obligación de Urotronic de acuerdo con esta garantía se limita a la reparación o sustitución de este dispositivo, y Urotronic no será responsable de ningún daño o perjuicio fortuito o consecuente, ni de ningún gasto que se derive directa o indirectamente del uso de este dispositivo. Urotronic no asume ninguna responsabilidad con respecto a los dispositivos reutilizados, reprocesados o reesterilizados ni ofrece ninguna garantía sobre ellos, ya sea explícita o implícita, para un fin determinado o para otro propósito.

15.0 SÍMBOLOS EMPLEADOS EN LAS ETIQUETAS DEL DISPOSITIVO

	Cantidad: 1 unidad por caja
	Precaución: La legislación federal restringe la venta de este dispositivo solo a médicos o por prescripción facultativa.
	Indica la fecha de fabricación del producto sanitario.
	No reesterilizar
	No reutilizar
	No utilizar si el envase está dañado
	Frágil
	Fecha de caducidad
	Mantener alejado de la luz solar
	Mantener seco
	Fabricante
	No contiene látex
	Límite de temperatura: 15 °C - 30 °C
	Precaución: Consultar las instrucciones de uso
	Esterilizado con óxido de etileno
	Número de referencia
	Numero de lote
	Marcado CE según la Directiva de dispositivos médicos 93/42/CEE de la Unión Europea (organismo notificado n.º 1434)
	Representante autorizado en la Unión Europea

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OPTILUME®

CATETER DE BALÃO URETRAL REVESTIDO POR FÁRMACO

Instruções de Utilização

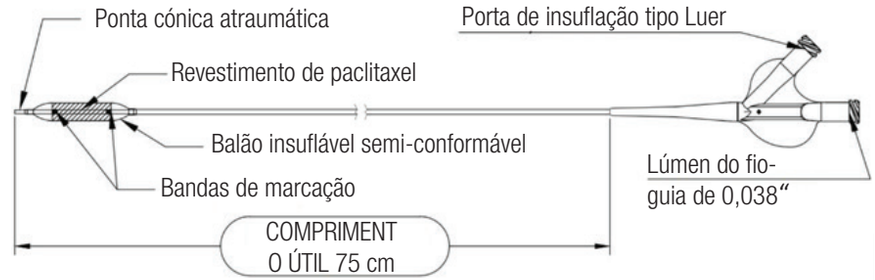
PORTUGUÊS

Índice

1.0 DESCRIÇÃO DO DISPOSITIVO

1.1 Cateter de balão

O Cateter de Balão Revestido por Fármaco (DCB) Uretral Optilume é um fio-guia de 0,97 mm (0,038") e um cateter de passagem sobre o fio-guia (OTW) compatível com cistoscópio flexível, com um design de duplo lúmen e uma ponta cónica atraumática. O Balão Revestido por Fármaco (DCB) é utilizado para exercer força radial e dilatar segmentos estreitos da uretra (estenoses). A extremidade distal do cateter possui um balão insuflável semi-conformável, o qual tem um revestimento exclusivo que contém paclitaxel como princípio ativo. O revestimento de fármaco cobre o comprimento de trabalho do corpo do balão. O dispositivo possui duas bandas de marcação radiopacas que indicam o comprimento de trabalho do balão.



O dispositivo é esterilizado utilizando óxido de etileno numa bolsa de Tyvek. Após a esterilização, o cateter na bolsa de Tyvek é selado numa bolsa de folha de alumínio com dessecante e colocado dentro de uma caixa de cartão individual. Cada Cateter de DCB é fornecido com uma bainha protetora que cobre a parte do balão revestido por fármaco do cateter. O rótulo da bolsa de Tyvek apresenta uma tabela de conformação do balão.

PORTUGUÊS

1.2 Revestimento de fármaco

O revestimento de fármaco consiste no ingrediente ativo paclitaxel e excipientes. O revestimento de fármaco cobre o comprimento de trabalho do componente do balão do cateter. O revestimento de fármaco está distribuído uniformemente pela superfície do balão a uma concentração de 3,5 µg/mm^2. A principal característica funcional do revestimento de fármaco é permitir a libertação de paclitaxel para o urotélio durante a insuflação do balão.

Matriz de dosagem do DCB

Número de catálogo	Diâmetro (Fr/mm)	Comprimento (mm)	Dose de paclitaxel (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

2.0 UTILIZAÇÃO PREVISTA

O Cateter de Balão Revestido por Fármaco (DCB) Uretral Optilume destina-se ao tratamento de estenoses na uretra anterior em adultos do sexo masculino.

3.0 INDICAÇÕES DE UTILIZAÇÃO

O Cateter DCB Uretral Optilume é utilizado para tratar homens ≥18 anos de idade com sintomas urinários incómodos, associados a estenose recorrente na uretra anterior. Foi concebido como um balão de dilatação para uma estenose uretral única, paralela ou difusa anterior com ≤3 cm de comprimento ou para utilização como terapia coadjuvante com outros dispositivos de dilatação e/ou procedimentos.

4.0 CONTRAINDICAÇÕES

O Cateter de Balão Uretral de Dilatação Revestido por Fármaco (DCB) está contraindicado para utilização em:

- Pacientes com hipersensibilidade conhecida ao paclitaxel ou compostos estruturalmente relacionados.
- Pacientes com lesões que não possam ser atravessadas com um fio-guia de 0,038".

5.0 ADVERTÊNCIAS

- O Cateter de DCB Uretral é fornecido ESTÉRIL apenas para uma única utilização. Não reprocessar nem reesterilizar. O reprocessamento e a reesterilização podem aumentar o risco de infeção do paciente e o risco de comprometimento do desempenho do dispositivo.
- A bolsa de folha de alumínio e a superfície externa da bolsa interior estão no estado NÃO ESTÉRIL. O CONTEÚDO da bolsa interior está ESTÉRIL. Utilizar imediatamente depois de abrir a bolsa de folha de alumínio.
- Não utilizar este dispositivo em caso de infeção na uretra (ITU) ou na bexiga. Dever-se-á eliminar a infeção antes de tratar a estenose com o Cateter de DCB Optilume.
- O Cateter de DCB só deve ser utilizado por médicos experientes e conhecedores dos aspetos clínicos e técnicos da dilatação por balão uretral.
- Antes de utilizarem o Cateter de DCB, os médicos devem ler e compreender as instruções de utilização. O não cumprimento das indicações, contraindicações, restrições, advertências e precauções pode dar origem a complicações.
- Não utilizar após o prazo de validade.
- O Cateter de DCB contém paclitaxel, uma genotoxina conhecida. Os homens devem ter relações sexuais protegidas (usar um preservativo) durante 30 dias após o tratamento.
- Monitorizar o paciente quanto a sinais de anafilaxia ou hipersensibilidade ao paclitaxel.
- Nunca utilizar ar nem nenhum meio gasoso para insuflar o DCB.
- Quando estiver a ser utilizado, o DCB deve ser manuseado sob visualização direta por cistoscopia ou observação fluoroscópica de alta qualidade.
- Não manusear o DCB no estado insuflado.
- Se sentir resistência em qualquer momento durante o procedimento de inserção, não forçar a passagem. A resistência pode provocar danos no dispositivo ou no lúmen. Retirar o cateter cuidadosamente.
- Os homens com parceiras sexuais em idade fértil devem usar um preservativo durante, no mínimo, 90 dias após o tratamento.
- As reações adversas ao paclitaxel e os sintomas observados com origem, principalmente, em estudos de infusão endovenosa do fármaco para o tratamento de indivíduos com cancro, incluem
    - Anomalias cromossómicas e risco de cancro
    - Riscos para o feto quando uma mulher grávida é exposta
    - Anafilaxia e hipersensibilidade ao paclitaxel
    - Inibição da cura da uretra após o procedimento
    - Mielossupressão, incluindo: neutropenia, leucopenia, trombocitopenia, anemia
    - Arritmia
    - Neuropatia periférica
    - Mialgia ou artralgia
    - Alopecia
    - Hipotensão
    - Náuseas, vómitos ou diarreia
    - Níveis elevados de bilirrubina, ALP e AST
    - O possível efeito no fígado e rins é desconhecido e não foi estudado.

A quantidade de paclitaxel administrado localmente durante o procedimento com o Cateter de DCB Optilume é muito inferior a uma dose única de quimioterapia sistémica administrada a pacientes com cancro e o fármaco parece permanecer localizado, essencialmente, na uretra.

6.0 PRECAUÇÕES

- Insuflar sempre com um líquido estéril (solução salina estéril ou mistura de contraste a 50%). Nunca insuflar com ar, dióxido de carbono ou qualquer outro gás. O DCB não deve ser insuflado para além da pressão de rutura nominal (RBP). Não insuflar o balão em demasia.
- Os cateteres de balão destinam-se a ser utilizados por médicos formados e experientes em técnicas de dilatação por cateter de balão.
- Para garantir uma regulação adequada da pressão do balão, é recomendável utilizar um dispositivo de insuflação de balão com manómetro.
- Aspirar o balão completamente antes de remover cuidadosamente o dispositivo da uretra. O uso de força excessiva para retirar o balão pode traumatizar o tecido.
- Antes da utilização, inspecionar cuidadosamente o Cateter de DCB e a embalagem. Não utilizar o cateter se estiver danificado ou se o tamanho, a forma ou o estado não forem adequados para o procedimento pretendido.
- Não mergulhar nem limpar a parte do DCB com nenhum líquido, uma vez que a integridade do revestimento de fármaco pode ficar danificada ou comprometida. Substituir qualquer Cateter de DCB em que o balão tenha entrado em contacto com fluidos antes da utilização.
- Usar luvas estéreis secas ou gazes secas para manusear o Cateter de DCB ante da utilização. Deve ter-se cuidado para minimizar o contacto com a parte do balão revestido do dispositivo.
- Nunca insuflar o DCB fora do corpo ou antes de atingir a estenose-alvo, pois pode comprometer a integridade do revestimento.

- Não tentar passar o DCB através de um cistoscópio de tamanho (Fr) inferior ao indicado no rótulo.
- O comprimento de trabalho do DCB deve cobrir todo o comprimento da estenose-alvo.
- Para a correta administração do fármaco na estenose-alvo, deixar o revestimento hidratar-se na uretra durante 60 segundos, no mínimo, antes da insuflação e manter a insuflação do DCB durante 5 minutos, no mínimo. Para otimizar a dilatação da estenose, pode utilizar-se um tempo de insuflação mais longos >5 minutos, ao critério do operador.
- Se o produto tiver uma falha antes ou durante a insuflação, substituir o Cateter de DCB e insuflar em conformidade com o procedimento pretendido. Se a falha ocorrer após a insuflação até à RBP, não repetir o procedimento do DCB.
- Após a utilização, este produto pode constituir um potencial risco biológico. Manusear e eliminar de acordo com a prática médica aceite e os regulamentos locais aplicáveis.
- Os profissionais de saúde devem evitar usar luvas de látex para impedir eventuais reações alérgicas por parte de pacientes que sejam alérgicos ao látex.
- A preparação do lúmen uretral da lesão-alvo, utilizando o método de preparação adequado do lúmen, determinado pelo médico responsável, é necessária antes da utilização do Cateter de DCB Optilume.
- A preparação do lúmen utilizando apenas pré-dilatação com um cateter de balão não revestido ou DVIU (uretrotomia interna sob visão direta) foi estudada no ensaio clínico Robust I.
- Em ensaios clínicos, a confirmação visual de uma estenose significativa (≤12F de diâmetro uretral) por cistoscopia ou uretrograma era obrigatória e a inscrição foi limitada a pacientes com sintomas subjetivos e objetivos de estenose uretral (Classificação Internacional de Sintomas da Próstata - International Prostate Symptom Score) [IPSS] >13, pico da taxa de fluxo urinário <15 ml/seg). Os indivíduos tinham realizado pelo menos um tratamento endoscópico prévio antes da sua inscrição nos ensaios clínicos.
- Não foram obtidos dados de segurança e eficácia durante o ensaio clínico para apoiar o tratamento de estenoses em pacientes com:
  - HBP
  - Prostatectomia radical
  - Radioterapia pélvica
  - Tratamento com Botox
  - Mais do que 1 estenose
  - Uretroplastia anterior na uretra anterior
  - Uretrite bacteriana ou gonorreia
  - Presença de implante peniano, esfíncter artificial ou stent da uretra/próstata
  - Bexiga neurogénica, anomalias do esfíncter ou má função do músculo detrusor conhecidos
  - Diagnosticado com líquen escleroso ou reparação anterior de hipospadia
  - Historial anterior, nos últimos 5 anos, de carcinoma da bexiga ou da próstata
  - Estenose devida a balanite xerótica obliterante (BXO)
  - Tumores uretrais ou cancro do pénis

7.0 UTILIZAÇÃO EM POPULAÇÕES ESPECIAIS

A segurança e eficácia do Cateter de DCB Uretral não foram estabelecidas em pacientes pediátricos (<18 anos de idade) ou em mulheres. A decisão da utilização do Cateter de DCB Uretral em pacientes com ≥18 anos de idade ou mais velhos cabe ao médico.

8.0 POSSÍVEIS COMPLICAÇÕES

As possíveis complicações associadas à utilização do Cateter de DCB Optilume são idênticas às associadas aos procedimentos padrão de dilatação da uretra. As possíveis complicações podem incluir, entre outras:

- Dor e sensibilidade
- Espasmo vesical devido à colocação de um cateter Foley
- Traumatismo do tecido em estruturas circundantes, incluindo lesões na uretra
- Hematúria
- Reações medicamentosas, reação alérgica ao meio de contraste utilizado durante o uretrograma de diagnóstico
- Infeção do trato urinário
- Perfuração do tecido
- Recidiva de estenose que obrigue a cirurgia adicional
- Incontinência
- Disúria
- Febre
- Retenção urinária

9.0 INFORMAÇÃO FARMACOLÓGICA

o MECANISMO DE AÇÃO

O revestimento do Cateter de DCB Uretral contém paclitaxel, um agente antimitótico que se liga especificamente aos microtúbulos e os estabiliza. Foi relatado que o paclitaxel inibe a proliferação e a migração de células musculares lisas e de fibroblastos, bem como a secreção de matriz extracelular. A combinação destes efeitos pode resultar na inibição da hiperplasia do urotélio e, por conseguinte, da recidiva da estenose.

o INTERAÇÕES MEDICAMENTOSAS

Não foram realizados estudos formais de interações medicamentosas para o Cateter de DCB Uretral. As instruções de utilização de todos os medicamentos utilizados em conjunto com o DCB devem ser consultadas quanto às interações com paclitaxel.

Deve considerar-se a possibilidade de ocorrência de interações medicamentosas sistémicas e locais na uretra num paciente que esteja a tomar um medicamento com interações conhecidas com o paclitaxel ou quando se decidir iniciar a terapia medicamentosa num paciente que foi tratado com o DCB. O metabolismo do paclitaxel é catalisado pelas isoenzimas CYP2C8 e CYP3A4 do citocromo P450 e é um substrato da glicoproteína-P. Podem ocorrer interações medicamentosas com qualquer medicamento que afete estas isoenzimas. Na ausência de estudos formais de interações medicamentosas, deve ter-se cuidado ao administrar paclitaxel.

- **CARCINOGENICIDADE, GENOTOXICIDADE E TOXICOLOGIA REPRODUTIVA**

  Não foram realizados estudos de longo prazo para avaliar o potencial carcinogénico do Cateter de DCB Optilume, e não existem estudos adequados e bem controlados publicados relativos a mulheres grávidas ou a homens que pretendam ter filhos. O paclitaxel inibe a proliferação celular ao interagir com microtúbulos, e uma consequência é a perda de cromossomas durante a divisão celular. Esta ação indireta é consistente com respostas positivas in vitro e ensaios de genotoxicidade do micronúcleo in vivo, que detetam fragmentos de ADN. Também foram relatados resultados positivos para aberrações cromossómicas em linfócitos humanos primários. Não se sabe se o paclitaxel tem uma ação direta separada no ADN no que se refere à geração de quebras ou fragmentos dos filamentos de ADN. É negativo em ensaios de mutação genética, incluindo salmonela e CHO/HPRT.

  Estudos realizados em ratos e coelhos aos quais foi administrado paclitaxel por via endovenosa durante organogénese, revelaram evidência de toxicidade materna, embriotoxicidade e fetotoxicidade em dosagens de 1 e 3 mg/kg, respetivamente (aproximadamente 13 e 39 vezes a dose fornecida pelo Cateter de DCB Optilume revestido com 5,5 mg de paclitaxel [balão de 10 mm x 50 mm] ajustada ao peso corporal). Não foi observada teratogenicidade em ratas grávidas às quais foram administradas diariamente doses endovenosas de paclitaxel de 1 mg/kg (uma dose diária de aproximadamente 13 vezes a dose do Cateter de DCB Optilume [10 mm x 50 mm], ajustada ao peso corporal).

  O médico responsável deve contrabalançar os possíveis benefícios médicos do Cateter de DCB Optilume contra estes riscos genotóxicos e reprodutivos. ADVERTÊNCIA: O Cateter de DCB Uretral contém paclitaxel, uma genotoxina conhecida. Os homens devem ter relações sexuais protegidas (usar um preservativo) durante 30 dias após o tratamento.

10.0 APRESENTAÇÃO

O Cateter de DCB Optilume é fornecido ESTÉRIL apenas para uma única utilização (esterilização com óxido de etileno). O Cateter de DCB está acondicionado num sistema de embalagem de bolsa dupla (bolsa de folha de alumínio e bolsa de Tyvek), estando inserido numa caixa individual.

11.0 ARMAZENAMENTO

O Cateter de DCB Uretral deve ser armazenado à temperatura ambiente, num local seco, na sua embalagem original. O dispositivo deve ser utilizado antes do prazo de validade indicado na embalagem.

12.0 ITENS RECOMENDADOS

Prepare os seguintes itens utilizando a técnica estéril:

- Fio-guia de tamanho apropriado com ponta flexível (consultar o rótulo do produto)
- Cistoscópio (preferencialmente flexível)
- Solução salina esterilizada
- Seringa de 10 cc
- Torneira de duas vias
- Dispositivo de insuflação com manómetro
- Meio de contraste – Nota: Opcional para utilização com procedimentos sob orientação fluoroscópica.

13.0 INDICAÇÕES DE UTILIZAÇÃO

13.1 ANTES DA UTILIZAÇÃO

Medicação peri-procedimento

Recomenda-se que os médicos sigam as diretrizes quanto à medicação peri-procedimento e a preparação para um procedimento endoscópico, incluindo a administração de antibiótico peri-procedimento conforme adequado. Também se recomenda a administração de AINEs orais antes do procedimento.

Em caso de presença de infeção do trato urinário (ITU) no momento do tratamento, o paciente deve ser tratado até à cura da infeção antes de se poder realizar o procedimento de tratamento.

13.2 PREPARAÇÃO DA ESTENOSE-ALVO

A pré-dilatação uretral da estenose-alvo, utilizando o método de preparação adequado determinado pelo médico responsável (balão de dilatação não revestido ou DVIU), é recomendada para estenoses gravemente estenosadas e difíceis de atravessar antes da utilização do Cateter de DCB Optilume. Realizar uma pré-dilatação para “fazer ceder” a estenose. Isto é definido como o diâmetro do lúmen da estenose dilatada >20F ou >50% maior do que o lúmen da estenose não dilatada.

13.3 SELEÇÃO DO TAMANHO DO DISPOSITIVO

Verificar se o diâmetro selecionado do balão do Cateter de DCB à pressão nominal é igual ou ligeiramente superior ao diâmetro da uretra saudável adjacente à extremidade distal da estenose. O diâmetro do balão dividido pela uretra distal saudável adjacente é definido como o rácio de distensão.

Cálculo das dimensões da uretra bulbar
No caso de estenoses bulbares, não exceder um rácio de distensão 1,3 de diâmetro do balão em relação à uretra distal saudável. Se o tamanho da uretra se encontrar os tamanhos de dispositivo disponíveis, utilize o tamanho maior desde que o rácio de distensão seja inferior ou igual a 1,3. Se o tamanho maior seguinte produzir um rácio de distensão superior a 1,3, utilize o dispositivo mais pequeno.

Cálculo das dimensões da uretra peniana
No caso de estenoses da uretra peniana, selecione o diâmetro do balão que melhor corresponde à uretra distal saudável. O rácio de distensão da uretra peniana não deve exceder 1:1. Se o tamanho da uretra se encontrar entre os tamanhos de balão disponíveis, selecione o tamanho de balão mais pequeno. NÃO EXCEDER um rácio de distensão de 1:1.

No caso da uretra peniana e da uretra bulbar, o comprimento do balão DCB não deve ser maior do que o comprimento da estenose a tratar. O comprimento do balão deve

estender aproximadamente 0,5-1 cm para além da estenose em ambos os lados. Por exemplo, se o comprimento da estenose for de 2 cm, escolha um balão DCB de 3 cm.

13.4 PREPARAÇÃO DO CATETER DE BALÃO

Evacuar o ar do Cateter de DCB. O lúmen do balão do cateter contém ar e este deve ser expelido para garantir que apenas líquido enche o balão enquanto o cateter se encontra na uretra.

1. Fixar a torneira na posição aberta no conector de insuflação do balão.
2. Fixar a seringa cheia até metade com solução salina na torneira.
3. Com a ponta da seringa voltada para baixo, retrair o êmbolo até a seringa estar cheia (o que cria pressão negativa máxima) e segurar até não se ver mais bolhas de ar a sair da solução salina na seringa. Repetir conforme necessário para pu gar o ar do cateter e substituir com solução salina. Manter o êmbolo retraído, rodar a torneira para manter o vácuo e remover a seringa. Encher um dispositivo de insuflação até meio com solução salina normal, ou com meio de contraste e solução salina na proporção de 1:1 em caso de fluoroscopia, e purgar o ar da linha.
4. Fixar o dispositivo de insuflação na torneira no cateter de balão, rodar a torneira e criar vácuo no dispositivo de insuflação.

13.5 INSERÇÃO DO CATETER DE DCB OPTILUME

1. Posicionar um fio-guia de 0,038” com a ponta flexível enrolada na bexiga com a ajuda de um cistoscópio.
2. Retirar o protetor do balão da ponta do Cateter de DCB.

   Atenção: *Ter cuidado ao passar um balão revestido com paclitaxel através de qualquer sistema de cistoscópio. Minimizar o manuseamento excessivo e não tocar no balão. Não limpar o balão com gaze seca, molhada ou lubrificada nem nenhum solvente que possa danificar a integridade do balão revestido por fármaco.*

3. Avançar o Cateter de DCB no interior do canal de trabalho do cistoscópio. Alternativamente, colocar o fio-guia e o cateter de balão separados do canal de trabalho do cistoscópio para uma colocação lado a lado.
4. Utilizar o cistoscópio para orientar a colocação do Cateter de DCB. Em alternativa, posicionar o Cateter de DCB sob fluoroscopia, utilizando os marcadores radiopacos localizados por baixo da transição do corpo do balão/cone.

   Atenção: *Não avançar o fio-guia nem o cateter de balão de dilatação se sentir resistência, sem primeiro determinar a sua causa e tomar medidas corretivas.*

13.6 INSUFLAÇÃO DO CATETER DE DCB OPTILUME

Atenção: *Os dispositivos de insuflação são capazes de atingir pressões muito elevadas com um esforço mínimo. Recomenda-se vivamente a utilização de um dispositivo de insuflação com um manómetro de alta pressão para otimizar a força de dilatação, com vista a fazer ceder a estenose uretral e permitir a pene tração do fármaco no urotélio que cedeu.*

1. Assegurar que a uretra é irrigada com solução salina.
2. Posicionar o Cateter de DCB na estenose com o cistoscópio distal ao balão (afastado da bexiga) para visualizar a correta colocação do balão na estenose. Deixar o balão posicionado e não insuflado durante, no mínimo, 1 minuto antes da insuflação. Verificar se os marcadores radiopacos do balão estão na posição correta, por meio de fluoroscopia.
3. Insuflar o balão até à pressão de rutura nominal utilizando o dispositivo de insuflação. Não exceder a pressão de rutura nominal (RBP) do balão. Manter a pressão durante 5 minutos, no mínimo, ou até atingir a dilatação desejada.
4. Esvaziar o balão aplicando vácuo ao balão com o dispositivo de insuflação. Quando o balão estiver completamente vazio, retirar lentamente o fio-guia e o Cateter de DCB. Se sentir uma ligeira resistência quando o balão estiver a ser removido, girar o cateter suavemente para ajudar o balão a dobrar-se à volta da haste do cateter e facilitar a remoção.

   Atenção: *Se sentir resistência ao remover um fio-guia através de um cateter por meio de um cistoscópio, PARAR e removê-los ao mesmo tempo, como uma unidade completa, para evitar danos no fio-guia, no cateter ou na anatomia do paciente.*

5. Se o produto tiver uma falha antes ou durante a insuflação (mas inferior à RBP), substituir o Cateter de DCB e insuflar em conformidade com o procedimento pre tendido. Se a falha ocorrer após a insuflação até à RBP, não repetir o procedimen to com o Cateter de DCB.
6. Inserir um cateter Foley lubrificado de 12-14 Fr e deixar no local durante, no mínimo, 2 dias ou segundo o padrão de cuidados, o que for mais longo.

13.7 TABELA DE CONFORMAÇÃO

18 Fr (6 mm) x 30 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

PORTUGUÊS

24 Fr (8 mm) x 50 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Pressão	kPa		(mm) Balão
6,0	600	**Nominal**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**RBP**	10,44

Atenção: *A pressão de rutura nominal não deve ser excedida. Consultar o rótulo do produto para saber as pressões de rutura nominais. A insuflação para além da pressão de rutura nominal pode provocar o rompimento do balão. Se ocorrer a perda de pressão no interior do balão durante a insuflação ou se o balão se romper durante a dilatação, interromper imediatamente o procedimento. Esvaziar o balão cuidadosamente e retirá-lo da uretra. Não voltar a insuflar.*

14.0 GARANTIA

A Urotronic garante que adotou cuidados razoáveis na conceção e no fabrico deste produto. Esta garantia substitui e exclui todas as restantes garantias não expressamente estabelecidas no presente documento, sejam explícitas ou implícitas, decorrentes da legislação ou não, incluindo, entre outras, quaisquer garantias implícitas de adequação a um determinado fim. O manuseamento, o armazenamento, a limpeza e a esterilização deste dispositivo, bem como outros fatores relacionados com o paciente, diagnóstico, tratamento, procedimentos cirúrgicos e outros fora do âmbito de controlo da Urotronic, afetam diretamente o dispositivo e os resultados obtidos com a sua utilização. A obrigação da Urotronic ao abrigo desta garantia está limitada à reparação ou substituição deste dispositivo e a Urotronic não será responsável por quaisquer perdas, danos ou despesas incidentais ou consequentes, decorrentes direta ou indiretamente da utilização deste dispositivo. A Urotronic não assume qualquer responsabilidade em relação aos dispositivos reutilizados, reprocessados ou reesterilizados e não oferece qualquer garantia, seja explícita ou implícita, incluindo, entre outras, garantias para um determinado fim, em relação a esses dispositivos.

15.0 SÍMBOLOS UTILIZADOS NOS RÓTULOS DO DISPOSITIVO

	Quantidade de 1 por caixa
	Atenção: A lei federal só permite a venda deste dispositivo a médicos ou mediante receita médica.
	Indica a data em que o dispositivo médico foi fabricado.
	Não reesterilizar
	Não reutilizar
	Não utilizar se a embalagem estiver danificada
	Frágil
	Prazo de validade
	Manter afastado da luz solar
	Manter seco
	Fabricante
	Não contém látex
	Limite de temperatura 15 °C - 30 °C
	Atenção: Consultar as instruções de utilização
	Esterilizado com óxido de etileno
	Número de catálogo
	Número de lote
	Marca CE de acordo com a Diretiva relativa a dispositivos médicos 93/42/CEE da União Europeia (Organismo notificado n.º 1434)
	Representante autorizado da União Europeia

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CE 1434

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OPTILUME®

CATETERE URETRALE A PALLONCINO CON RIVESTIMENTO DI FARMACO

Istruzioni per l'uso

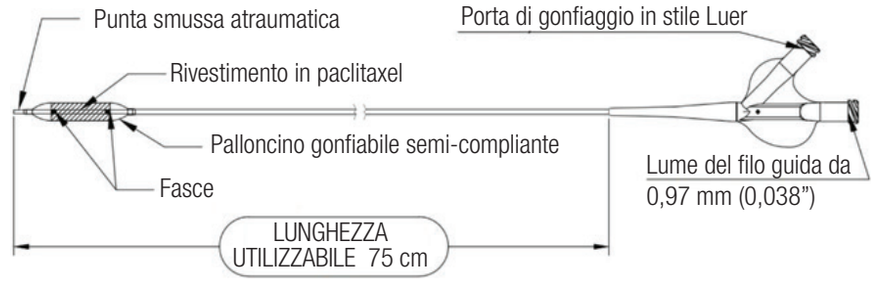
ITALIANO

Sommario

1.0 DESCRIZIONE DEL DISPOSITIVO

1.1 Catetere a palloncino

Il catetere uretrale a palloncino con rivestimento di farmaco (DCB) Optilume è un catetere over-the-wire (OTW) compatibile con cistoscopio flessibile e dotato di filo guida da 0,97 mm (0,038"), con doppio lume e punta smussa atraumatica. Il DCB è utilizzato al fine di esercitare una forza radiale per dilatare segmenti uretrali stretti (stenosi). L'estremità distale del catetere è dotata di un palloncino gonfiabile semi-compliante con rivestimento brevettato contenente il farmaco attivo paclitaxel. Il rivestimento di farmaco ricopre la lunghezza operativa del corpo del palloncino. Il dispositivo è dotato di due fasce radiopache che indicano la lunghezza operativa del palloncino.



Il dispositivo viene sterilizzato con ossido di etilene in una busta in Tyvek. Dopo la sterilizzazione, il catetere imbustato viene sigillato in una busta in alluminio con essicante e contenuto in una scatola singola. Ciascun DCB viene fornito con una guaina protettiva che ricopre la parte del catetere con il palloncino con rivestimento di farmaco. La tabella di compliance del palloncino si trova sull'etichetta della busta in Tyvek.

1.2 Rivestimento di farmaco

Il rivestimento di farmaco è composto dal principio attivo paclitaxel e da eccipienti. Il rivestimento di farmaco ricopre la lunghezza operativa del palloncino del catetere. Il rivestimento di farmaco è distribuito uniformemente su tutta la superficie del palloncino a una concentrazione di 3,5 µg/mm^2. La caratteristica funzionale principale del rivestimento di farmaco è consentire il rilascio di paclitaxel all'urotelio durante il gonfiaggio del palloncino.

Matrice del dosaggio del DCB

Numero di catalogo	Diametro (Fr/mm)	Lunghezza (mm)	Dose di paclitaxel (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

ITALIANO

2.0 USO PREVISTO

Il catetere uretrale a palloncino con rivestimento di farmaco (DCB) Optilume è destinato al trattamento delle stenosi nell'uretra anteriore nei maschi adulti.

3.0 INDICAZIONI PER L'USO

Il catetere uretrale DCB Optilume è indicato per il trattamento di pazienti maschi con età ≥18 anni con sintomi urinari fastidiosi associati a stenosi uretrale anteriore ricorrente. È progettato per essere utilizzato come palloncino di dilatazione di stenosi uretrale anteriore singola, doppia o diffusa con una lunghezza ≤3 cm, oppure come terapia aggiuntiva con altri dispositivi e/o procedure di dilatazione.

4.0 CONTROINDICAZIONI

L'uso del catetere uretrale per dilatazione a palloncino con rivestimento di farmaco (DCB) è controindicato nei seguenti casi:

- Pazienti con ipersensibilità nota a paclitaxel o a composti strutturalmente correlati.
- Pazienti con lesioni che non possono essere attraversate con un filo guida da 0,97 mm (0,038").

5.0 AVVERTENZE

- Il DCB uretrale è fornito STERILE ed è esclusivamente monouso. Non ricondizionare né risterilizzare. Il ricondizionamento e la risterilizzazione potrebbero aumentare il rischio di infezione per il paziente e il rischio di compromettere le prestazioni del dispositivo.
- La busta in alluminio e la superficie esterna della busta interna NON sono sterili. Il CONTENUTO della busta interna è STERILE. Dopo aver aperto la busta in alluminio, utilizzarne immediatamente il contenuto.
- Non utilizzare questo dispositivo se è presente un'infezione dell'uretra (UTI) o della vescica. Eliminare l'infezione prima di trattare la stenosi con il DCB Optilume.
- Il DCB deve essere utilizzato solo da medici esperti e con una conoscenza approfondita degli aspetti clinici e tecnici della dilatazione uretrale con palloncino.
- Prima di utilizzare il DCB, i medici devono leggere e comprendere le istruzioni per l'uso. La mancata osservanza di istruzioni, controindicazioni, limitazioni, avvertenze e precauzioni può portare a complicanze.
- Non utilizzare dopo la data di scadenza.
- Il DCB contiene paclitaxel, una genotossina nota. Gli uomini devono avere rapporti sessuali protetti (utilizzo del preservativo) per 30 giorni dopo il trattamento.
- Monitorare l'eventuale presenza di segni di anafilassi o ipersensibilità a paclitaxel.
- Per gonfiare il DCB non utilizzare mai aria né altri mezzi gassosi.
- Quando utilizzato, il DCB deve essere manipolato con visualizzazione diretta mediante cistoscopia o sotto osservazione fluoroscopica con apparecchiature di alta qualità.
- Non manipolare il DCB quando gonfio.
- Qualora si incontri resistenza in qualunque momento durante la procedura di inserimento, non forzare il passaggio. La resistenza può causare danni al dispositivo o al lume. Estrarre attentamente il catetere.
- Gli uomini con partner potenzialmente fertili devono utilizzare il preservativo per almeno 90 giorni dopo il trattamento.
- Tra le reazioni avverse al paclitaxel e i sintomi osservati derivati principalmente da studi con infusione EV sul farmaco durante il trattamento di soggetti affetti da cancro sono comprese:
    - Anomalie cromosomiche e rischio cancerogeno
    - Danno al feto in caso di esposizione di una donna in gravidanza
    - Anafilassi e ipersensibilità a paclitaxel
    - Inibizione della guarigione dell'uretra dopo la procedura
    - Nella mielosoppressione sono incluse: neutropenia, trombocitopenia, anemia
    - Aritmia
    - Neuropatia periferica
    - Mialgia o artralgia
    - Alopecia
    - Ipotensione
    - Nausea, vomito o diarrea
    - Livelli elevati di bilirubina, ALP e AST
    - Non sono noti e non sono stati studiati potenziali effetti su fegato e reni

La quantità di paclitaxel erogato localmente durante la procedura con DCB Optilume è notevolmente inferiore a una dose singola di chemioterapico sistemico somministrato a pazienti affetti da cancro e sembra che il farmaco resti essenzialmente localizzato nell'uretra.

6.0 PRECAUZIONI

- Gonfiare sempre utilizzando un liquido sterile (soluzione salina sterile o miscela di contrasto al 50%). Non gonfiare mai con aria, anidride carbonica né altri gas. Il DCB non deve essere gonfiato oltre la pressione nominale di scoppio (RBP). Non gonfiare eccessivamente il palloncino.
- I cateteri a palloncino sono indicati per l'uso da parte di medici qualificati ed esperti nelle tecniche di dilatazione con catetere a palloncino.
- Per garantire la corretta regolazione della pressione del palloncino, è necessario utilizzare un dispositivo di gonfiaggio del palloncino dotato di manometro.
- Aspirare completamente il palloncino prima di rimuovere delicatamente il dispositivo dall'uretra. L'uso di una forza eccessiva per estrarre il palloncino può causare un trauma ai tessuti.
- Ispezionare attentamente il DCB e la confezione prima dell'utilizzo. Non utilizzare il catetere se è danneggiato o se la sua dimensione, forma o condizione non è idonea alla procedura prevista.
- Non immergere né pulire con alcun liquido la sezione a palloncino del DCB, poiché il rivestimento di farmaco potrebbe danneggiarsi o risultare compromesso. Sostituire qualsiasi DCB qualora il palloncino sia entrato a contatto con dei liquidi prima dell'uso.
- Utilizzare guanti sterili asciutti o tamponi di garza asciutti per manipolare il DCB prima dell'uso. Prestare attenzione al fine di ridurre il contatto con la parte del dispositivo in cui si trova il palloncino con rivestimento.

- Non gonfiare mai il DCB all'esterno del corpo o prima di raggiungere la stenosi target, poiché tale operazione può compromettere l'integrità del rivestimento.
- Non tentare di introdurre il DCB attraverso un cistoscopio con misura in French inferiore a quella indicata sull'etichetta.
- La lunghezza operativa del DCB deve coprire l'intera lunghezza della stenosi target.
- Per favorire il corretto rilascio di farmaco nella stenosi target, lasciare idratare il rivestimento nell'uretra per un minimo di 60 secondi prima del gonfiaggio e mantenere il gonfiaggio del DCB per un minimo di 5 minuti. Per ottimizzare la dilatazione della stenosi, tempi di gonfiaggio più lunghi >5 minuti devono essere eseguiti a discrezione dell'operatore.
- Se il prodotto presenta un guasto prima o durante il gonfiaggio, sostituire il DCB e gonfiarlo secondo la procedura. Se il guasto si verifica dopo il gonfiaggio alla RBP, non ripetere la procedura con DCB.
- Dopo l'utilizzo, questo prodotto può costituire un potenziale rischio biologico. Manipolare e smaltire in conformità con le pratiche mediche accettate e le normative locali applicabili.
- Gli operatori sanitari devono evitare l'uso di guanti in lattice al fine di prevenire possibili reazioni allergiche da parte dei pazienti allergici al lattice.
- Prima di utilizzare il DCB Optilume è necessario preparare il lume uretrale della lesione target, utilizzando l'idoneo metodo di preparazione secondo le indicazioni del medico curante.
- La preparazione del lume mediante solo predilatazione con un catetere a palloncino non rivestito o DVIU è stata esaminata nello studio clinico Robust I.
- Negli studi clinici, era necessaria la conferma visiva di una stenosi significativa (diametro uretrale ≤12F) tramite cistoscopia o uretrografia e l'arruolamento è stato limitato ai pazienti che presentavano sintomi soggettivi e oggettivi di stenosi uretrale (International Prostate Symptom Score [IPSS] >13, velocità di flusso urinario di picco <15 mL/sec). I soggetti sono stati sottoposti ad almeno un precedente trattamento endoscopico prima dell'arruolamento negli studi clinici.
- Non sono stati definiti i dati di sicurezza ed efficacia durante lo studio clinico per supportare il trattamento di stenosi in pazienti affetti da:
  - IPB
  - Prostatectomia radicale
  - Radiazione pelvica
  - Trattamento con Botox
  - Più di 1 stenosi
  - Precedente uretroplastica all'interno dell'uretra anteriore
  - Uretrite batterica o gonorrea
  - Presenza di protesi peniena, sfintere artificiale o uretra/stent prostatico
  - Vescica neurogenica nota, anomalie dello sfintere o scarsa funzionalità del muscolo detrusore
  - Diagnosi di Lichen Sclerosus o precedente riparazione di ipospadia
  - Anamnesi di carcinoma della vescica o della prostata negli ultimi 5 anni
  - Stenosi dovuta a balanite xerotica obliterante (BXO)
  - Tumori uretrali o cancro penieno

7.0 USO IN POPOLAZIONI SPECIALI

La sicurezza e l'efficacia del DCB uretrale non sono state stabilite in pazienti pediatrici (<18 anni d'età) o nelle donne. L'utilizzo del DCB uretrale in pazienti di età ≥18 anni è a discrezione del medico.

8.0 POSSIBILI COMPLICANZE

Le possibili complicanze associate all'utilizzo del catetere DCB Optilume sono simili a quelle associate alle procedure standard per la dilatazione dell'uretra. Le possibili complicanze possono includere, ma non sono limitate a:

- Dolore e sensibilità
- Spasmo della vescica da inserimento del catetere Foley
- Trauma tissutale nelle strutture circostanti, compreso danno uretrale
- Ematuria
- Reazioni da farmaco, reazione allergica al mezzo di contrasto utilizzato durante l'uretrografia diagnostica
- Infezione delle vie urinarie
- Perforazione dei tessuti
- Stenosi ricorrente che richiede ulteriore intervento chirurgico
- Incontinenza
- Disuria
- Febbre
- Ritenzione urinaria

9.0 INFORMAZIONI SUL FARMACO

o MECCANISMO D'AZIONE

Il rivestimento del DCB uretrale contiene paclitaxel, un farmaco antimitotico che fissa e stabilizza in modo specifico i microtubuli. È stato riscontrato che paclitaxel inibisce la proliferazione e la migrazione dei fibroblasti e delle cellule dei muscoli lisci, nonché la secrezione di matrice extracellulare. La combinazione di questi effetti può causare l'inibizione dell'iperplasia uroteliale e, di conseguenza, la ricorrenza di stenosi.

o INTERAZIONI DEL FARMACO

Non sono stati condotti studi formali sull'interazione tra farmaci con il DCB uretrale. Per le interazioni con paclitaxel, è necessario consultare le istruzioni per l'uso di tutti i farmaci utilizzati in combinazione con il DCB.

Occorre valutare il potenziale rischio di interazioni, sia sistemiche che locali, tra farmaci nell'uretra in pazienti che assumono un farmaco con interazioni note con paclitaxel, oppure al momento di decidere di iniziare una terapia in pazienti che sono stati trattati con il DCB. Il metabolismo di paclitaxel è catalizzato dagli isoenzimi CYP2C8 e CYP3A4 del citocromo P450 e si tratta di un substrato della P-glicoproteina. Potenziali interazioni tra farmaci possono verificarsi con qualsiasi farmaco che agisce su questi isoenzimi. In assenza di studi formali sull'interazione tra farmaci, è necessario prestare attenzione durante la somministrazione di paclitaxel.

o CANCEROGENICITÀ, GENOTOSSICITÀ E TOSSICOLOGIA RIPRODUTTIVA

Non è stato eseguito alcuno studio a lungo termine al fine di valutare il potenziale di cancerogenicità del farmaco paclitaxel o del DCB Optilume e non vi sono studi adeguati e ben controllati pubblicati su donne in gravidanza o in uomini che intendono procreare. Paclitaxel inibisce la proliferazione cellulare interagendo con i microtubuli e la perdita degli interi cromosomi durante la divisione cellulare è una conseguenza. Questa azione indiretta è coerente con le risposte positive dei test in vitro e in vivo sulla genotossicità del micronucleo, che rilevano i frammenti di DNA. Sono stati riferiti anche risultati positivi per aberrazioni cromosomiche nei linfociti umani primari. Non è noto se paclitaxel abbia un'azione separata diretta sul DNA nel generare rotture dei filamenti o frammenti di DNA. Risulta negativo nei test per mutazione genica, tra cui salmonella e CHO/HPRT.

Gli studi eseguiti su ratti e conigli riceventi paclitaxel per endovena durante l'organogenesi hanno rivelato evidenza di tossicità materna, embriotossicità e fetotossicità rispettivamente ai dosaggi di 1 e 3 mg/kg (circa 13 e 39 volte la dose erogata dal DCB Optilume rivestito con 5,5 mg di paclitaxel (palloncino da 10 mm x 50 mm) aggiustata per peso corporeo). Non è stata osservata alcuna teratogenicità in ratti gravidi riceventi dosi giornaliere di paclitaxel per endovena di 1 mg/kg (una dose giornaliera di circa 13 volte la dose di DCB Optilume (10 mm x 50 mm) aggiustata per peso corporeo).

Il medico curante deve equilibrare i potenziali benefici medici del catetere DCB Optilume con questi rischi genotossici e riproduttivi. AVVERTENZA: il DCB uretrale contiene paclitaxel, una genotossina nota. Gli uomini devono avere rapporti sessuali protetti (utilizzo del preservativo) per 30 giorni dopo il trattamento.

10.0 MODALITÀ DI FORNITURA

Il catetere DCB Optilume è fornito STERILE ed è esclusivamente monouso (sterilizzazione mediante ossido di etilene). Il DCB è contenuto in un sistema di confezionamento a doppia busta (busta in alluminio e in Tyvek), contenuto all'interno di una confezione singola.

11.0 CONSERVAZIONE

Il DCB uretrale deve essere conservato nella sua confezione originale, a temperatura ambiente e in un ambiente asciutto. Il dispositivo deve essere utilizzato prima della data di scadenza indicata sulla confezione.

12.0 ARTICOLI CONSIGLIATI

Preparare i seguenti articoli utilizzando una tecnica sterile:

- Filo guida della misura appropriata con punta flessibile (fare riferimento all'etichettatura del prodotto)
- Cistoscopio (preferibilmente flessibile)
- Soluzione salina sterile
- Siringa da 10 cc
- Rubinetto a due vie
- Dispositivo di gonfiaggio con manometro
- Mezzi di contrasto – Nota: opzionali, da utilizzare con procedure guidate da fluoroscopia

13.0 ISTRUZIONI PER L'USO

13.1 PRIMA DELL'USO

Medicazione periprocedurale
Si raccomanda che i medici si attengano alle linee guida per le medicazioni e la preparazione preprocedurali e per una procedura endoscopica, tra cui la somministrazione di un antibiotico preprocedurale, laddove appropriato. Si raccomandano anche FANS orali da somministrare prima della procedura.

Qualora sia presente un'infezione delle vie urinarie (UTI) al momento del trattamento, il paziente deve essere trattato fino alla guarigione dell'infezione prima di poter applicare la procedura di trattamento.

13.2 PREPARAZIONE DELLA STENOSI TARGET

Prima di utilizzare il DCB Optilume si raccomanda di eseguire la predilatazione uretrale della stenosi target, utilizzando l'idoneo metodo di preparazione secondo le indicazioni del medico curante (palloncino per dilatazione non rivestito o DVIU) per stenosi di elevato livello o di difficile attraversamento. Eseguire la predilatazione per "aprire" la stenosi. Si tratta del diametro del lume di stenosi dilatata >20 F o >50% maggiore rispetto al lume di stenosi non dilatata.

13.3 DIMENSIONI DEL DISPOSITIVO

Verificare che il diametro del palloncino del DCB selezionato alla pressione nominale sia identico o leggermente più grande del diametro dell'uretra sana, adiacente al margine distale della stenosi. Si definisce "coefficiente di elasticità" il diametro del palloncino diviso per il diametro dell'uretra sana adiacente.

Dimensioni dell'uretra bulbare
In caso di stenosi bulbare, non superare un coefficiente di elasticità di 1,3 del diametro del palloncino rispetto all'uretra sana adiacente. Se la dimensione dell'uretra ricade tra due dimensioni disponibili del dispositivo, utilizzare la dimensione più grande purché il coefficiente di elasticità sia inferiore o uguale a 1,3. Se la dimensione più grande successiva comporta un coefficiente di elasticità superiore a 1,3, usare il dispositivo con la dimensione più piccola.

Dimensioni dell'uretra peniena
In caso di stenosi uretrale peniena, selezionare il diametro del palloncino che si abbina meglio all'uretra sana distale. Il coefficiente di elasticità dell'uretra peniena non deve essere maggiore di 1:1. Se la dimensione dell'uretra ricade tra due dimensioni disponibili del palloncino, selezionare la dimensione del palloncino più piccola tra le due. NON SUPERARE il coefficiente di elasticità di 1:1.

Per l'uretra sia peniena che bulbare il palloncino del DCB deve avere una lunghezza superiore a quella della stenosi da trattare. La lunghezza del palloncino deve estendersi di circa 0,5-1 cm oltre la stenosi su entrambi i lati. Ad esempio, se la lunghezza della stenosi è 2 cm, scegliere un palloncino del DCB da 3 cm.

13.4 PREPARAZIONE DEL CATETERE A PALLONCINO

Eliminare l'aria dal catetere DCB. Il lume del palloncino del catetere contiene aria, che deve essere rimossa al fine di garantire che solo il liquido riempia il palloncino mentre il catetere si trova nell'uretra.

1. Collegare il rubinetto, in posizione aperta, al connettore di gonfiaggio del palloncino.
2. Collegare al rubinetto la siringa riempita per metà con soluzione salina sterile.
3. Tenendo la punta della siringa verso il basso, tirare indietro lo stantuffo per riempire il volume della siringa, creando una pressione massima negativa, e mantenere in questa posizione fino a quando non si vedono più uscire delle bollicine d'aria dalla soluzione salina nella siringa. Ripetere se necessario per eliminare l'aria dal catetere e sostituirla con soluzione salina. Tenendo lo stantuffo retratto, ruotare il rubinetto per mantenere il vuoto e rimuovere la siringa. Riempire per metà un dispositivo di gonfiaggio con normale soluzione salina o con liquido di contrasto e soluzione salina in rapporto 1:1 se si utilizza la fluoroscopia, ed eliminare l'aria dalla linea.
4. Collegare il dispositivo di gonfiaggio al rubinetto sul catetere a palloncino, ruotare il rubinetto e creare il vuoto nel dispositivo di gonfiaggio.

13.5 INSERIMENTO DEL DCB OPTILUME

1. Con l'aiuto di un cistoscopio, posizionare nella vescica un filo guida da 0,97 mm (0,038") con la punta flessibile avvolta.
2. Rimuovere la protezione del palloncino dalla punta del catetere DCB.

   Attenzione: *prestare attenzione durante il passaggio del palloncino rivestito con paclitaxel attraverso qualsiasi cistoscopio. Ridurre al minimo la manipolazione e non toccare il palloncino. Non pulire il palloncino con garze asciutte, bagnate o lubrificate, né con alcun solvente, poiché tale operazione può danneggiare l'in tegrità del palloncino con rivestimento di farmaco.*

3. Far avanzare il catetere DCB all'interno del canale operativo del cistoscopio. In alternativa, posizionare il filo guida e il catetere a palloncino fianco a fianco, in posizione separata dal canale operativo del cistoscopio.
4. Utilizzare il cistoscopio per aiutarsi nel posizionamento del DCB. In alternativa, posizionare il DCB con l'ausilio della fluoroscopia mediante i marker radiopachi posizionati sotto l'area di transizione tra il palloncino e il cono.

   Attenzione: *se si avverte resistenza, non far avanzare il filo guida né il catetere per dilatazione a palloncino senza prima determinare la causa della resistenza e aver risolto il problema.*

13.6 GONFIAGGIO DEL DCB OPTILUME

Attenzione: *i dispositivi di gonfiaggio sono in grado di raggiungere pressioni molto elevate con il minimo sforzo. L'uso di un dispositivo di gonfiaggio con un manometro ad alta pressione è fortemente raccomandato per ottimizzare la forza di dilatazione per aprire la stenosi uretrale e consentire la penetrazione all'interno dell'urotelio aperto.*

1. Assicurarsi che l'uretra sia irrorata con soluzione salina.
2. Posizionare il DCB nella stenosi con il cistoscopio posto distalmente al palloncino (distante dalla vescica) per visualizzare il corretto posizionamento del palloncino nella stenosi. Lasciare il palloncino in posizione sgonfia per almeno 1 minuto prima del gonfiaggio. Verificare che la posizione dei marker radiopachi del palloncino sia corretta, utilizzando la fluoroscopia.
3. Gonfiare il palloncino alla pressione nominale di scoppio utilizzando il dispositivo di gonfiaggio. Non superare la pressione nominale di scoppio (RBP) del palloncino. Mantenere la pressione per almeno 5 minuti o fino a ottenere la dilatazione desiderata.
4. Sgonfiare il palloncino applicando l'aspirazione utilizzando un dispositivo di gon fiaggio. Quando il palloncino è completamente sgonfio, estrarre lentamente il filo guida e il DCB. Se si avverte una lieve resistenza quando si tira il palloncino, ruotare delicatamente il catetere per aiutare il palloncino ad arrotolarsi sull'asta del catetere e facilitare l'estrazione.

   Attenzione: *se si avverte resistenza mentre si rimuove il filo guida attraverso un catetere attraverso un cistoscopio, INTERROMPERE la procedura e rimuoverli insieme contemporaneamente come un'unità completa, al fine di prevenire danni al filo guida o al catetere, o lesioni anatomiche a carico del paziente.*

5. Se il prodotto presenta un guasto prima o durante il gonfiaggio (ma inferiore alla RBP), sostituire il DCB e gonfiarlo secondo la procedura. Se il guasto si verifica dopo il gonfiaggio alla RBP, non ripetere la procedura con DCB.
6. Inserire un catetere Foley liscio da 12-14 Fr e lasciarlo in posizione per almeno 2 giorni o secondo lo standard di cura, in base a quale delle due opzioni è maggiore.

13.7 TABELLA DI COMPLIANCE

18 Fr (6 mm) x 30 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	6,11 (18 Fr)
8,0	800		6,23
10,0	1.000		6,34
12,0	1.200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	5,87 (18 Fr)
8,0	800		6,03
10,0	1.000		6,16
12,0	1.200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	7,98 (24 Fr)
8,0	800		8,16
10,0	1.000		8,32
12,0	1.200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	8,00 (24 Fr)
8,0	800		8,20
10,0	1.000		8,37
12,0	1.200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	9,83 (30 Fr)
8,0	800		10,09
10,0	1.000	**RBP**	10,29

30 Fr (10 mm) x 30 mm

Pressione (ATM)	kPa		Palloncino (mm)
6,0	600	**Nominale**	9,98 (30 Fr)
8,0	800		10,23
10,0	1.000	**RBP**	10,44

Attenzione: *non superare la pressione nominale di scoppio. Per le pressioni nominali di scoppio, fare riferimento all'etichetta del prodotto. Il gonfiaggio oltre la pressione nominale di scoppio può causare la rottura del palloncino. Se si verifica una perdita di pressione all'interno del palloncino durante il gonfiaggio o se il palloncino si rompe durante la dilatazione, interrompere immediatamente la procedura. Sgonfiare attentamente il palloncino e rimuoverlo dall'uretra. Non gonfiare nuovamente.*

14.0 GARANZIA

Urotronic garantisce che è stata utilizzata ragionevole accuratezza nella progettazione e nella realizzazione di questo prodotto. Questa garanzia sostituisce ed esclude qualsiasi altra garanzia non espressamente indicata nel presente documento, esplicita o implicita, imposta per legge o altro, inclusa, a titolo esemplificativo ma non esaustivo, qualsiasi garanzia implicita per uno scopo particolare. La manipolazione, la conservazione, la pulizia e la sterilizzazione di questo dispositivo, nonché altri fattori correlati a paziente, diagnosi, trattamenti, interventi chirurgici e altre questioni al di fuori del controllo di Urotronic influiscono direttamente sul dispositivo e sui risultati ottenuti mediante il suo utilizzo. Gli obblighi di Urotronic nell'ambito della presente garanzia sono limitati alla riparazione o sostituzione di questo dispositivo e Urotronic non sarà responsabile di perdite, danni o spese accidentali o consequenziali, direttamente o indirettamente derivanti dall'utilizzo di questo dispositivo. Urotronic non si assume alcuna responsabilità in merito al riutilizzo, ricondizionamento o risterilizzazione dei dispositivi e non rilascia alcuna garanzia, esplicita o implicita, inclusa, a titolo esemplificativo ma non esaustivo, per uno scopo particolare, per quanto riguarda questi dispositivi.

15.0 SIMBOLI UTILIZZATI NELLE ETICHETTE DEL DISPOSITIVO

	Quantità: 1 per scatola
	Attenzione: la legge federale limita la vendita di questo dispositivo ai medici o su prescrizione medica
	Indica la data in cui il dispositivo medico è stato prodotto
	Non risterilizzare
	Non riutilizzare
	Non utilizzare se la confezione è danneggiata
	Fragile
	Data di scadenza
	Tenere al riparo dalla luce del sole
	Conservare all'asciutto
	Produttore
	Non contiene lattice
	Limite di temperatura 15 °C - 30 °C
	Attenzione: consultare le istruzioni per l'uso
	Sterilizzato con ossido di etilene
	Numero di catalogo
	Numero di lotto
	Marchio CE secondo la Direttiva sui dispositivi medici 93/42/CEE dell'Unione Europea (Organismo Notificato n. 1434)
	Rappresentante autorizzato per l'Unione Europea

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OPTILUME®

URETHRALE GENEESMIDDEL-GECOATE BALLONKATHETER

Gebruiksaanwijzing

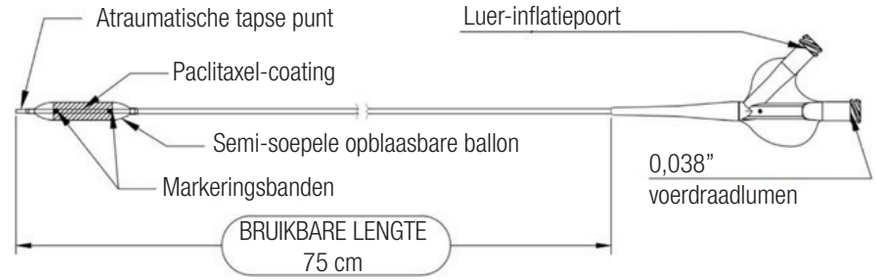
NEDERLANDSE

Inhoudsopgave

1.0 BESCHRIJVING HULPMIDDEL

1.1 Ballonkatheter

De Optilume urethrale geneesmiddel-gecoate ballondilatatiekatheter (DCB, drug coated balloon) bestaat uit een 0,038" (0,97 mm) voerdraad en een flexibele over-de-draad-katheter (OTW, over-the-wire), geschikt voor een cystoscoop, met een dubbel lumen en een tapse atraumatische punt. De DCB wordt gebruikt voor het uitoefenen van radiale kracht om vernauwde urethrale segmenten (stricturen) te dilateren. Het distale uiteinde van de katheter is voorzien van een semi-soepele opblaasbare ballon die is gecoat met een bedrijfseigen coating die het actieve geneesmiddel paclitaxel bevat. De geneesmiddelcoating is over de gehele werklengte van de ballonromp aanwezig. Het hulpmiddel is voorzien van twee radiopake markeringsbanden waarmee de werklengte van de ballon wordt aangeduid.



Het hulpmiddel is met behulp van ethyleenoxide in een Tyvek-zakje gesteriliseerd. Na sterilisatie wordt de katheter in het zakje verzegeld in een foliezakje met droogmiddel en in een doosje voor één exemplaar verpakt. Elke DCB wordt geleverd met een beschermhuls die het met geneesmiddel gecoate ballondeel van de katheter bedekt. Op het etiket op het Tyvek-zakje staat een balloncompliantieschema.

NEDERLANDSE

1.2 Geneesmiddelcoating

De geneesmiddelcoating bestaat uit de actieve farmaceutische stof paclitaxel en hulpstoffen. De geneesmiddelcoating bedekt de werklengte van het ballononderdeel van de katheter. De geneesmiddelcoating is gelijkmatig verdeeld over het ballonoppervlak in een concentratie van 3,5 µg/mm^2. De belangrijkste functionele eigenschap van de geneesmiddelcoating is de afgifte van paclitaxel aan het urotheel wanneer de ballon opgeblazen is.

Doseringsmatrix DCB

Catalogusnummer	Diameter (Fr/mm)	Lengte (mm)	Dosis paclitaxel (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

2.0 BEOOGD GEBRUIK

De Optilume urethrale geneesmiddel-gecoate ballonkatheter (DCB) is bedoeld voor de behandeling van stricturen in de anterieure urethra bij volwassen mannen.

3.0 INDICATIES VOOR GEBRUIK

De Optilume urethrale DCB-katheter wordt gebruikt voor het behandelen van mannen ≥ 18 jaar met hinderlijke urinaire klachten in verband met herhaaldelijk optredende strictuur van de anterieure urethra. De katheter is ontworpen voor gebruik als dilatatie-ballon voor één, tandem of diffuse anterieure urethrastrictuur met een lengte ≤ 3 cm, of voor gebruik als aanvullende therapie met andere dilatatiehulpmiddelen en/of -ingrepen.

4.0 CONTRA-INDICATIES

De urethrale geneesmiddel-gecoate ballondilatatiekatheter (DCB) is gecontra-indiceerd voor gebruik bij:

- Patiënten met een bekende overgevoeligheid voor paclitaxel of structureel aanverwante bestanddelen.
- Patiënten met laesies die niet kunnen worden gekruist met een 0,038” voerdraad.

5.0 WAARSCHUWINGEN

- De urethrale DCB wordt STERIEL geleverd en is uitsluitend bedoeld voor eenmalig gebruik. Niet herverwerken of hersteriliseren. Herverwerking en hersterilisatie kunnen het risico op infectie bij de patiënt en het risico op een minder goede werking van het hulpmiddel vergroten.
- Het foliezakje en het uitwendige oppervlak van het binnenzakje zijn NIET STERIEL. De INHOUD van het binnenzakje is STERIEL. Gebruik het hulpmiddel onmiddellijk na het openen van het foliezakje.
- Gebruik dit hulpmiddel niet indien sprake is van een infectie in de urethra (UWI) of in de blaas. De infectie moet verdwenen zijn voordat de strictuur met de Optilume DCB kan worden behandeld.
- De DCB mag uitsluitend worden gebruikt door artsen met ervaring in en kennis van de klinische en technische aspecten van urethrale ballondilatatie.
- Voorafgaand aan het gebruik van de DCB moet de arts de gebruiksaanwijzing gelezen en begrepen hebben. Het niet volgen van de indicaties, contra-indicaties, beperkingen, waarschuwingen en voorzorgsmaatregelen kan resulteren in complicaties.
- Niet gebruiken na de uiterste gebruiksdatum.
- De DCB bevat paclitaxel, een bekend genotoxine. Mannen moeten gedurende 30 dagen na de behandeling bescherming (een condoom) gebruiken tijdens de geslachtsgemeenschap.
- Let op tekenen van anafylaxie of overgevoeligheid voor paclitaxel.
- Gebruik nooit lucht of een ander gasvormig medium om de DCB op te blazen.
- Tijdens gebruik moet de DCB onder directe visualisatie middels cystoscopie of hoogwaardige fluoroscopie worden gemanipuleerd.
- Manipuleer de DCB nooit in opgeblazen staat.
- Als er op enig moment tijdens het inbrengen weerstand wordt ervaren, mag het opvoeren niet worden geforceerd. Weerstand kan het hulpmiddel of het lumen beschadigen. Trek de katheter voorzichtig terug.
- Mannen met seksuele partners die zwanger kunnen worden, moeten een con doom gebruiken gedurende een periode van ten minste 90 dagen na de behandeling.
- De bijwerkingen van paclitaxel en de waargenomen symptomen zijn voornamelijk afgeleid uit onderzoek naar intraveneuze infusie van het geneesmiddel voor de behandeling van kankerpatiënten en omvatten:
  - chromosomale afwijkingen en risico op kanker;
  - schade aan de foetus, bij blootstelling van zwangere vrouwen;
  - anafylaxie en overgevoeligheid voor paclitaxel;
  - remming van de genezing van de urethra na de ingreep;
  - myelosuppressie waaronder neutropenie, leukopenie, trombocytopenie, anemie;
  - aritmie;
  - perifere neuropathie;
  - myalgie of artralgie;
  - alopecie;
  - hypotensie;
  - misselijkheid, braken of diarree;
  - verhoogde bilirubine, ALP en AST;
  - de mogelijke gevolgen voor de lever en nieren zijn onbekend en niet be studeerd.

De hoeveelheid paclitaxel die tijdens de Optilume DCB-ingreep plaatselijk wordt af-gegeven, is aanzienlijk kleiner dan één dosis voor systemische chemotherapie zoals verstrekt aan kankerpatiënten, en het geneesmiddel lijkt voornamelijk in de urethra gelokaliseerd te blijven.

6.0 VOORZORGSMAATREGELEN

- Altijd opblazen met een steriele vloeistof (steriele fysiologische zoutoplossing of een 50%-contrastmengsel). Nooit opblazen met lucht, kooldioxide of een ander gas. De DCB mag niet verder worden opgeblazen dan de aangegeven barstdruk (rated burst pressure, RBP). Blaas de ballon niet te ver op.
- Ballonkatheters zijn bedoeld voor gebruik door getrainde artsen met ervaring in de technieken voor ballonkatheterdilatatie.
- Gebruik van een balloninflatiehulpmiddel met drukmeter voor het goed reguleren van de ballondruk wordt aanbevolen.
- Aspireer de ballon volledig alvorens het hulpmiddel voorzichtig uit de urethra te verwijderen. Het uitoefenen van overmatige kracht om de ballon terug te trekken kan weefseltrauma veroorzaken.
- Inspecteer de DCB en de verpakking zorgvuldig voorafgaand aan het gebruik. Gebruik de katheter niet als deze beschadigd is of als de grootte, vorm of toestand ongeschikt is voor de beoogde ingreep.
- Het ballondeel van de DCB niet onderdompelen in of afnemen met vloeistof, omdat dit de integriteit van de geneesmiddelcoating kan beschadigen of aantasten. Vervang een DCB indien de ballon voorafgaand aan het gebruik in contact is geweest met vloeistof.
- Gebruik droge, steriele handschoenen of droge gaasjes om de DCB voorafgaand aan het gebruik te hanteren. Contact met het gecoate ballondeel van het hulp middel moet zo veel mogelijk worden beperkt.

- Blaas de DCB nooit op buiten het lichaam of voordat de doelstrictuur wordt bereikt, omdat hierdoor de integriteit van de coating kan worden verstoord.
- Probeer de DCB niet op te voeren door een cystoscoop met een kleinere French-maat dan aangegeven op het etiket.
- De werklengte van de DCB moet de volledige lengte van de doelstrictuur bedekken.
- Voor een goede geneesmiddelafgifte aan de doelstrictuur moet de coating minimaal 60 seconden in de urethra hydrateren alvorens de DCB op te blazen. Handhaaf de inflatie van de DCB ten minste 5 minuten. Voor een optimale strictuurdilatatie kan naar goeddunken van de gebruiker een inflatieduur van > 5 minuten worden aangehouden.
- Als er sprake is van een defect voorafgaand aan of tijdens de inflatie, vervangt u de DCB en blaast u deze op zoals nodig voor de ingreep. Als het defect na het opblazen tot de RBP plaatsvindt, herhaalt u de DCB-ingreep niet.
- Na gebruik kan dit product een potentieel biologisch gevaar vormen. Hanteer dit product en voer dit product af in overeenstemming met de geaccepteerde medische praktijk en toepasselijke lokale regelgeving.
- Zorgverleners moeten het gebruik van latex handschoenen vermijden om mogelijke allergische reacties bij patiënten met een allergie voor latex te voorkomen.
- Voorafgaand aan gebruik van de Optilume DCB moet de doellaesie in het urethralumen worden voorbereid met een gepaste, door de behandelend arts te bepalen methode voor lumenpreparatie.
- In het klinisch onderzoek Robust I werd lumenpreparatie met alleen predilatatie met een ongecoate ballonkatheter of DVIU bestudeerd.
- In klinische onderzoeken was visuele bevestiging van significante vernauwing (≤ 12F urethrale diameter) via cystoscopie of urethrogram vereist en inschrijving was beperkt tot patiënten die subjectieve en objectieve symptomen van urethrastrictuur vertoonden (International Prostate Symptom Score [IPSS] > 13, maximale urinestroomsnelheid < 15 ml/sec). De proefpersonen hadden ten minste één eerdere endoscopische behandeling ondergaan voordat ze aan de klinische onderzoeken deelnamen.
- Dit klinische onderzoek gaf geen ondersteunende veiligheids- en werkzaamheidsgegevens voor de behandeling van structuren bij patiënten met:
  - BPH;
  - radicale prostatectomie;
  - bekkenbestraling;
  - botoxbehandeling;
  - meer dan 1 strictuur;
  - eerdere urethroplastiek in de anterieure urethra;
  - bacteriële urethritis of gonorroe;
  - aanwezigheid van een penisprothese, sfincterprothese of urethra-/prostaatstent;
  - bevestiging van neurogene blaas, sfincterafwijkingen of slechte werking van de detrusor;
  - diagnose van lichen sclerosus of eerdere correctie voor hypospadie;
  - voorgeschiedenis in de afgelopen 5 jaar van blaas- of prostaatcarcinoom;
  - strictuur vanwege balanitis xerotica obliterans (BXO);
  - urethratumoren of peniskanker.

7.0 GEBRUIK BIJ SPECIALE GROEPEN PATIËNTEN

De veiligheid en werkzaamheid van de urethrale DCB zijn niet vastgesteld voor pediatrische patiënten (< 18 jaar) of voor vrouwen. Gebruik van de urethrale DCB bij patiënten ≥ 18 jaar oud wordt ter discretie van de arts gelaten.

8.0 MOGELIJKE COMPLICATIES

De mogelijke complicaties die worden geassocieerd met het gebruik van de Optilume DCB-katheter zijn gelijk aan de complicaties die worden geassocieerd met standaard-dilatatieprocedures van de urethra. De mogelijke complicaties kunnen onder andere het volgende omvatten:

- pijn en gevoeligheid;
- blaasspasme als gevolg van plaatsing van de Foley-katheter;
- weefseltrauma in omringende structuren, inclusief urethraletsel;
- hematurie;
- geneesmiddelreacties, allergische reactie op contrastmiddel dat is gebruikt tijdens diagnostisch urethrogram;
- urineweginfectie;
- weefselperforatie;
- terugkerende strictuur die aanvullende operatie vereist;
- incontinentie;
- strangurie;
- koorts;
- urineretentie.

9.0 INFORMATIE OVER HET GENEESMIDDEL

o WERKINGSMECHANISME

De urethrale DCB-coating bevat paclitaxel, een antimitotisch farmaceutisch middel dat specifiek bindt aan microtubuli en deze stabiliseert. Van paclitaxel is gemeld dat het de proliferatie en migratie van gladde spiercellen en fibroblasten alsmede de secretie van extracellulaire matrix remt. De combinatie van deze effecten kan resulteren in de remming van urotheelhyperplasie en daarmee van het opnieuw ontstaan van stricturen.

o GENEESMIDDELENINTERACTIE

Voor de urethrale DCB heeft geen formeel onderzoek naar geneesmiddeleninteractie plaatsgevonden. De respectievelijke gebruiksaanwijzingen voor alle geneesmiddelen die worden gebruikt in combinatie met de DCB moeten worden geraadpleegd voor mogelijke interacties met paclitaxel.

Rekening dient te worden gehouden met de kans op systemische en lokale geneesmiddelinteracties in de urethra bij een patiënt die een geneesmiddel gebruikt met een bekende interactie met paclitaxel of bij de besluitvorming een geneesmiddelbehandeling te starten bij een patiënt die met de DCB is behandeld. Het metabolisme van paclitaxel betreft katalysatie door cytochroom P450 iso-enzymen CYP2C8 en CYP3A4; het is een substraat van P-glycoproteïne. Er zou geneesmiddeleninteractie kunnen optreden met elk geneesmiddel dat deze iso-enzymen beïnvloedt. Vanwege het ontbreken van formeel onderzoek naar de geneesmiddeleninteractie is bij het toedienen van paclitaxel voorzichtigheid geboden.

o **CARCINOGENICITEIT, GENOTOXICITEIT EN REPRODUCTIEVE TOXICOLOGIE**
Er zijn geen langetermijnonderzoeken uitgevoerd om de mogelijke carcinogeniteit van het geneesmiddel paclitaxel of van de Optilume DCB te evalueren, en er zijn geen adequate en goed-gecontroleerde onderzoeken gepubliceerd over zwangere vrouwen of mannen die kinderen wensten te verwekken. Paclitaxel remt de celproliferatie via interactie met microtubuli. Een van de gevolgen hiervan is dat de hele chromosomen tijdens de celsplitsing verloren gaan. Deze indirecte werking is consistent met de positieve respons bij assays van de micronucleaire genotoxiciteit in vitro en in vivo, waarbij DNA-fragmenten werden aangetroffen. Er zijn tevens positieve resultaten gemeld voor chromosomale afwijkingen in primaire humane lymfocyten. Het is niet bekend of paclitaxel op een afzonderlijke wijze direct inwerkt op het DNA bij de generatie van breuken of fragmenten van DNA-strengen. Het is negatief in assays voor genmutatie, inclusief salmonella en CHO/HPRT.

Bij onderzoek met ratten en konijnen die paclitaxel intraveneus kregen toegediend tijdens de organogenese werd bewijs gezien van maternale toxiciteit, embryotoxiciteit en fetotoxiciteit bij doses van respectievelijk 1 en 3 mg/kg (circa 13 en 39 keer de dosis die wordt afgegeven door de Optilume DCB met coating met 5,5 mg paclitaxel [ballon van 10 mm x 50 mm], aangepast voor lichaamsgewicht). Er werd geen teratogeniciteit waargenomen bij zwangere ratten die een dagelijkse intraveneuze paclitaxeldosis van 1 mg/kg ontvingen (dagelijkse dosis van circa 13 keer de dosis van de Optilume DCB [10 mm x 50 mm], aangepast voor lichaamsgewicht).

De behandelend arts moet de mogelijke medische voordelen van de Optilume DCB-katheter afwegen tegen deze risico's op genotoxiciteit en risico's voor de voortplanting. WAARSCHUWING: De urethrale DCB bevat paclitaxel, een bekend genotoxine. Mannen moeten gedurende 30 dagen na de behandeling bescherming (een condoom) gebruiken tijdens de geslachtsgemeenschap.

10.0 WIJZE VAN LEVERING

De Optilume DCB-katheter wordt STERIEL geleverd (ethyleenoxidesterilisatie) en is uitsluitend bedoeld voor eenmalig gebruik. De DCB is verpakt in twee zakken (folie en Tyvek) in een doos met één exemplaar.

11.0 OPSLAG

De urethrale DCB moet in de originele verpakking op een droge locatie bij kamertemperatuur worden opgeslagen. Het hulpmiddel moet worden gebruikt vóór de uiterste gebruiksdatum op de verpakking.

12.0 AANBEVOLEN PRODUCTEN

Maak de volgende producten gereed met gebruikmaking van een steriele techniek:

- voerdraad met flexibele tip van de juiste maat (zie productetiket);
- cystoscoop (bij voorkeur flexibel);
- steriele fysiologische zoutoplossing;
- spuit van 10 ml;
- tweewegkraantje;
- inflatiehulpmiddel met manometer;
- contrastmedium (optioneel voor gebruik met fluoroscopisch geleide ingrepen).

13.0 GEBRUIKSAANWIJZING

13.1 VÓÓR GEBRUIK

Perioperatieve medicatie

Artsen wordt aangeraden de richtlijnen voor perioperatieve medicatie en voorbereiding voor een endoscopische ingreep in acht te nemen, inclusief preoperatieve toediening van een antibioticum waar gepast. Tevens wordt aangeraden voor aanvang van de ingreep orale NSAID's te geven.

Bij urineweginfectie (UWI) ten tijde van de behandeling moet de patiënt worden behandeld totdat de infectie is genezen voordat de behandeling kan plaatsvinden.

13.2 VOORBEREIDEN VAN DE DOELSTRICTUUR

Voorafgaand aan gebruik van de Optilume DCB in sterk gestenoteerde en moeilijk te passeren stricturen moet de doellaesie in de urethra worden gedilateerd met een gepaste preparatiemethode ter keuze van de behandelend arts (niet-gecoate dilatatieballon of DVIU). Verricht voordilatatie om de strictuur te laten 'meegeven'. Dit wordt gedefinieerd als dilatatie van de strictuur tot een lumendiameter die > 20 F of > 50% groter is dan het lumen van de niet-gedilateerde strictuur.

13.3 KEUZE VAN DE JUISTE MAAT VOOR HET HULPMIDDEL

Controleer of de diameter van de geselecteerde DCB bij de nominale druk hetzelfde is als of iets groter is dan de diameter van de gezonde urethra naast de distale rand van de strictuur. De ballondiameter gedeeld door de naastgelegen distale gezonde urethra wordt de uitrekratio genoemd.

Maatbepaling bulbaire urethra
Voor bulbaire stricturen mag de uitrekratio van 1,3 van de ballondiameter ten opzichte van de distale gezonde urethra niet worden overschreden. Als de grootte van de urethra tussen twee beschikbare maten valt, moet de grotere maat worden gebruikt, mits de uitrekratio minder is dan of gelijk is aan 1,3. Als de eerstvolgende grotere maat resulteert in een uitrekratio van meer dan 1,3 moet het kleinere hulpmiddel worden gebruikt.

Maatbepaling peniele urethra
Voor peniele urethrale stricturen moet de ballondiameter worden gekozen die het beste overeenkomt met de distale gezonde urethra. De uitrekratio van de peniele urethra mag niet groter zijn dan 1:1. Als de grootte van de urethra tussen twee beschikbare ballonmaten valt, moet de kleinere ballonmaat worden gebruikt OVERSCHRIJD de 1:1 uitrekratio NIET.

Voor zowel de peniele urethra als de bulbaire urethra moet de lengte van de DCB groter zijn dan de lengte van de te behandelen strictuur. De ballon moet zo lang zijn dat deze aan weerszijden van de strictuur circa 0,5-1 cm uitsteekt. Dit betekent bijvoorbeeld dat voor een strictuurlengte van 2 cm een DCB van 3 cm moet worden gekozen.

13.4 VOORBEREIDEN VAN DE BALLONKATHETER

Verwijder de lucht uit de DCB-katheter. Het ballonlumen van de katheter bevat lucht en deze lucht moet worden verwijderd om er zeker van te zijn dat de ballon alleen met vloeistof wordt gevuld wanneer de katheter in de urethra zit.

1. Sluit het kraantje in open stand aan op de aansluiting voor het opblazen van de ballon.
2. Sluit een spuit die voor de helft gevuld is met fysiologische zoutoplossing aan op het kraantje.
3. Houd de spuitpunt omlaag, trek de plunjer over het gehele volume van de spuit terug (waardoor maximale onderdruk wordt opgebouwd) en houd deze druk in stand totdat er geen luchtbellen meer uit de fysiologische zoutoplossing in de spuit komen. Herhaal dit naar vereist om alle lucht uit de katheter te verwijderen en deze door fysiologische zoutoplossing te vervangen. Houd de plunjer uitget rokken, sluit het kraantje om de onderdruk in stand te houden, en verwijder de spuit. Vul het inflatiehulpmiddel voor de helft met normale fysiologische zoutoplossing of met 1:1 contrastmiddel:fysiologische zoutoplossing als u fluoroscopie gebruikt, en verwijder de lucht uit de lijn.
4. Sluit het inflatiehulpmiddel aan op het kraantje op de ballonkatheter, open het kraantje en trek vacuüm op het inflatiehulpmiddel.

13.5 INBRENGEN VAN DE OPTILUME DCB

1. Positioneer met behulp van een cystoscoop een voerdraad van 0,038 inch met de flexibele tip opgerold in de blaas.
2. Verwijder de ballonbescherming van de tip van de DCB-katheter.

   Let op: *Voorzichtigheid is geboden bij het opvoeren van een met paclitaxel gecoate ballon door een cystoscoopsysteem. Beperk het hanteren tot een minimum en raak de ballon niet aan. Veeg de ballon niet af met een droog, nat of bevochtigd gaasje, of met een oplossingsmiddel dat de integriteit van de geneesmiddel-gecoate ballon kan beschadigen.*

3. Voer de DCB-katheter op in het werkkanaal van de cystoscoop. Of plaats de voerdraad en ballonkatheter separaat van het cystoscoopwerkkanaal, voor plaatsing naast elkaar.
4. Gebruik de cystoscoop om de plaatsing van de DCB te begeleiden. Of plaats de DCB onder fluoroscopie onder raadpleging van de radiopake markeringen onder de romp/kegel-overgang van de ballon.

   Let op: *Voer de voerdraad of de ballondilatatiekatheter niet verder op als u weerstand ondervindt zonder eerst de oorzaak van de weerstand te bepalen en deze te verhelpen.*

13.6 OPBLAZEN VAN DE OPTILUME DCB

Let op: *Inflatiehulpmiddelen kunnen met minimale inspanning een zeer hoge druk genereren. Het gebruik van een inflatiehulpmiddel met een hogedrukmeter wordt ten zeerste aanbevolen om de dilatatiekracht te optimaliseren, zodat de urethrastrictuur wordt opgeheven en het geneesmiddel in het opgerekte urotheel kan doordringen.*

1. Zorg dat de urethra met fysiologische zoutoplossing is gespoeld.
2. Plaats de DCB in de strictuur met de cystoscoop distaal van de ballon (van de blaas vandaan) om goede plaatsing van de ballon in de strictuur te kunnen visualiseren. Laat de onopgeblazen ballon ten minste 1 minuut op zijn plaats zitten voordat u deze opblaast. Controleer met behulp van fluoroscopie of de positie van de radiopake ballonmarkeringen correct is.
3. Blaas met het inflatiehulpmiddel de ballon op tot de nominale barstdruk. Overschrijd de aangegeven barstdruk (rated burst pressure, RBP) van de ballon niet. Houd de druk ten minste 5 minuten in stand, of totdat de gewenste mate van dilatatie is verkregen.
4. Leeg de ballon door met het inflatiehulpmiddel onderdruk op de ballon uit te oefenen. Nadat de ballon helemaal geleegd is, trekt u de voerdraad en DCB langzaam terug. Als u lichte weerstand ondervindt terwijl u de ballon verwijdert, draait u de katheter voorzichtig zodat de ballon zich om de katheterschacht wikkelt, waardoor het terugtrekken wordt vergemakkelijkt.

Let op: *Als u weerstand ondervindt wanneer u een voerdraad door een katheter via een cystoscoop verwijdert, STOP dan en verwijder deze samen tegelijkertijd als één geheel om beschadiging van de voerdraad, katheter of anatomie van de patiënt te voorkomen.*

5. Als er voorafgaand aan of tijdens het opblazen (tot minder dan de RMP) een productdefect optreedt, vervangt u de DCB en blaast u deze op zoals vereist voor de ingreep. Als het defect na het opblazen tot de RBP plaatsvindt, herhaalt u de DCB-ingreep niet.
6. Plaats een Foley-katheter met glijmiddel van 12-14 Fr en laat deze ten minste 2 dagen zitten, of volgens de zorgnorm, afhankelijk van de periode die het langste is.

13.7 COMPLIANTIESCHEMA

18 Fr (6 mm) x 30 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Druk	kPa		(mm) Ballon
6,0	600	**Nominaal**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**RBP**	10,44

Let op: *De nominale barstdruk mag niet worden overschreden. Raadpleeg het productetiket voor de nominale barstdruk. Opblazen tot voorbij de nominale barstdruk kan resulteren in het scheuren van de ballon. Als er sprake is van drukverlies in de ballon tijdens het opblazen of als de ballon scheurt tijdens dilatatie, moet de ingreep onmiddellijk worden gestaakt. Leeg de ballon voorzichtig en verwijder deze uit de urethra. Blaas de ballon niet opnieuw op.*

14.0 GARANTIE

Urotronic garandeert dat er redelijke zorg is betracht bij het ontwerpen en produceren van dit product. Deze garantie komt in de plaats van en sluit alle overige garanties uit die niet expliciet hierin zijn genoemd, expliciet dan wel impliciet van rechtswege of anderszins, met inbegrip van maar niet beperkt tot impliciete garanties voor een bepaald doel. Hantering, opslag, reiniging en sterilisatie van dit hulpmiddel, alsmede andere factoren met betrekking tot de patiënt, diagnose, behandeling, chirurgische ingrepen en andere aangelegenheden buiten de controle van Urotronic zijn rechtstreeks van invloed op het hulpmiddel en de resultaten die door het gebruik worden verkregen. De verplichting van Urotronic volgens deze garantie beperkt zich tot reparatie of vervanging van dit hulpmiddel en Urotronic is niet aansprakelijk voor eventuele incidentele of gevolgschade, beschadiging of onkosten die direct of indirect voortvloeien uit het gebruik van dit hulpmiddel. Urotronic aanvaardt geen aansprakelijkheid ten aanzien van hulpmiddelen die opnieuw zijn gebruikt, herverwerkt of gehersteriliseerd, en biedt geen garantie, expliciet dan wel impliciet, met inbegrip van maar niet beperkt tot voor een bepaald doel, ten aanzien van dergelijke hulpmiddelen.

15.0 ETIKETTERINGSSYMBOLEN

1	Inhoud 1 per doos
Rx only	Let op: Volgens de federale wetgeving van Verenigde Staten van Amerika is de verkoop van dit hulpmiddel beperkt tot aan of in opdracht van een arts.
	Verwijst naar de datum waarop het medische hulpmiddel is vervaardigd.
	Niet hersteriliseren
	Niet hergebruiken
	Niet gebruiken als de verpakking beschadigd is
	Breekbaar
	Uiterste gebruiksdatum
	Buiten bereik van zonlicht houden
	Droog bewaren
	Fabrikant
LATEX	Bevat geen latex
	Temperatuurlimiet 15 °C - 30 °C
	Let op: Raadpleeg de gebruiksaanwijzing
STERILE EO	Gesteriliseerd met ethyleenoxide
REF	Catalogusnummer
LOT	Partijnummer
CE 1434	CE-gemarkeerd volgens de richtlijn medische hulpmiddelen 93/42/EEG van de Europese Unie (aangemelde instantie # 1434)
EC REP	Geautoriseerde vertegenwoordiger van de Europese Unie

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Minneapolis, MN 55441
USA

EC REP
MDSS GmbH
Schiffgraben 41
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CE 1434

OPTILUME®

URETRALT LÆGEMIDDELBELAGT BALLONKATETER

Brugsanvisning

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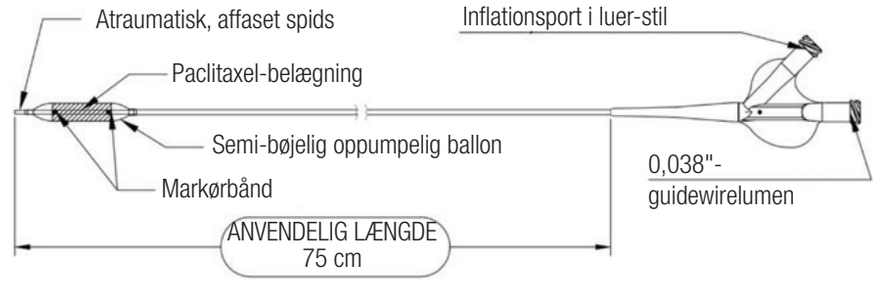
Indholdsfortegnelse

1.0 BESKRIVELSE AF ANORDNINGEN

1.1 Ballonkateter

Optilume uretralt lægemiddelbelagt ballon (DCB)-kateter er et over-the-wire (OTW)-kateter med et dobbeltlumen-design og en affaset, atraumatisk spids, som er kompatibelt med en 0,038" (0,97 mm)-guidewire og et fleksibelt cystoskop. Det har et dobbeltlumendesign og en affaset, atraumatisk spids. DCB anvendes til at udøve radialkraft med henblik på dilatation af snævre uretrasegmenter (strikturer). Kateterets distale ende er udformet med en semicompliant inflaterbar ballon, som er dækket af en patentbeskyttet belægning, der indeholder det aktive lægemiddel paclitaxel. Lægemiddelbelægningen dækker ballonlegemets arbejdslængde. Anordningen er udstyret med to røntgenfaste markørbånd, som angiver ballonens arbejdslængde.



Anordningen er steriliseret med ethylenoxid i en Tyvek-pose. Efter sterilisering forsegles det indpakkede kateter i en foliepose med tørremiddel og opbevares i en æske beregnet til en enkelt enhed. Hver DCB leveres med en beskyttende sheath, som dækker kateterdelen med den lægemiddelbelagte ballon. Der findes et ballon-complianceskema på Tyvek-posens mærkat.

1.2 Lægemiddelbelægning

Lægemiddelbelægningen består af den aktive lægemiddelingrediens paclitaxel og hjælpestoffer. Lægemiddelbelægningen dækker arbejdslængden på kateterets ballonkomponent. Lægemiddelbelægningen er jævnt fordelt over ballonens overflade med en koncentration på 3,5 µg/mm^2. Lægemiddelbelægningens væsentligste funktion er at frigive paclitaxel til uroteliet under fyldning af ballonen.

DCB-doseringsmatrix

Katalognummer	Diameter (Fr/mm)	Længde (mm)	Paclitaxeldosis (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

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2.0 TILSIGTET BRUG

Optilume uretralt lægemiddelbelagt ballon (DCB)-kateter er beregnet til behandling af anteriore ureterstrikturer hos voksne mænd.

3.0 INDIKATIONER

Optilume uretralt DCB-kateter bruges til at behandle mænd ≥ 18 år med generende urinvejssymptomer forbundet med recidiverende anterior ureterstriktur. Det er designet til anvendelse som dilatationsballon til en enkelt, dobbelt eller diffus anterior ureterstriktur med en længde på ≤ 3 cm eller som adjuverende behandling sammen med andre dilatationsanordninger og/eller procedurer.

4.0 KONTRAINDIKATIONER

Det uretrale lægemiddelbelagte ballon (DCB)-kateter er kontraindiceret til brug hos:

- Patienter med kendt overfølsomhed over for paclitaxel eller strukturelt relaterede stoffer.
- Patienter med læsioner, der ikke kan krydses med en 0,038”-guidewire.

5.0 ADVARSLER

- Det uretrale DCB leveres STERILT og er udelukkende til engangsbrug. Må ikke genbehandles eller resteriliseres. Genbehandling og resterilisering kan øge risikoen for patientinfektion og risikoen for at forringe anordningens ydeevne.
- Folieposen og den indvendige poses udvendige overflade er IKKESTERILE. INDHOLDET af den indvendige pose er STERILT. Skal anvendes omgående, når folieposen er blevet åbnet.
- Denne anordning må ikke anvendes, hvis der er infektion i uretra (UTI) eller blæren. En infektion skal være væk inden behandling af strikturen med Optilume DCB.
- DCB må udelukkende anvendes af læger, som har erfaring med og viden om de kliniske og tekniske aspekter af uretral ballondilatation.
- Lægen skal læse og forstå brugsanvisningen inden anvendelse af DCB. Manglende overholdelse af indikationer, kontraindikationer, begrænsninger, advarsler og forholdsregler kan medføre komplikationer.
- Må ikke anvendes efter udløbsdatoen.
- DCB indeholder paclitaxel, som er et kendt genotoksin. Mænd skal have beskyttet sex (have kondom på) i 30 dage efter behandlingen.
- Monitorér for tegn på anafylaksi eller overfølsomhed over for paclitaxel.
- Benyt aldrig luft- eller gasmedier til fyldning af DCB.
- Når DCB er i brug, skal den håndteres under direkte visualisering ved brug af cystoskopi eller under fluoroskopi af høj kvalitet.
- DCB må ikke håndteres i fyldt tilstand.
- Passage må ikke forceres, hvis der mødes modstand på noget tidspunkt under indføringsproceduren. Modstand kan medføre beskadigelse af anordningen eller lumenet. Træk forsigtigt kateteret ud.
- Mænd med seksuelle partnere i den fødedygtige alder skal anvende kondom i mindst 90 dage efter behandlingen.
- Bivirkninger over for paclitaxel og symptomer, der primært er observeret i studier af i.v.-infusion af lægemidlet som behandling til forsøgspersoner med cancer, omfatter
    - Kromosomafvigelser og risiko for cancer
    - Fosterskade, når en gravid kvinde eksponeres
    - Anafylaksi eller overfølsomhed over for paclitaxel
    - Hæmmet opheling af uretra efter indgrebet
    - Myelosuppression, herunder: neutropeni, leukopeni, thrombocytopeni, anæmi
    - Arytmi
    - Perifer neuropati
    - Myalgi eller artralgi
    - Alopeci
    - Hypotension
    - Kvalme, opkastning eller diarré
    - Forhøjet bilirubin, ALP og ASAT
    - En mulig indvirkning på lever og nyrere er ukendt og er ikke blevet undersøgt.

Mængden af paclitaxel, der gives lokalt under Optilume DCB-indgrebet, er meget lavere end en enkelt dosis systemisk kemoterapi, der gives til cancerpatienter, og lægemidlet synes hovedsageligt at forblive lokalt i uretra.

6.0 FORHOLDSREGLER

- Fyld altid med en steril væske (sterilt saltvand eller 50 % kontrastblanding). Fyld aldrig med luft, kuldioxid eller andre luftarter. DCB må ikke fyldes ud over det nominelle sprængningstryk (RBP). Ballonen må ikke fyldes for meget.
- Ballonkatetre er beregnet til anvendelse af læger, som er uddannet i og har erfaring med teknikker til ballonkateterdilatation.
- For at sikre korrekt regulering af ballontrykket anbefales brug af en ballonfyldningsanordning med trykmåler.
- Aspirer ballonen fuldstændigt, inden anordningen forsigtigt fjernes fra uretra. Hvis ballonen trækkes for kraftigt ud, kan det forårsage vævsskader.
- Efterse omhyggeligt DBC'en og pakningen inden brug. Kateteret må ikke anvendes, hvis det er beskadiget eller hvis dets størrelse, form eller tilstand er uegnet til det tilsigtede indgreb.
- Ballonsektionen på DCB må ikke nedsænkes i eller aftørres med nogen form for væske, da lægemiddelbelægningen kan blive beskadiget eller forringet. Udskift DCB, hvis ballonen har været i kontakt med væsker inden brug.
- Brug tørre, sterile handsker eller tørre gazekompresser til håndtering af DCB inden brug. Der skal udvises forsigtighed for at minimere kontakten med anordningens belagte ballondel.
- DCB må aldrig fyldes uden for kroppen, eller inden den har nået målstrikturen, da det kan beskadige belægningen.
- DCB må ikke føres gennem et cystoskop med en mindre French-størrelse end den, der er angivet på etiketten.
- DCB's arbejdslængde skal dække hele målstrikturens længde.

- For at opnå korrekt administration af lægemidlet til målstrikturen skal belægningen have tid til at hydrere i uretra i mindst 60 sekunder inden fyldning, og fyldningen af DCB skal opretholdes i mindst 5 minutter. For at optimere dilatation af strikturen kan der efter operatørens skøn anvendes længere fyldningstider > 5 minutter.
- Hvis der forekommer fejl ved produktet inden eller under fyldning, skal DCB udskiftes og fyldes i henhold til proceduren. Hvis fejlen opstår efter fyldning til RBP, må DCB-proceduren ikke gentages.
- Dette produkt kan efter brug udgøre en potentiel biologisk risiko. Det skal håndteres og bortskaffes i henhold til godkendt medicinsk praksis og gældende lokale forskrifter.
- Sundhedspersonale bør undgå at benytte latexhandsker for at forhindre mulige allergiske reaktioner hos patienter, som er allergiske over for latex.
- Det er nødvendigt at forberede det uretrale lumen ved mållæsionen ved hjælp af den relevante lumenforberedelsesmetode som fastsat af den behandlende læge, inden Optilume DCB tages i brug.
- Lumenforberedelse kun ved hjælp af prædilatation med et ubelagt ballonkateter eller DVIU er blevet undersøgt i det kliniske studie Robust I.
- I kliniske studier var visuel bekræftelse af signifikant striktur (≤ 12 F uretral diameter) via cystoskopi eller uretrografi påkrævet, og indskrivning var begrænset til patienter, der udviste subjektive og objektive symptomer på ureterstriktur (international prostatasymptomscore [IPSS] > 13, maks. urinstrømning < 15 ml/sek.). Forsøgspersonerne havde gennemgået mindst én tidligere endoskopisk behandling, før de tilmeldte sig de kliniske studier.
- Der er ikke fastlagt sikkerheds- og effektivitetsdata under den kliniske undersøgelse til støtte for behandling af strikturer hos patienter med:
  - BPH
  - Radikal prostatektomi
  - Stråling af bækkenet
  - Botox-behandling
  - Mere end 1 striktur
  - Tidligere uretraplastik i den forreste del af uretra
  - Bakteriel urinrørsbetændelse eller gonoré
  - Tilstedeværelse af penisimplantat med kunstig sphincter eller stent i uretra/prostata
  - Kendt neurogen blære, abnormiteter i sphincter eller dårlig funktion af detrusormusklen
  - Diagnosticeret med Lichen sclerosus eller tidligere operation for hypospadi
  - Carcinom i blæren eller prostata inden for de seneste 5 år
  - Striktur pga. balanitis xerotica obliterans (BXO)
  - Uretrale tumorer eller peniscancer

7.0 ANVENDELSE HOS SÆRLIGE POPULATIONER

Sikkerheden og virkningen af det uretrale DCB er ikke fastlagt for pædiatriske patienter (< 18 år) eller kvinder. Anvendelse af den uretrale DCB hos patienter ≥ 18 år sker efter lægens skøn.

8.0 MULIGE KOMPLIKATIONER

Mulige komplikationer i forbindelse med brugen af Optilume DCB-kateteret er de samme som dem, der forbindes med almene uretra-dilatationsprocedurer. Mulige komplikationer kan omfatte, men er ikke begrænset til:

- Smerte og ømhed
- Blærespasme som følge af anlæggelse af Foley-kateter
- Vævstraume i omgivende strukturer, herunder skade på uretra
- Hæmaturi
- Lægemiddelreaktioner, allergisk reaktion over for det kontrastmiddel, som anvendes under diagnostisk urethrogram
- Urinvejsinfektion
- Vævsperforation
- Recidiverende striktur, som kræver yderligere operation
- Inkontinens
- Dysuri
- Feber
- Urinretention

9.0 LÆGEMIDDELOPLYSNINGER

o VIRKNINGSMEKANISME

Den uretrale DCB-belægning indeholder paclitaxel, et anti-mitotisk lægemiddel, som specifikt binder sig til og stabiliserer mikrotubuli. Der har været indberetninger om, at paclitaxel hæmmer glat muskelcelle- og fibroblast-proliferation og -migration samt sekretion af ekstracellulært matrix. Kombinationen af disse virkninger kan forårsage hæmning af urothelial hyperplasi og derfor af recidiverende striktur.

o LÆGEMIDDELINTERAKTIONER

Der er ikke udført formelle interaktionsstudier med den uretrale DCB. Der henvises til de respektive brugsanvisninger til alle lægemidler, som benyttes sammen med DCB, vedrørende interaktioner med paclitaxel.

Der skal tages højde for potentialet for systemiske og lokale lægemiddelinteraktioner i uretra hos patienter, som tager et lægemiddel med kendte interaktioner med paclitaxel, eller når det besluttes at påbegynde lægemiddelbehandling hos en patient, som er blevet behandlet med DCB. Metabolismen for paclitaxel katalyseres af cytochrom-P450-isoenzymerne CYP2C8 og CYP3A4 og er et substrat af P-glykoprotein. Potentielle lægemiddelinteraktioner kan forekomme med ethvert lægemiddel, som indvirker på disse isoenzymer. Som følge af manglende formelle interaktionsstudier skal der udvises forsigtighed ved administration af paclitaxel.

o CARCINOGENICITET, GENOTOKSICITET OG REPRODUKTIV TOKSIKOLOGI

Der er ikke udført langvarige studier for at evaluere det carcinogene potentiale af lægemidlet paclitaxel eller af Optilume DCB, og der er ingen passende og velkontrollerede studier hos gravide kvinder eller hos mænd, der har til hensigt at få børn. Paclitaxel hæmmer celleproliferation ved at interagere med mikrotubuli, og en konsekvens af dette er tabet af hele kromosomer under celledeling. Denne indirekte virkning stemmer overens med positivt respons i

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in vitro- og in vivo-analyser af genotoksiciteten i mikronuklei, hvor DNA-fragmenter kan detekteres. Der er også indberettet positive resultater for kromosomafvigelser i primære humane lymfocytter. Det vides ikke, om paclitaxel har en separat, direkte indvirkning på DNA i dannelsen af DNA-strengbrud eller -fragmenter. Det er negativt i analyser for genmutation, herunder salmonella og CHO/HPRT.

Studier med rotter og kaniner, der fik paclitaxel i.v. under organogenese, påviste maternel toksicitet, embryotoksicitet og føtal toksicitet ved doser på hhv. 1 og 3 mg/kg (ca. 13 og 39 gange den dosis, der leveres af Optilume DCB belagt med 5,5 mg paclitaxel (10 mm x 50 mm ballon), justeret for kropsvægt). Der blev ikke observeret teratogenicitet hos drægtige rotter, der fik daglige doser af paclitaxel i.v. på 1 mg/kg (en daglig dosis på ca. 13 gange dosis fra Optilume DCB (10 mm x 50 mm), justeret for kropsvægt).

Den behandlende læge bør opveje de potentielle medicinske fordele ved Optilume DCB-kateteret mod disse genotoksiske risici og reproduktionsrisici. ADVARSEL: Den uretrale DCB indeholder paclitaxel, som er et kendt genotoksin. Mænd skal have beskyttet sex (have kondom på) i 30 dage efter behandlingen.

10.0 LEVERING

Optilume DCB-kateteret leveres STERILT og er udelukkende til engangsbrug (sterilisering med ethylenoxid). DCB leveres i et emballagesystem med dobbeltpose (folie og Tyvek-poser), som er pakket i en æske beregnet til en enkelt enhed.

11.0 OPBEVARING

Det uretrale DCB skal opbevares ved stuetemperatur på et tørt sted i den oprindelige emballage. Anordningen skal anvendes inden udløbsdatoen på emballagen.

12.0 ANBEFALEDE ARTIKLER

Klargør følgende emner ved brug af steril teknik:

- Guidewire i korrekt størrelse, med fleksibel spids (se produktmærkningen)
- Cystoskop (gerne fleksibelt)
- Sterilt saltvand
- 10 ml-sprøjte
- Tovejsstophane
- Fyldningsanordning med manometer
- Kontrastmiddel – Bemærk: Valgfrit til brug ved fluoroskopivejledte indgreb

13.0 BRUGERVEJLEDNING

13.1 INDEN BRUG

Medicinering under indgrebet

Det anbefales, at lægerne følger retningslinjerne for medicinering før indgrebet og forberedelse til et endoskopisk indgreb, herunder administration af et antibiotikum før indgrebet efter behov. Det anbefales også at give orale NSAID inden indgrebet.

Ved tilstedeværelse af urinvejsinfektion (UTI) på behandlingstidspunktet, skal patienten behandles, indtil infektionen er forsvundet, inden indgrebet kan foretages.

13.2 KLARGØRING AF MÅLSTRIKTUREN

Uretral prædilatation af målstrikturen ved hjælp af den rette forberedelsesmetode som fastsat af den behandlende læge (ubelagt dilatationsballon eller DVIU) anbefales ved strikturer, der er kraftigt stenoserede og vanskelige at krydse, inden anvendelse af Optilume DCB. Udfør en prædilatation for at få strikturen til at ”give sig”. Dette defineres som en dilateret striktur med en lumendiameter > 20 F eller > 50 % større end det ikke-dilaterede strikturlumen.

13.3 BESTEMMELSE AF ANORDNINGENS STØRRELSE

Bekræft, at diameteren på den valgte DCB-ballon ved det nominelle tryk er lig med eller lidt større end diameteren på den raske del af uretra, som støder umiddelbart op til strikturens distale afgrænsning. Ballondiameteren divideret med den umiddelbart tilstødende distale raske del af uretra, defineres som strækforholdet.

Valg af størrelse til uretra i bulbus
Ved strikturer i bulbus må strækforholdet mellem ballondiameteren og den distale raske uretra ikke være større end 1,3. Hvis uretras størrelse ligger mellem to tilgængelige størrelser af anordningen, skal den største af de to anordninger bruges, under forudsætning af at strækforholdet er mindre end eller lig med 1,3. Hvis den største af de to anordninger giver et strækforhold på over 1,3, skal den mindre anordning bruges.

Valg af størrelse til uretra i penis
Ved uretrastrikturer i penis skal der vælges den ballondiameter, der bedst matcher den distale raske uretra. Strækforholdet for uretra i penis må ikke være større end 1:1. Hvis størrelsen af uretra ligger mellem tilgængelige ballonstørrelser, skal den mindste ballonstørrelse vælges. Strækforholdet MÅ IKKE VÆRE STØRRE END 1:1.

DCB ballonen skal være længere end den striktur, der skal behandles både i uretra i penis og i bulbus. Ballonens længde skal gå ca. 0,5-1 cm ud over strikturen på begge sider. Eksempel: Hvis strikturlængden er 2 cm, skal der vælges en DCB ballon på 3 cm.

13.4 KLARGØRING AF BALLONKATETERET

Tøm DCB-kateteret for luft. Kateterets ballonlumen indeholder luft, og luften skal fortrænges for at sikre, at ballonen udelukkende er fyldt med væske, mens kateteret er i uretra.

1. Sæt stophanen i åben position på ballonens fyldningskonnektor.
2. Sæt en sprøjte, som er halvt fyldt med saltvand, på stophanen.
3. Træk – med sprøjtespidsen vendt nedad – stemplet tilbage til sprøjtens fulde volumen (dette danner maksimalt undertryk), og hold det, indtil der ikke kan ses luftbobler komme ud af saltvandet i sprøjten. Gentag efter behov for at udtømme luften fra kateteret og erstatte den med saltvand. Hold sprøjtestemplet trukket tilbage, drej stophanen for at opretholde vakuum, og fjern sprøjten. Fyld en fyldningsanordning halvt med normalt saltvand eller kontrastmiddel/saltvand i forholdet 1:1, hvis der benyttes fluoroskopi, og tøm luften ud af slangen.
4. Sæt fyldningsanordningen til stophanen på ballonkateteret, drej stophanen, og træk vakuum på fyldningsanordningen.

13.5 INDFØRING AF OPTILUME DCB

1. Placer ved hjælp af et cytoskop en 0,038” (0,97 mm) guidewire med den fleksible spids oprullet i blæren.

2. Fjern ballonbeskytteren fra spidsen af DCB-kateteret.

Forsigtig: *Der skal udvises forsigtighed ved fremføring af en ballon, som er belagt med paclitaxel, gennem et hvilket som helst cystoskopisk system. Minimer håndteringen og undgå at røre ved ballonen. Ballonen må ikke aftørres med tør, våd eller fugtet gaze eller nogen form for opløsningsmiddel, som kan skade den lægemiddelbelagte ballons integritet.*

3. Fremfør DCB-kateteret inden i cystoskopets arbejdskanal. Alternativt placeres guidewire og ballonkateter adskilt fra cystoskopets arbejdskanal med henblik på anlæggelse side om side.
4. Brug cystoskopet til at guide placeringen af DCB. Alternativt placeres DCB med fluoroskopi ved at bruge de røntgenfaste markørbånd, der sidder under overgangen mellem ballonens legeme og konus.

   Forsigtig: *Guidewiren eller ballondilatationskateteret må ikke fremføres, hvis der mødes modstand, medmindre årsagen til modstanden først er blevet fastlagt, og modstanden er blevet afhjulpet.*

13.6 FYLDNING AF OPTILUME DCB

Forsigtig: *Fyldningsanordninger kan opnå meget høje tryk ved minimal anstrengelse. Brug af en fyldningsanordning med højtryksmåler anbefales kraftigt for at optimere dilatationskraften på uretrastrikturen og muliggøre indtrængen af lægemidlet i uroteliet efter dilatation.*

1. Sørg for, at uretra gennemskylles med saltvand.
2. Anbring DCB gennem strikturen med cystoskopet distalt for ballonen (væk fra blæren) for at visualisere korrekt placering af ballonen gennem strikturen. Lad ballonen være i ikke-fyldt position i mindst 1 minut inden fyldning. Kontrollér, at ballonens røntgenfaste markører er i den korrekte position ved hjælp af fluoroskopi.
3. Fyld ballonen til det nominelle sprængningstryk ved hjælp af fyldningsanordningen. Ballonens nominelle sprængningstryk (RBP) må ikke overskrides. Oprethold tryk i mindst 5 minutter, eller indtil den ønskede dilatation er opnået.
4. Tøm ballonen ved at anvende vakuum på ballonen med fyldningsanordningen. Når ballonen er helt tømt, trækkes guidewire og DCB langsomt ud. Hvis der mødes let modstand, når ballonen fjernes, drejes kateteret forsigtigt for at hjælpe ballonen med at folde sig rundt om kateterskaftet, hvorved udtrækningen lettes.

   Forsigtig: *Hvis der mødes modstand, når en guidewire fjernes gennem et kateter gennem et cystoskop, skal man STOPPE og fjerne dem sammen på samme tid som én enhed for at forhindre skader på guidewiren, kateteret eller patientens anatomi.*

5. Hvis der er fejl ved produktet inden eller under fyldning (men så længe trykket er under RBP), udskiftes DCB, og ballonen fyldes ifølge proceduren. Hvis der sker en fejl efter fyldning til RBP, må DCB-proceduren ikke gentages.
6. Indfør et 12-14 Fr smurt Foley-kateter, og lad det sidde i mindst 2 dage eller ifølge standardbehandling, hvad end der er længst.

13.7 COMPLIANCE-SKEMA

18 Fr (6 mm) x 30 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	5.87 (18 Fr)
8,0	800		6.03
10,0	1000		6.16
12,0	1200	**RBP**	6.25

24 Fr (8 mm) x 30 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	8.00 (24 Fr)
8,0	800		8.20
10,0	1000		8.37
12,0	1200	**RBP**	8.54

30 Fr (10 mm) x 30 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Tryk	kPa		(mm) Ballon
6,0	600	**Nominelt**	9.98 (30 Fr)
8,0	800		10.23
10,0	1000	**RBP**	10.44

Forsigtig: *Det nominelle sprængningstryk må ikke overskrides. Se produktetiketten vedrørende nominelle sprængningstryk. Fyldning ud over det nominelle sprængningstryk kan få ballonen til at briste. Indgrebet skal omgående afbrydes, hvis der opstår tryktab i ballonen under fyldning, eller hvis ballonen brister under dilatation. Tøm forsigtigt ballonen, og fjern den fra uretra. Må ikke genopfyldes.*

14.0 GARANTI

Urotronic garanterer, at der er blevet udvist rimelig omhu ved udformning og fremstilling af dette produkt. Denne garanti træder i stedet for og udelukker alle andre garantier, som ikke udtrykkeligt er fremsat heri, hvad enten de er udtrykte eller underforståede ved lovkraft eller på anden vis, herunder, men ikke begrænset til, enhver underforstået garanti til et specifikt formål. Håndtering, opbevaring, rengøring og sterilisering af denne anordning samt andre faktorer, som vedrører patienten, diagnosen, behandlingen eller de kirurgiske indgreb, samt andre forhold som Urotronic ikke har kontrol over, indvirker direkte på anordningen og de resultater, der opnås ved anvendelse af den. Urotronics forpligtelse under denne garanti er begrænset til reparation eller udskiftning af denne anordning, og Urotronic hæfter ikke for nogen hændelige skader eller følgeskader, tab eller omkostninger, som direkte eller indirekte opstår som følge af brugen af denne anordning. Urotronic påtager sig intet erstatningsansvar, hvad angår genanvendte, genbehandlede eller resteriliserede anordninger, og giver ingen garantier, hverken udtrykte eller underforståede, herunder, men ikke begrænset til, til et specifikt formål, hvad angår sådanne anordninger.

15.0 ANVENDTE SYMBOLER PÅ ANORDNINGENS ETIKETTER

1	1 stk. pr. æske
Rx only	Forsigtig: Føderal lovgivning i USA begrænser salget af denne anordning til læger eller på en læges bestilling.
	Angiver den dato, den medicinske anordning blev fremstillet.
	Må ikke resteriliseres
	Må ikke genanvendes
	Må ikke anvendes hvis emballagen er beskadiget
	Skrøbelig
	Udløbsdato
	Beskyttes mod sollys
	Opbevares tørt
	Fabrikant
LATEX	Indeholder ikke latex
	Temperaturgrænse 15 °C - 30 °C
	Forsigtig: Se brugsanvisningen
STERILE EO	Steriliseret med ethylenoxid
REF	Katalognummer
LOT	Lotnummer
CE 1434	CE-mærket i henhold til Den Europæiske Unions direktiv om medicinsk udstyr 93/42/EØF (bemyndiget organ nr. 1434)
EC REP	Autoriseret repræsentant i Den Europæiske Union

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CE 1434

EC REP MDSS GmbH
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OPTILUME®

VIRTSAPUTKEN LÄÄKEPINNOITETTU PALLOKATETRI

Käyttöohjeet

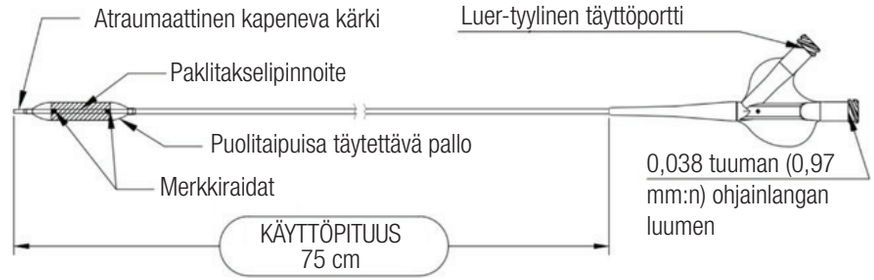
SUOMEN

Sisällysluettelo

1.0 LAITTEEN KUVAUS

1.1 Pallokatetri

Virtsaputken lääkepinnoitettu Optilume-pallokatetri (DCB-katetri) on 0,97 mm:n (0,038 tuuman) ohjainlangan ja joustavan kystoskoopin kanssa yhteensopiva, langan yli vietävä (OTW) katetri, jossa on kaksoisluumen ja kapeneva atraumaattinen kärki. DCB-katetria käytetään ahtaiden virtsaputkisegmenttien (striktuuroiden) laajentamiseen radiaalivoimaa kohdistamalla. Katetrin distaalipäässä on puolitaipuisa täytettävä pallo, joka on päällystetty yksinoikeudella valmistetulla, vaikuttavaa lääkeainetta paklitakselia sisältävällä pinnoitteella. Lääkepinnoite peittää pallon rakenteen työskentelypituuden. Laitteessa on kaksi röntgenpositiivista merkkiraitaa, jotka ilmaisevat pallon työskentelypituuden.



Laite on steriloitu eteenioksidilla Tyvek-pussissa. Steriloinnin jälkeen pussissa oleva katetri on suljettu foliopussiin kuivausaineen kanssa ja asetettu yhden laitteen laatikkoon. Jokainen DCB katetri toimitetaan katetrin lääkepinnoitetun pallo-osion peittävän suojuksen kanssa. Pallon yhteensopivuuskaavio sijaitsee Tyvek-pussin etiketissä.

SUOMEN

1.2 Lääkepinnoite

Lääkepinnoite koostuu vaikuttavasta lääkeaineesta paklitakselista ja apuaineista. Lääkepinnoite peittää katetrin pallo-osan sen työskentelypituudelta. Lääkepinnoite peittää pallon pinnan tasaisesti pitoisuudella 3,5 µg/mm^2. Lääkepinnoitteen tärkein toiminnallinen ominaisuus on, että se sallii paklitakselin vapautumisen uroteeliin pallon täyttämisen aikana.

DCB-katetrin annostelumatriisi

Luettelonumero	Halkaisija (Fr/mm)	Pituus (mm)	Paklitakseliannos (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

2.0 KÄYTTÖTARKOITUS

Virtsaputken lääkepinnoitettu Optilume-pallokatetri (DCB-katetri) on tarkoitettu aikuisten miesten anteriorisen virtsaputken striktuuroiden hoitoon.

3.0 KÄYTTÖAIHEET

Virtsaputken Optilume-DCB-katetria käytetään sellaisten ≥ 18-vuotiaiden miesten hoitoon, joilla on anteriorisen virtsaputken toistuviin striktuuroihin liittyviä häiritseviä virtsaoireita. Se on suunniteltu käytettäväksi pallolaajennuskatetrina hoidettaessa virtsaputken yksittäisiä, diffuuseja tai tandem-striktuuroita, jotka ovat pituudeltaan ≤ 3 cm, tai lisähoitona muiden laajennuslaitteiden ja/tai -toimenpiteiden kanssa.

4.0 VASTA-AIHEET

Virtsaputken lääkepinnoitettu pallolaajennuskatetri (DCB-katetri) on vasta-aiheinen seuraavissa tapauksissa:

- potilaat, joilla on tunnettu yliherkkyys paklitakselille tai rakenteellisesti samankaltaisille yhdisteille
- Potilaat, joilla on leesioita, joita ei voi ylittää 0,97 mm:n (0,038 tuuman) ohjainlangalla.

5.0 VAROITUKSET

- Virtsaputken DCB-katetri toimitetaan STERIILINÄ vain kertakäyttöön. Älä käsittele tai steriloi uudelleen. Uudelleenkäsittely tai uudelleensterilointi voi lisätä potilaan infektioriskiä ja laitteen vaarantuneen suorituskyvyn riskiä.
- Foliopussi ja sisemmän pussin ulkopinta ovat EPÄSTERIILEJÄ. Sisemmän pussin SISÄLTÖ on STERIILI. Käytä välittömästi foliopussin avaamisen jälkeen.
- Älä käytä tätä laitetta, jos potilaalla on virtsatieinfektio (UTI) tai virtsarakkoinfektio. Infektio on hoidettava ennen striktuuran hoitoa Optilume DCB -katetrilla.
- DCB-katetria saavat käyttää vain lääkärit, joilla on kokemusta ja tietämystä virtsaputken pallolaajennuksen kliinisistä ja teknisistä näkökohdista.
- Ennen DCB-katetrin käyttöä lääkäreiden on luettava ja ymmärrettävä käyttöohjeet. Käyttöaiheiden, vasta-aiheiden, rajoitusten, varoitusten ja varotoimien noudattamatta jättäminen voi aiheuttaa komplikaatioita.
- Älä käytä viimeisen käyttöpäivän jälkeen.
- DCB-katetri sisältää paklitakselia, joka on tunnettu genotoksiini. Miehet saavat harrastaa vain turvaseksiä (heidän on käytettävä kondomia) 30 päivän ajan hoidon jälkeen.
- Tarkkaile potilasta anafylaksian tai paklitakseliyliherkkyyden varalta.
- Älä koskaan käytä ilmaa tai mitään kaasua DCB-katetrin täyttämiseen.
- Käytön aikana DCB-katetria on käsiteltävä suorassa näköyhteydessä virtsarakon tähystyksen tai korkealaatuisen läpivalaisun avulla.
- Älä käsittele DCB-katetria sen ollessa täytetyssä tilassa.
- Jos tunnet vastustusta milloin tahansa sisäänvientitoimenpiteen aikana, älä vie katetria sisään väkisin. Vastustus voi vahingoittaa laitetta tai luumenia. Vedä katetri varovasti pois.
- Miesten, joiden seksikumppani voi tulla raskaaksi, on käytettävä kondomia vähintään 90 päivää hoidon jälkeen.
- Paklitakselin aiheuttamat haittavaikutukset ja havaitut oireet on kerätty pääasiassa syöpäpotilaille lääkkeen suonensisäistä infuusiota käsittelevistä tutkimuksista, kuten:
    - kromosomipoikkeavuudet ja syöpäriski
    - sikiövauriot raskaana olevan naisen altistuessa
    - anafylaksia ja yliherkkyys paklitakselille
    - virtsaputken paranemisen estyminen toimenpiteen jälkeen
    - luuydinlama, kuten neutropenia, leukopenia, trombosytopenia, anemia
    - rytmihäiriö
    - perifeerinen neuropatia
    - lihaskipu tai nivelkipu
    - alopesia
    - matala verenpaine
    - pahoinvointi, oksentelu tai ripuli
    - kohonnut bilirubiini, ALP ja AST
    - mahdollisia vaikutuksia maksaan ja munuaisiin ei tunneta eikä niitä ole tutkittu.

Paikallisesti annettavan paklitakselin määrä Optilume DCB -toimenpiteen aikana on paljon pienempi kuin yksittäinen annos syöpäpotilaille annettavassa systeemisessä kemoterapiassa, ja lääke vaikuttaa pääasiallisesti jäävän paikallisesti vain virtsaputken alueelle.

6.0 VAROTOIMET

- Täytä aina steriilillä nesteellä (steriilillä keittosuolaliuoksella tai 50-prosenttisella varjoaineseoksella). Älä koskaan täytä ilmalla, hiilidioksidilla tai millään muulla kaasulla. DCB katetria ei saa täyttää nimellisen murtumispaineen (RBP) yli. Älä ylitäytä palloa.
- Pallokatetrit on tarkoitettu pallokatetrilaajennukseen koulutettujen ja siinä kokeneiden lääkäreiden käyttöön.
- Pallon paineen asianmukaisen sääntelyn varmistamiseksi suositellaan pallontäyttölaitteen ja painemittarin käyttöä.
- Aspiroi pallo kokonaan tyhjäksi, ennen kuin poistat laitteen varovasti virtsaputkesta. Liiallinen voimankäyttö palloa pois vedettäessä voi aiheuttaa kudosvaurion.
- Tarkista DCB-katetri ja pakkaus huolellisesti ennen käyttöä. Älä käytä katetria, jos se on vaurioitunut tai jos sen koko, muoto tai kunto ei sovellu aiottuun toimenpiteeseen.
- Älä upota DCB-katetrin pallo-osiota mihinkään nesteeseen tai pyyhi sitä millään nesteellä, sillä tämä voi vahingoittaa lääkepinnoitetta tai vaarantaa sen. Vaihda DCB-katetri, jos sen pallo on joutunut kosketuksiin nesteiden kanssa ennen käyttöä.
- Käytä kuivia steriilejä käsineitä tai kuivia sideharsotaitoksia DCB-katetrin käsittelyyn ennen käyttöä. Kontaktia laitteen pinnoitetun pallo-osion kanssa on vältettävä.
- Älä täytä DCB-katetria kehon ulkopuolella tai ennen kohdestriktuuran saavuttamista, sillä tämä voi heikentää pinnoitteen eheyttä.

- Älä yritä viedä DCB-katetria etiketissä ilmaistua F-kokoa pienemmän kystoskoopin läpi.
- DCB-katetrin työskentelypituuden on katettava kohdestriktuuran koko pituus.
- Jotta asianmukainen lääkkeenanto kohdestriktuuraan onnistuisi, anna pinnoitteen hydratoitua virtsaputkessa vähintään 60 sekunnin ajan ennen täyttämistä ja pidä DCB-katetri täytettynä vähintään 5 minuutin ajan. Striktuuran laajennus voidaan optimoida pidentämällä täyttöaikaa yli 5 minuuttiin toimenpiteen suorittajan harkinnan mukaan.
- Jos tuotteessa on vika ennen täyttöä tai sen aikana, vaihda DCB-katetri uuteen ja täytä se toimenpiteen mukaisesti. Jos vika havaitaan nimelliseen murtumispaineeseen täyttämisen jälkeen, älä toista DCB-toimenpidettä.
- Käytön jälkeen tämä tuote voi olla biovaarallinen. Käsittele ja hävitä hyväksyttyjen lääketieteellisten käytäntöjen ja paikallisten säännösten mukaisesti.
- Terveydenhuollon ammattilaisten on vältettävä lateksikäsineiden käyttöä lateksille allergisten potilaiden mahdollisten allergisten reaktioiden välttämiseksi.
- Hoitavan lääkärin määrittämä kohdeleesion mukainen virtsaputken luumenin valmistelu soveltuvalla luumenin valmistelumenetelmällä on tehtävä ennen Optilume DCB -katetrin käyttöä.
- Luumenin valmistelua vain esilaajentamalla pinnoittamattomalla pallokatetrilla tai uretromialla näkökontrollissa (DVIU) tutkittiin kliinisessä Robust I -tutkimuksessa.
- Kliinisissä tutkimuksissa huomattavan striktuuran (≤ 12 F:n virtsaputken läpimitta) visuaalinen varmistus oli tehtävä kystoskopialla tai uretrogrammilla, ja tutkimukseen otettiin vain potilaita, joilla oli subjektiivisia ja objektiivisia virtsaputken striktuuran oireita (International Prostate Symptom Score [IPSS] > 13, virtsan huippuvirtausnopeus < 15 ml/s). Tutkimushenkilöille oli tehty vähintään yksi aiempi endoskooppinen hoito ennen kliinisiin tutkimuksiin osallistumista.
- Kliinisen tutkimuksen aikana ei saatu turvallisuus- ja tehokkuustietoja, jotka tukisivat striktuurojen hoitoa potilailla, joilla on jokin seuraavista:
  - eturauhasen liikakasvu (BPH)
  - radikaali prostatektomia
  - lantionalueen sädehoito
  - Botox-hoito
  - enemmän kuin 1 striktuura
  - aiempi uretroplastia anteriorisessa virtsaputkessa
  - bakteeriperäinen uretriitti tai tippuri
  - penisimplantti, keinotekoinen sulkija tai virtsaputken/eturauhasen stentti
  - tunnetut neurogeeniset virtsarakon/sulkijan poikkeavuudet tai alasvetäjäli haksen heikko toiminta
  - diagnosoitu valkojäkälä tai aiempi hypospadian korjaus
  - viimeisen 5 vuoden aikainen virtsarakon tai eturauhasen karsinoomahistoria
  - umpeuttavan terskatulehduksen (BXO) aiheuttama striktuura
  - virstaputken kasvaimet tai penissyöpä.

7.0 KÄYTTÖ ERITYISRYHMILLE

Virtsaputken DCB-katetrin turvallisuutta ja tehokkuutta ei ole vahvistettu pediatrisille potilaille (< 18-vuotiaat) tai naisille. Virtsaputken DCB-katetrin käyttö ≥ 18-vuotiaille ja sitä vanhemmille on lääkärin harkinnan varaista.

8.0 MAHDOLLISET KOMPLIKAATIOT

Optilume-DCB-katetrin käyttöön liittyvät mahdolliset komplikaatiot ovat samankaltaisia kuin tavallisiin virtsaputken laajennustoimenpiteisiin liittyvät komplikaatiot. Mahdollisia komplikaatioita voivat olla muun muassa seuraavat:

- kipu ja arkuus
- Foley-katetrin asetuksesta johtuvat virtsarakon spasmit
- kudosvaurio ympäröivissä kudoksissa, kuten virtsaputken vauriot
- hematuria
- lääkereaktiot ja allergiset reaktiot virtsarakon diagnostisen röntgenkuvauksen aikana käytettävälle varjoaineelle
- virtsatieinfektio
- kudoksen puhkeaminen
- striktuuran uusiutuminen, joka edellyttää lisätoimenpidettä
- inkontinenssi
- dysuria
- kuume
- virtsaumpi.

9.0 LÄÄKETIEDOT

o VAIKUTUSMEKANISMI

Virtsaputken DCB-katetrin pinnoite sisältää paklitakselia, antimitoottista lääkeainetta, joka sitoutuu spesifisti mikrotubuluksiin ja stabiloi niitä. Paklitakselin on raportoitu estävän sileiden lihassolujen ja fibroblastien proliferaatiota ja migraatiota sekä soluväliaineen eritystä. Näiden vaikutusten yhdistelmä voi johtaa uroteelin liikakasvuun ja tämän myötä striktuuran uusiutumiseen.

o LÄÄKEYHTEISVAIKUTUKSET

Virtsaputken DCB-katetreja koskevia virallisia lääkeyhteisvaikutustutkimuksia ei ole tehty. Kaikkien DCB-katetrin kanssa yhdessä käytettävien lääkkeiden käyttöohjeet on tarkistettava paklitakselia koskevien yhteisvaikutusten varalta.

Systeemisten ja virtsaputken paikallisten lääkeyhteisvaikutusten mahdollisuus on otettava huomioon, jos potilas käyttää lääkettä, jolla on tunnettuja yhteisvaikutuksia paklitakselin kanssa, tai kun ollaan tekemässä päätöstä DCB-katetrilla hoidetun potilaan lääkehoidon aloittamisesta. Paklitakselin metabolia katalysoituu sytokromi P450-isoentsyymien CYP2C8 ja CYP3A4 avulla, ja se on P-glykoproteiinin substraatti. Mahdollisia lääkeyhteisvaikutuksia voi esiintyä minkä tahansa näihin isoentsyymeihin vaikuttavan lääkkeen kanssa. Koska virallisia lääkeyhteisvaikutustutkimuksia ei ole tehty, paklitakselin annossa on noudatettava varovaisuutta.

o KARSINOGEENISUUS, GENOTOKSISUUS JA LISÄÄNTYMISTOKSIKOLOGIA

Paklitakselin tai virtsaputken Optilume DCB -katetrin karsinogeenisuuden mahdollisuutta arvioivia pitkäaikaisia tutkimuksia ei ole tehty, eikä asianmukaisia ja hyvin kontrolloituja tutkimuksia käytöstä raskaana oleville naisille tai lapsen saamista yrittäville miehille ole julkaistu. Paklitakseli estää solujen proliferaation vaikuttamalla mikrotubuluksiin, mistä mm. seuraa kokonaisten kromosomien menettäminen solujen jakautumisen aikana. Tämä epäsuora vaikutus on yhtäpitävä DNA-fragmentteja havaitsevissa mikrotuman genotoksisuuden in vitro- ja in vivo -määrityksissä saatujen positiivisten tulosten kanssa. Positiivisia tuloksia on raportoitu myös ensisijaisten ihmisen lymfosyyttien kromosomipoikkeavuuksien osalta. Ei ole tiedossa, vaikuttaako paklitakseli erikseen suoraan DNA:han aiheuttamalla DNA-ketjun rikkoutumisia tai fragmentteja. Sen tulokset ovat negatiivisia määritettäessä geenimutaatiota, kuten salmonella- ja CHO/HPRT-mutaatioita.

Tutkimuksissa, joissa rotille ja kaniineille annettiin paklitakselia suonensisäisesti organogeneesin aikana, ilmeni todisteita toksisuudesta äidille, alkiolle ja sikiölle tutkittaessa 1 ja 3 mg/kg:n annoksia. (Nämä annokset ovat noin 13- ja 39-kertaisia verrattuna kehonpainoon suhteutettuun annokseen, jonka 5,5 mg:lla paklitakselia pinnoitettu Optilume DCB -katetri [10 × 50 mm:n pallo] antaa.) Teratogeenisyyttä ei havaittu raskaana olevilla rotilla, jotka saivat päivittäin paklitakseliannoksen 1 mg/kg suonensisäisesti (päivittäinen annos noin 13-kertainen verrattuna kehonpainoon suhteutettuun annokseen, jonka Optilume DCB -katetri [10 × 50 mm] antaa).

Hoitavan lääkärin on harkittavia mahdollisia Optilume DCB -katetrin käytöstä koituvia lääketieteellisiä hyötyjä nämä genotoksisuuteen ja lisääntymiseen liittyvät riskit huomioiden. VAROITUS: Virtsaputken DCB-katetri sisältää paklitakselia, joka on tunnettu genotoksiini. Miehet saavat harrastaa vain turvaseksiä (heidän on käytettävä kondomia) 30 päivän ajan hoidon jälkeen.

10.0 TOIMITUSTAPA

Optilume DCB -katetri toimitetaan STERIILINÄ vain kertakäyttöön (steriloitu eteenioksidilla). DCB-katetri on kahden pussin pakkausjärjestelmässä (folio- ja Tyvek-pussit) yhden laitteen laatikossa.

11.0 SÄILYTTÄMINEN

Virtsaputken DCB-katetria on säilytettävä huoneenlämmössä kuivassa paikassa alkuperäisessä pakkauksessaan. Laite on käytettävä ennen pakkaukseen merkittyä viimeistä käyttöpäivää.

12.0 SUOSITELTAVAT VÄLINEET

Valmistele seuraavat välineet noudattaen steriiliä menetelmää:

- sopivan kokoinen ohjainlanka, jossa on joustava kärki (katso tuotteen etiketti)
- kystoskooppi (mieluiten joustava)
- steriiliä keittosuolaliuosta
- 10 cc:n ruisku
- kaksisuuntainen sulkuhana
- täyttölaite, jossa on painemittari
- varjoainetta – huomautus: valinnainen läpivalaisuohjatuissa toimenpiteissä.

13.0 KÄYTTÖOHJEET

13.1 ENNEN KÄYTTÖÄ

Lääkitys ennen toimenpidettä, sen aikana ja sen jälkeen

On suositeltavaa, että lääkärit noudattavat endoskooppisille toimenpiteille annettuja ohjeistuksia ennen toimenpidettä annettavasta lääkityksestä ja valmisteluista sekä tarpeen mukaan ohjeistuksiin kuuluvaa ohjeistusta ennen toimenpidettä annettavista antibiooteista. Suun kautta annettavia NSAID-lääkkeitä suositellaan myös annettavaksi ennen toimenpidettä.

Jos potilaalla on virtsatieinfektio (UTI) hoidon aikana, tätä virtsatieinfektiota on hoidettava, kunnes se on parantunut, ennen kuin hoitotoimenpide voidaan tehdä.

13.2 KOHDESTRIKTUURAN VALMISTELU

Virtsaputken kohdestriktuuran esilaajennusta suositellaan erittäin stenosoituneille ja vaikeasti ohitettaville striktuuroille hoitavan lääkärin määrittämällä menetelmällä (pinnoittamaton laajennuspallo tai uretromia näkökontrollissa [DVIU]) ennen Optilume DCB -katetrin käyttöä. Tee esilaajennus striktuuran sivuun työntämistä varten. Tämän katsotaan onnistuneen, kun laajennetun striktuuran luumenin läpimitta on > 20 F tai > 50 % suurempi kuin laajentamattoman striktuuran luumen.

13.3 LAITTEEN KOON MÄÄRITTÄMINEN

Varmista, että valitun DCB-pallon halkaisija on nimellispaineessa sama tai hieman suurempi kuin striktuuran distaalireunan viereisen terveen virtsaputken halkaisija. Pallon halkaisijaa jaettuna viereisellä distaalisella terveellä virtsaputkella kutsutaan venytyssuhteeksi.

Bulbaarisen virtsaputken koko
Bulbaarisissa striktuuroissa pallon halkaisijan venytyssuhde distaaliseen terveeseen virtsaputkeen ei saa olla yli 1,3. Jos virtsaputken koko osuu saatavien laitekokojen väliin, käytä suurempaa laitekokoa, jos venytyssuhde on sillä korkeintaan 1,3. Jos suuremmalla koolla venytyssuhde on suurempi kuin 1,3, käytä pienempää laitetta.

Virtsaputken siitinosan koko
Valitse siittimessä olevissa virtsaputkistriktuuroissa pallon halkaisija, joka on lähimpänä distaalista tervettä virtsaputkea. Virtsaputken siitinosan venytyssuhde ei saa olla yli 1:1. Jos virtsaputken koko osuu saatavien pallokokojen väliin, valitse pienempi. ÄLÄ YLITÄ venytyssuhdetta 1:1.

Sekä virtsaputken siitinosan että bulbaarisen virtsaputken kohdalla DCB-pallon on oltava hoidettavaa striktuuraa pidempi. Pallon pituuden on yletyttävä noin 0,5–1 cm striktuuran yli sen molemmista päistä. Jos esimerkiksi striktuuran pituus on 2 cm, valitse 3 cm:n DCB-pallo.

13.4 PALLOKATETRIN VALMISTELU

Tyhjennä ilma DCB-katetrista. Katetrin pallon luumen sisältää ilmaa, ja ilma on korvattava siten, että pallossa on vain nestettä katetrin ollessa virtsaputkessa.

1. Liitä sulkuhana avoimessa asennossa pallon täyttöliittimeen.
2. Liitä keittosuolaliuoksella puoliksi täytetty ruisku sulkuhanaan.

3. Luo alipaine vetämällä mäntä taakse ruiskun koko tilavuuteen ja pidä siinä, kunnes ruiskussa olevassa keittosuolaliuoksessa ei näy enää ilmakuplia. Toista tarvittaessa, kunnes kaikki ilma on poistettu katetrista ja korvattu suolaliuoksella. Pidä mäntä takana, ylläpidä alipaine kääntämällä sulkuhanaa ja poista ruisku. Täytä täyttölaite puoliksi normaalilla keittosuolaliuoksella tai 1:1-varjoaineella – läpivalaisua käytettäessä keittosuolaliuoksella – ja tyhjennä ilma linjasta.
4. Liitä täyttölaite pallokatetrin sulkuhanaan, käännä sulkuhanaa ja vedä alipaine täyttölaitteeseen.

13.5 OPTILUME DCB:N SISÄÄNVIENTI

1. Vie 0,038 tuuman (0,97 mm:n) ohjainlanka, jossa on joustava kärki, kystoskoopin avulla kerälle virtsarakkoon.
2. Poista pallon suojus DCB-katetrin kärjestä.
   Huomio: Varovaisuutta on noudatettava, kun paklitakselilla päällystettyä palloa viedään minkä tahansa kystoskooppijärjestelmän läpi. Vältä liiallista käsittelyä äläkä kosketa palloa. Älä pyyhi palloa kuivalla, märällä tai liukastetulla harsolla tai millään liuottimella, joka voi vahingoittaa lääkepinnoitetun pallon eheyttä.
3. Vie DCB-katetria kystoskoopin työskentelykanavaa pitkin. Voit myös asettaa ohjainlangan ja pallokatetrin erilleen kystoskoopin työskentelykanavasta rinnakkain asetusta varten.
4. Ohjaa DCB-katetrin asettamista kystoskoopilla. Vaihtoehtoisesti voit asettaa pallon läpivalaisussa käyttämällä pallon rungon/kartion alla olevia röntgenpositiivisia merkkejä asettamisen apuna.

Huomio: *Älä vie ohjainlankaa tai pallolaajennuskatetria eteenpäin, jos tunnet vastustusta, ennen kuin olet määrittänyt vastustuksen syyn ja tehnyt korjaavat toimenpiteet.*

13.6 OPTILUME DCB:N TÄYTTÄMINEN

Huomio: *Täyttölaitteilla voidaan saavuttaa erittäin korkea paine hyvin vähäisellä vaivalla. Täyttölaitteen ja korkeapainemittarin käyttöä suositellaan vakavasti, jotta laajennusvoima voidaan optimoida niin, että virtsaputken striktuura antaa periksi ja lääke pääsee tunkeutumaan uroteelin.*

1. Varmista, että virtsaputki on huuhdeltu keittosuolaliuoksella.
2. Aseta DCB-katetri striktuuran mukaisesti niin, että kystoskooppi on distaalisesti palloon nähden (kauimpana rakosta), jotta voit tarkistaa pallon oikean asetumisen striktuuran päälle. Jätä täyttämätön pallo sijaintiin vähintään 1 minuutin ajaksi ennen pallon täyttämistä. Tarkista läpivalaisun avulla, että pallon röntgenpositiiviset merkit ovat oikeassa kohdassa.
3. Täytä pallo nimelliseen murtumispaineeseen täyttölaitteen avulla. Älä ylitä pallon nimellistä murtumispainetta (RBP). Pidä painetta yllä vähintään 5 minuutin ajan tai kunnes haluttu laajennus saavutetaan.
4. Tyhjennä pallo kohdistamalla siihen alipainetta täyttölaitteen avulla. Kun pallo on tyhjentynyt kokonaan, vedä ohjainlanka ja DCB-katetri hitaasti pois. Jos tunnet lievää vastustusta vetäessäsi palloa pois, kierrä katetria varovasti auttaaksesi palloa taittumaan katetrin varren ympärille ja helpottaaksesi pois vetämistä.

Huomio: *Jos tunnet vastustusta poistaessasi ohjainlankaa katetrin läpi ja kystoskoopin läpi, estä ohjainlangan, katetrin tai potilaan anatomian vahingoittuminen LOPETTAMALLA ja poistamalla ne yhtä aikaa yhtenä yksikkönä.*

5. Jos tuotteessa on vika ennen täyttöä tai sen aikana (täytön ollessa alle nimellisen murtumispaineen), vaihda DCB-katetri uuteen ja täytä se toimenpiteen mukaisesti. Jos vika havaitaan nimelliseen murtumispaineeseen täyttämisen jälkeen, älä toista DCB toimenpidettä.
6. Vie 12–14 Fr:n liukastettu Foley-katetri sisään ja jätä se paikalleen vähintään 2 vuorokaudeksi tai hoitostandardin mukaiseksi ajaksi. Noudata pidempää aikaa.

13.7 YHTEENSOPIVUUSKAAVIO

18 Fr (6 mm) x 30 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	6,11 (18 Fr)
8,0	800		6,23
10,0	1 000		6,34
12,0	1 200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	5,87 (18 Fr)
8,0	800		6,03
10,0	1 000		6,16
12,0	1 200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	7,98 (24 Fr)
8,0	800		8,16
10,0	1 000		8,32
12,0	1 200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	8,00 (24 Fr)
8,0	800		8,20
10,0	1 000		8,37
12,0	1 200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	9,83 (30 Fr)
8,0	800		10,09
10,0	1 000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(atm) Paine	kPa		(mm) Pallo
6,0	600	**Nimellinen**	9,98 (30 Fr)
8,0	800		10,23
10,0	1 000	**RBP**	10,44

Huomio: *Nimellistä murtumispainetta ei saa ylittää. Katso nimelliset murtumispaineet tuotteen etiketistä. Jos palloa täytetään yli nimellisen murtumispaineen, se voi rikkoutua. Jos paine pallon sisällä laskee täyttämisen aikana tai pallo rikkoutuu laajennuksen aikana, keskeytä toimenpide välittömästi. Tyhjennä pallo varovasti ja poista se virtsaputkesta. Älä täytä palloa uudelleen.*

14.0 TAKUU

Urotronic takaa, että tämän tuotteen suunnittelussa ja valmistuksessa on noudatettu kohtuullista huolellisuutta. Tämä takuu korvaa ja sulkee pois kaikki muut takuut, joita tässä ei ole nimenomaisesti määritetty, olivat ne sitten suoria tai epäsuoria lain mukaan tai muuten, mukaan lukien muun muassa kaikki epäsuorat tiettyä tarkoitusta koskevat takuut. Tämän laitteen käsittely, säilytys, puhdistus ja sterilointi sekä muut potilaaseen, diagnoosiin, hoitoon, kirurgisiin toimenpiteisiin ja muihin Urotronicin hallinnan ulkopuolella oleviin seikkoihin liittyvät tekijät vaikuttavat suoraan laitteeseen ja sen käytöstä saatuihin tuloksiin. Urotronicin tämän takuun mukainen velvollisuus rajoittuu tämän laitteen korjaamiseen tai vaihtamiseen, eikä Urotronic ole vastuussa mistään satunnaisista tai välillisistä menetyksistä, vahingoista tai kuluista, jotka johtuvat suoraan tai epäsuorasti tämän laitteen käytöstä. Urotronic ei ota mitään vastuuta uudelleenkäytetyistä, uudelleenkäsitellyistä tai uudelleensteriloiduista laitteista eikä anna tällaisille laitteille mitään suoria tai epäsuoria takuita, mukaan lukien muun muassa tiettyä tarkoitusta koskevat takuut.

15.0 LAITTEEN MERKINNÖISSÄ KÄYTETYT SYMBOLIT

1	1 kpl laatikkoa kohden
Rx only	Huomio: Yhdysvaltain liittovaltion lain mukaan tämän laitteen saa myydä vain lääkäri tai lääkärin määräyksestä.
	Ilmoittaa päivämäärän, jona lääkinnällinen laite on valmistettu.
	Älä steriloi uudelleen
	Älä käytä uudelleen
	Älä käytä, jos pakkaus on vaurioitunut
	Särkyvää
	Viimeinen käyttöpäivä
	Suojaa suoralta auringonvalolta
	Pidä kuivana
	Valmistaja
LATEX	Ei sisällä lateksia
	Lämpötilaraja 15–30 °C
	Huomio: Lue käyttöohjeet
STERILE EO	Steriloitu eteenioksidilla
REF	Luettelonumero
LOT	Eränumero
CE 1434	CE-merkintä lääkinnällisistä laitteista annetun Euroopan unionin direktiivin 93/42/ETY mukaisesti (ilmoitettu laitos #1434)
EC REP	Valtuutettu edustaja Euroopan unionin alueella

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OPTILUME®

ÞVAGFÆRALYFHÚÐAÐUR BLÖÐRUHOLLEGGUR

Notkunarleiðbeiningar

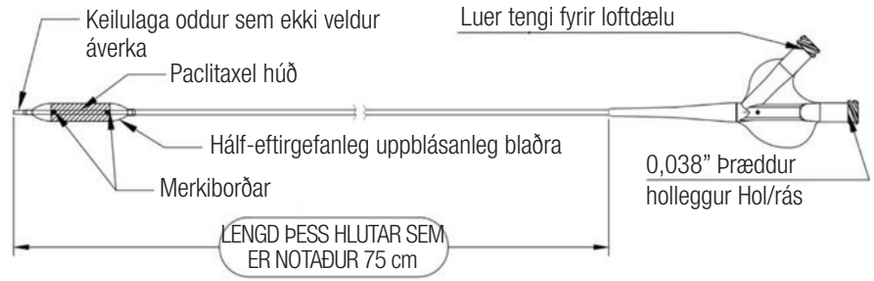
ÍSLENSKU

Efnisyfirlit

1.0 LÝSING Á BÚNAÐI

1.1 Blöðruholleggur

Optilume lyfjahúðaði blöðruholleggurinn fyrir þvagrás er 0,038” (0,97 mm) leiðarvír og sveigjanlegur yfir-vírinn holleggur samhæfur við blöðrusjá, af tvíhola gerð og með frammjóum áverkaminnkandi enda. Holleggurinn er notaður við að beita geislalægum krafti til að víkka út þvagfærahluta (þrengsli). Fjærendi holleggs er útbúinn hálf-eftirgefanlegri uppblásanlegri blöðru sem er húðuð með eignarréttarvarinni húð sem inniheldur virka lyfið paclitaxel. Lyfjahúðin þekur sveigjanlega hluta blöðrunnar. Búnaðurinn er með tvo geislaþétta merkiborða sem sýna þann hluta blöðrunnar sem er sveigjanlegur.



Búnaðurinn er sæfður með etýlenoxíði í Tyvek poka. Að lokinni sæfingu er holleggurinn, sem komið er fyrir í poka, þéttlokaður í málmþynnupoka með rakadrægu þurrkefni og komið fyrir í öskju sem gerð er fyrir eina einingu. Hver einstakur holleggur er útbúinn hlífðarhjúp sem þekur lyfhúðaðan blöðruhluta holleggsins. Tafla yfir samræmi fyrir blöðru er á merkimiðanum á Tyvek pokanum.

1.2 Lyfjahúðun

Lyfjahúðunin samanstendur af hinu virka lyfjaefni paclitaxel og hjálparefnum. Lyfjahúðunin þekur verklæga hluta blöðrunnar sem fylgir holleggnum. Lyfjahúðuninni er dreift jafnt um yfirborðsflöt blöðrunnar í efnastyrk sem nemur 3,5 µg/mm^2. Mikilvægasti starfræni eiginleiki lyfjahúðarinnar er að gera losun paclitaxel kleifa í þvagfæraþekjuna meðan blaðran er blásin út.

Skömmtunartafla lyfhúðaðrar blöðru

Vörulistanúmer	Þvermál (Fr/mm)	Lengd (mm)	Paclitaxel skammtur (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

ÍSLENSKU

2.0 ÆTLUÐ NOTKUN

Optilume lyfjahúðaði blöðruholleggurinn fyrir þvagrás er ætlaður fyrir meðferð á þrengslum í framanverðri þvagrás fullorðinna karlmanna.

3.0 ÁBENDINGAR UM NOTKUN

Optilume lyfjahúðaði blöðruholleggurinn fyrir þvagrás er notaður til meðferðar á karlmönnum ≥18 ára að aldri sem eru með truflandi þvagfæraeinkenni sem tengjast þrálátum þrengslum í framanverðri þvagrás. Hann er hannaður til notkunar sem útvíkkunarblaðra fyrir ein, fleiri eða útbreidd þrengsli í framanverðri þvagrás ≤3 cm að lengd eða sem viðbótarmeðferð með öðrum útvíkkunartækjum og/eða aðferðum.

4.0 FRÁBENDINGAR

Lyfhúðaður blöðruholleggur (DCB) fyrir útvíkkun er með frábendingar vegna notkunar hjá:

- Sjúklingum sem eru með þekkt ofurnæmi gagnvart paclitaxel eða efnasamböndum sem eru skyld að uppbyggingu.
- Sjúklingar með vefjaskemmdir sem ekki er hægt að fara í gegnum með 0,038” leiðarvír.

5.0 VIÐVARANIR

- Holleggurinn er afhentur SÆFÐUR og einungis sem einnota. Má ekki endurnýta eða endursæfa. Endurnýting og endursæfing gætu aukið hættuna á að sjúklingur fái sýkingu og áhættuna á því að búnaður starfi ekki sem skyldi.
- Málmþynnupokinn og ytra yfirborð innri poka er EKKI SÆFT. INNIHALD innri poka er SÆFT. Notið umsvifalaust eftir að búið er að opna málmþynnupoka.
- Notið ekki þennan búnað sé um að ræða sýkingu í þvagrás (UTI) eða þvagblöðru. Hreinsa skal sýkingu áður en meðferð við þrengslum á sér stað með Optilume lyfhúðaðri blöðru.
- Holleggurinn ætti einungis að vera notaður af læknum sem eru með reynslu og hafa þekkingu á klínískum og tæknilegum hliðum þvagfæraútvíkkunar með blöðru.
- Áður en holleggurinn er notaður ættu læknar að lesa og skilja leiðbeiningar um notkun hans. Vanræksla á að fylgja leiðbeiningum, frábendingum, takmörkunum, viðvörunum og varúðarreglum kann að hafa í för með sér vandkvæði.
- Notið ekki eftir fyrningardagsetningu.
- Holleggurinn inniheldur paclitaxel sem er þekkt erfðaeiturefni. Karlar ættu að nota getnaðarvörn (smokk) við kynmök í 30 daga eftir meðferð.
- Fylgist í sífellu með vísbendingum um bráðaofnæmi eða ofurnæmi gagnvart Paclitaxel
- Notið aldrei loft eða gaskennd efni til að blása upp hollegginn.
- Þegar verið er að nota hollegginn ætti að handstýra honum á grundvelli myndbirtingar með blöðruspeglun eða með skoðun gegnum hágæða skyggnitækni.
- Ekki færa til hollegginn þegar hann er uppblásinn.
- Komi fram viðnám eða mótstaða á einhverjum tímapunkti meðan á uppsetningu stendur á ekki að þvinga búnaðinn áfram. Viðnám kann að orsaka skemmd á búnaði eða holi. Gætið varúðar þegar holleggurinn er dreginn út.
- Menn sem eiga bólfélaga sem eiga möguleika á að verða barnshafandi skulu nota smokk í a.m.k. 90 daga eftir meðferð.
- Aukaverkun við paclitaxel og einkenni sem tekið var eftir komu aðallega frá rannsóknum IV blöndu lyfsins við meðferð krabbameinsviðfangsefna og innihalda
    - Litningaafbrigðileiki og áhætta á krabbameini
    - Fósturskaði þegar barnshafandi kona verður fyrir váhrifum
    - Bráðaofnæmi og ofurnæmi gagnvart paclitaxel
    - Hindranir á að þvagrásin grói eftir aðgerð
    - Mergbæling að meðtaldri: daufkyrningafæð, hvítfrumnafæð, blóðflagnafæð, blóðleysi
    - Hjartsláttartruflun
    - Óverulegur taugakvilli
    - Vöðvaverkir eða liðverkir
    - Hártap
    - Lágþrýstingur
    - Ógleði, uppköst eða niðurgangur
    - Hækkaður gallrauði, ALP og AST
    - Möguleg áhrif á lifur og nýru eru óþekkt og hafa ekki verið rannsökuð.

Það magn paclitaxel sem er gefið staðbundið meðan á aðgerð Optilume lyfhúðaðri blöðru stendur er mun minna en einstakur skammtur af kerfisbundinni lyfjameðferð sem krabbameinssjúklingum er gefin og lyfið virðist í meginatriðum vera staðbundið í þvagrásinni.

6.0 VARÚÐARRÁÐSTAFANIR

- Notið ávallt sæfðan vökva við uppblástur (sæft saltvatn eða 50% skuggaefnisblöndu). Notið aldrei loft, kolefnistvíoxíð eða aðrar gastegundir við uppblástur. Ekki á að blása hollegginn upp meira en sem nemur mældum sprengiþrýstingi (RBP). Ofblásið ekki blöðruna.
- Blöðruholleggir eru ætlaðir til notkunar af læknum sem hafa þjálfun og reynslu í tækni er snýr að útvíkkun með blöðruhollegg.
- Til að tryggja rétt eftirlit með blöðruþrýstingi er mælt með notkun blöðruuppblásturstækis með þrýstingsmæli.
- Sogið algerlega úr blöðrunni áður en búnaður er fjarlægður varlega úr þvagrás. Sé notað of mikið afl þegar blaðra er fjarlægð getur það valdið skemmdum á vef.
- Skoðið hollegginn vandlega svo og umbúðir fyrir notkun. Notið ekki hollegginn sé hann laskaður eða ef stærð, lögun eða ástand hans er óviðeigandi fyrir hina væntanlegu aðgerð.
- Ekki sökkva í neinn vökva eða þurrka blöðruhluta holleggsins með neinum vökva þar eð slíkt getur skemmt eða vásett lyfhúðina. Skiptið út holleggnum ef blaðra hefur komist í snertingu við vökva fyrir notkun.
- Notið sæfða hanska eða þurrar grisjur til að meðhöndla hollegginn fyrir notkun. Gæta skal að því að lágmarka alla snertingu við húðaða blöðruna sem er hluti búnaðarins.

- Blásið aldrei hollegginn upp utan líkamans, eða áður en komið er að þrengslum þeim sem aðgerðinni er beint að þar sem slíkt getur rofið húðunina.
- Reynið ekki að koma holleggnum í gegnum minni blöðrusjá af franskri stærð heldur en greint er frá á miðanum.
- Hin virka lengd holleggsins verður að ná yfir alla lengd þrengsla sem aðgerð miðast við.
- Til þess að rétt lyfjagjöf að markþrengingunni geti átt sér stað þarf að láta húðunina soga til sín vatn í þvagrásinni í að lágmarki 60 sekúndur fyrir uppblástur og holleggurinn verður að vera uppblásinn í a.m.k. 5 mínútur. Til að hámarka útvíkkun þrengsla getur stjórnandi aðgerðar ákveðið að halda holleggnum uppblásnum lengur en í 5 mínútur.
- Komi upp bilun í búnaði fyrir eða meðan á uppblæstri stendur verður að skipta út holleggnum og blása upp að nýju í samræmi við verklag. Komi upp bilun eftir uppblástur að mældum sprengiþrýstingi skal ekki endurtaka aðgerðina með hollegg.
- Eftir notkun kann þessi vara að fela í sér hugsanlega líffræðilega hættu. Meðhöndlið og fargið í samræmi við viðurkennt læknisfræðilegt verklag og gildandi lög og reglur á viðkomandi stað.
- Heilbrigðisstarfsmenn ættu að forðast að nota latex hanska til þess að koma í veg fyrir hugsanleg ofnæmisviðbrögð hjá sjúklingum sem eru með ofnæmi fyrir latexi.
- Undirbúningur holrúms þvagrásarinnar vegna skemmda sem ná skal til, með því að nota viðeigandi undirbúningsaðferðir holrúms eins og skilgreindar eru af meðferðarlækninum, er krafist áður en að notkun á Optilume lyfhúðuðu blöðrunni á sér stað.
- Undirbúningur holrúms með því að nota einungis forútvíkkun með blöðruhollegg sem er ekki húðaður eða DVIU, var rannsakaður í Robust I klínískri rannsókn.
- Í klínískum rannsóknum var krafist sjónrænnar staðfestingar á verulegum þrengslum (≤12F þvermál þvargrásar) með blöðrusjá eða þvagrásarmynd og þátttaka var takmörkuð við sjúklinga sem sýndu huglæg og hlutlæg einkenni þrengsla í þvagrás (alþjóðleg flokkun blöðruhálskirtilseinkenna [IPSS] >13, hámarkshraði þvagflæðis <15 mL/sek.). Þátttakendur höfðu undirgengist a.m.k. eina holsjármeðferð áður en þeir tóku þátt í klínísku rannsóknunum.
- Ekki fengust gögn úr klínísku rannsókninni sem sanna öryggi og skilvirkni fyrir meðferð á þrengslum í sjúklingum með:
  - Góðkynja blöðruhálskirtilsofvöxt
  - Róttækt blöðruhálskirtilsnám
  - Grindargeislun
  - Bótoxmeðferð
  - Meira en 1 þrengsli
  - Fyrri þvagrásarlögun innan fremri hluta þvagrásar
  - Bakteríuþvagrásarbólga eða lekandi
  - Viðurvist reðurígrædds gerviþrengis eða stoðnets þvagrásar/blöðruhálskirtils
  - Þekkta taugræna þvagblöðru, afbrigðileika þrengis, eða litla virkni tæmivöðva þvagblöðru.
  - Greinda húðskæniherðingu, eða fyrri lagfæringu á neðanrás.
  - Sögu um krabbamein á þvagblöðru eða blöðruhálskirtli innan síðustu 5 ára
  - Þrengsli vegna herslisskorpnunarhúfubólgu
  - Æxli á þvagfærum eða reðurkrabbamein

7.0 NOTKUN HJÁ BERSKJÖLDUÐUM HÓPUM

Öryggi og skilvirkni lyfhúðaðs blöðruholleggs hefur ekki verið staðfest hjá sjúlkingum barnalækninga (<18 ára aldur) eða hjá konum. Notkun á lyfhúðuðum blöðruhollegg hjá sjúklingum ≥18 ára aldur og eldri er undir þagmælsku læknisins.

8.0 HUGSANLEGIR FYLGIKVILLAR

Hugsanlegir fylgikvillar sem tengjast notkun Optilume þvagfæralyfhúðaðs blöðruholleggs eru sambærilegir við þá sem tengjast stöðluðum þvagfæravíkkunaraðferðum. Hugsanlegir fylgikvillar kunna að vera, en takmarkast ekki við:

- Verkur og eymsli
- Þvagblöðrukrampi vegna uppsetningar á Foley hollegg
- Skemmdir á vefjum í samsetningunum í kring, að meðtöldum skemmdum á þvagfærum
- Blóðmiga
- Viðbrögð við lyfjum, ofnæmisviðbrögð við skuggaefni sem notað er við þvagrásarmyndatöku vegna greiningar
- Þvagfærasýking
- Götun á vef
- Endurkoma þrengsla sem kallar á frekari skurðaðgerð
- Lausheldni
- Þvaglátstregða
- Hiti
- Þvagteppa

9.0 LYFJAUPPLÝSINGAR

o VERKUNARMÁTI

Húðun holleggsins innihaldur paclitaxel sem er lyf sem vinnur gegn mítósu og binst sértækt við og kemur jafnvægi á örpíplur. Tilkynnt hefur verið um að paclitaxel hamli fjölgun og fari sléttra vöðvafruma og trefjakímfruma, sem og seyti utanfrumuefnis. Sambland þessara áhrifa kann að leiða til hömlunar á ofvexti þvagfæraþekju og þess vegna til endurkomu þrengsla.

o MILLIVERKANIR LYFJA

Formlegar rannsóknir á milliverkunum lyfja hafa ekki farið fram vegna þvagfæralyfhúðaðs blöðruholleggs. Skoða þarf notkunarleiðbeiningar allra lyfja sem notuð eru í tengslum við hollegginn varðandi milliverkanir við paclitaxel.

Taka þarf tillit til hugsanlegra og staðbundinna lyfjamilliverkana í þvagfærum sjúklings sem tekur lyf sem er með þekkta milliverkun við paclitaxel eða þegar tekin er ákvörðun um að hefja lyfjameðferð hjá sjúklingi sem hefur gengist undir meðferð með holleggnum. Efnaskipti paclitaxel eru hvött af sýtókróm P450 samsætuensímunum CYP2C8 og CYP3A4 og það er hvarfefni P-glýkóprótíns. Hugsanlegar lyfjamilliverkanir kunna að eiga sér stað við önnur lyf sem hafa áhrif á þessi samsætuensím. Þar sem ekki hafa farið fram formlegar rannsóknir á milliverkunum lyfja skal gæta varúðar við notkun paclitaxel.

o KRABBAMEINSVALDANDI VERKUN, ERFÐAEITURHRIF OG EITURHRIF Á ÆXLUN

Engar langtímarannsóknir hafa verið framkvæmdar til þess að meta krabbameinsvaldandi möguleika lyfsins paclitaxel eða Optilume lyfhúðaða blöðru og það eru engar fullnægjandi eða vel stjórnaðar rannsóknir sem hafa verið gefnar út varðandi barnshafandi konur eða menn sem hafa hug á að feðra börn. Paclitaxel hamlar fjölgun á frumum með því að verka á víxl við örpípur, og ein afleiðing er missir á heilum litningum á meðan á frumuskiptingu stendur. Þessi óbeina aðgerð er í samræmi við jákvæða svörun í könnunum á smákjarna erfðaeituráhrifa í tilraunaglasi og í lifandi líkama, sem greinir erfðaefniseiningar. Einnig hefur verið tilkynnt um jákvæðar niðurstöður við litningaafbrigðileika aðallega í mannlegum eitilfrumum. Það er ekki þekkt hvort að paclitaxel hafi aðgreind bein áhrif á erfðaefni við myndun skemmda eða brots á erfðaefni. Það er neikvætt í könnunum á genastökkbreytingu, að meðtaldri salmonellu og CHO/HPRT.

Rannsóknir sem fóru fram á rottum og kanínum sem fengu paclitaxel í æð meðan á líffæramyndun stóð sýndu fram á móðurlega eiturverkun, eiturverkun fósturvísa og fósturskemmdir við skammtastærðir 1 og 3 mg/kg, eftir því sem við á (hér um bil 13 og 39 sinnum sú skammtastærð sem veitt er af Optilume lyfhúðaðri blöðru sem húðuð er með 5,5 mg paclitaxel (10 mm x 50 mm blaðra) aðlagað að líkamsþyngd). Ekki var tekið eftir neinni vansköpun hjá ungafullum rottum sem fengu daglega 1 mg/kg af paclitaxel í æð (daglegur skammtur hér um bil 13 sinnum skammturinn af Optilume lyfhúðaðri blöðru (10 mm x 50 mm), aðlagað að líkamsþyngd).

Meðferðarlæknir skal jafna út mögulegan læknisfræðilegan ávinning af Optilume þvagfæralyfhúðaðri blöðru gegn þessum erfðaeitrandi og æxlunaráhættum.
VIÐVÖRUN: Hollegurinn inniheldur paclitaxel sem er þekkt erfðaeiturefni. Karlar ættu að nota getnaðarvörn (smokk) við kynmök í 30 daga eftir meðferð.

10.0 HVERNIG ER BÚNAÐUR AFHENTUR

Þvagfæralyfhúðaða blaðran er afhent SÆFÐ og einungis sem einnota (sæfing með etýlenoxíði). Lyfhúðaða blaðran er tvöfaldri pakkningu (málþynnu og Tyvek poka) sem komið er fyrir í öskju sem gerð er fyrir eina einingu.

11.0 GEYMSLA

Geyma ætti lyfhúðaða blöðruhollegginn við herbergishita á þurrum stað í upprunalegum umbúðum. Nota skal búnaðinn fyrir fyrningardagsetningu sem tilgreind er á umbúðum á eftir „notist fyrir“.

12.0 ATRIÐI SEM RÁÐLÖGÐ ERU

Undirbúið eftirfarandi atriði með sæfðum aðferðum:

- Þráð af viðeigandi stærð með hreyfanlegum oddi (sjá merkingar á vöru)
- Þvagblöðrusjá (sveigjanleg er æskileg)
- Sæft saltvatn
- 10 rúmsentimetra sprauta
- Tvíátta loki
- Uppblásturstæki með þrýstingsmæli
- Skuggaefni – Athugið: Valkvætt til nota með verklagi á grundvelli skyggnitækni

13.0 NOTKUNARLEIÐBEININGAR

13.1 ÁÐUR EN NOTKUN HEFST

Lyf fyrir aðgerð

Það er mælt með því að læknar fylgi leiðbeiningum lyfs fyrir aðgerð og undirbúning fyrir holsjáraðgerð, þ.m.t. umsjón með sýklalyfjum fyrir aðgerð eins og viðeigandi er. Einnig er mælt með því að gefa NSAID munnlega fyrir aðgerð.

Ef að þvagfærasýking er til staðar við meðferð, þá verður sjúklingurinn að fá meðferð við henni og ná bata áður en meðferðaraðgerðin getur átt sér stað.

13.2 UNDIRBÚNINGUR ÞRENGSLA SEM NÁ SKAL TIL

Mælt er með forútvíkkun þvagfæra á þrengslum sem ná skal til, með því að nota viðeigandi undirbúningsaðferðir sem skilgreindar eru af meðferðarlækninum (útvíkkunarblaðra sem er ekki húðuð eða DVIU), fyrir þrengsli sem hafa þrengst mikið eða er erfitt að komast yfir, áður en Optilume lyfhúðuð blaðra er notuð. Stjórnið forútvíkkun til þess að þrengslin gefi eftir. Þetta er skilgreint sem útvíkkað þvermál holrásar þrengsla >20F eða >50% stærra en holrás þrengsla sem hefur ekki verið útvíkkuð.

13.3 STÆRÐARMAT BÚNAÐAR

Gangið úr skugga um þvermál valda DCB belgsins við lágmarksþrýsting sé það sama eða aðeins stærra en þvermál heilbrigðu þvagrásarinnar sem liggur að fjarlægu brún þrengslanna. Þvermál belgsins deilt með þvermáli fjarlægu heilbrigðu aðliggjandi þvagrásarinnar er skilgreint sem útþensluhlutfall.

Stærð miðhluta þvagrásar (bulbar urethra)
Ef um er að ræða þrengsli í miðhluta þvagrásar má útþensluhlutfallið fyrir þvermál belgs og fjarlægrar þvagrásar ekki vera stærra en 1,3. Ef stærð þvagrásarinnar fellur á milli fáanlegra stærða tækisins, skal nota stærri stærðina að því tilskildu að útþensluhlutfallið sé minna en eða jafnt og 1,3. Ef stærðin þar fyrir ofan gefur útþensluhlutfall sem er stærra en 1,3 á að nota minna tækið.

Stærð reðurhluta þvagrásar (penile urethra)
Ef um er að ræða þrengsli í reðurhluta þvagrásar á að velja þvermál belgs sem passar best við fjarlægu heilbrigðu þvagrásina. Útþensluhlutfall reðurhluta þvagrásarinnar má ekki vera stærra en 1:1. Ef stærð þvagrásarinnar fellur á milli fáanlegra stærða belgsins, skal nota minni belgstærðina. EKKI MÁ FARA YFIR 1:1 útþensluhlutfallið.

Lengd DCB belgsins á ekki að vera lengri en þrengslin sem á að meðhöndla, bæði hvað varðar reðurhluta og miðhluta þvagrásar. Belgurinn þarf að ná u.þ.b. 0,5-1 cm fram yfir þrengslin á báðum hliðum. Til dæmis, ef þrengslin eru 2 cm á að velja DCB belg sem er 3 cm.

13.4 UNDIRBÚNINGUR BLÖÐRUHOLLEGGS

Lofttæmið hollegg lyfhúðuðu blöðrunnar. Holrúm blöðrunnar í blöðruholleggnum inniheldur loft og loftið þarf að færa úr stað til að ganga úr skugga um að einungis vökvi fylli blöðruna meðan hollegurinn er í þvagrásinni.

1. Tengið loka í opinni stöðu við uppblásturstengil blöðru.
2. Tengið sprautu hálffyllta með saltvatni við loka.

3. Dragið bulluna aftur með oddi sprautunnar sem nemur heildarrúmmáli sprautunnar (þetta myndar hámarks neikvæðan þrýsting) og haldið uns engar loftbólur sjást koma út úr saltvatnslausninni í sprautunni. Endurtakið eins og þörf er á til þess að hreinsa loftið frá holleggnum og skiptið því út fyrir saltlausn. Haldið bullunni aftur, snúið lokanum til þess að viðhalda lofttæmi og fjarlægið sprautuna. Hálffyllið uppblásturstæki með eðlilegri saltlausn eða með 1:1 skuggaefni: saltlausn ef skygging er notuð og hreinsið loft úr línunni.
4. Festið uppblásturstæki við lokann á blöðruholleggnum, snúið lokanum og dragið lofttæmi á upplásturstækinu.

13.5 INNSETNING OPTILUME LYFHÚÐAÐRAR BLÖÐRU

1. Staðsetjið 0,038” þráðhol með sveigjanlega oddinum sem er vafinn um blöðruna með aðstoð blöðrusjá.
2. Fjarlægið blöðruvarann af oddi lyfhúðaða blöðruholleggsins.

   Varúð: *Gæta skal varúðar þegar verið er að færa blöðru sem húðuð er með pacli taxel gegnum þvagblöðrusjá. Lágmarkið óþarfa meðhöndlun og snertið ekki blöðruna. Þurrkið ekki blöðruna með þurri, votri eða smurðri grisju, eða með hvers konar leysi sem gæti valdið skemmdum á lyfhúðaðri blöðrunni.*

3. Færið fram lyfhúðaða blöðruholllegginn innan í starfsrás þvagblöðrusjárinnar. Að öðrum kosti er hægt að hafa þráðinn og holllegginn aðgreindan frá vinnurás þvag blöðrusjárinnar og koma þeim fyrir samsíða.
4. Notið þvagblöðrusjá til leiðbeiningar um staðsetningu lyfhúðuðu blöðrunnar. Að öðrum kosti skal staðsetja lyfhúðuðu blöðruna með skuggaefni með því að nota geislaþétta merkiborða sem staðsettir eru undir blöðrunni/keilunni.

   Varúð: *Færið ekki fram þráðinn eða blöðruhollegg til útvíkkunnar komi fram mót staða án þess fyrst að ákvarða orsök mótstöðu og grípa til ráðstafana til úrbóta.*

13.6 OPTILUME DÆLING LYFHÚÐAÐRAR BLÖÐRU

Varúð: *Uppblásturstæki geta náð mjög háum þrýstingi með lágmarks áreynslu. Eindregið er mælt með notkun uppblásturstækis með háþrýstimæli til að hámarka útvíkkunarafl til að yfirvinna þvagfæraþrengsli og til að gera það mögulegt að lyf smjúgi í gegn inn í yfirunnu þvagfæraþekjuna.*

1. Tryggið að þvagrásin sé skoluð með saltvatni.
2. Staðsetjið lyfhúðuðu blöðruna yfir þrengslin með blöðrusjána fjarlæga frá blöðrunni (frá blöðrunni) til þess að sjá almennilega staðsetningu blöðrunnar yfir þrengslunum. Skiljið blöðruna eftir á sínum stað þegar ekki er búið að blása hana upp, í a.m.k. 1 mínútu áður en hún er blásin upp. Notið skyggingu til að sjá hvort geislaþéttir merkiborðar blöðru séu rétt staðsettir.
3. Blásið upp blöðruna að mældum sprengiþrýstingi með því að nota blöðruuppblás turstækið. Farið ekki fram úr sprengiþrýstingi blöðrunnar. Viðhaldið þrýstingi að lágmarki í 5 mínútur þar til æskileg útvíkkun næst.
4. Hleypið úr blöðrunni með því að beita sogi á blöðruna með blöðruupplásturstækinu. Þegar búið er að hleypa fullkomlega úr blöðrunni dragið þá hægt út þráðinn og lyfhúðuðu blöðruna. Verði vart við örlitla mótstöðu þegar verið er að fjarlægja blöðruna skal hægt og rólega snúa holleggnum til að hjálpa blöðrunni við að vefjast um holleggsstokkinn og til að auðvelda útdrátt.

   Varúð: *Verði vart við mótstöðu þegar verið er að fjarlægja þráðinn gegnum hollegg gegnum þvagblöðrusjá, skal STÖÐVA og fjarlægja búnaðinn allan samtímis eins og fullkomna einingu til að koma í veg fyrir skemmdir á þræðinum, holleggnum eða á líkama sjúklings.*

5. Ef að upp kemur bilun í búnaði fyrir eða meðan á uppblæstri stendur (en minni en mældur sprengiþrýstingur) verður að skipta út lyfhúðuðu blöðrunni og blása upp að nýju í samræmi við verklag. Komi upp bilun eftir uppblástur að mældum sprengiþrýstingi skal ekki endurtaka aðgerðina með hollegg.
6. Setjið inn 12-14 Fr sleipan Foley hollegg og skiljið hann eftir á stað sínum í að lágmarki 2 daga eða samkvæmt hefðbundinni umönnun, hvort sem er mikilvægara.

13.7 TAFLA YFIR SAMRÆMI

18 Fr (6 mm) x 30 mm

(LOFTÞYNGD) Þrýstingur	**kPa**		**(mm) Blaðra**
6,0	600	**Nafngildi**	6,11 (18Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**Mældur sprengiþrýstingur**	6,45

18 Fr (6 mm) x 50 mm

(LOFTÞYNGD) Þrýstingur	**kPa**		**(mm) Blaðra**
6,0	600	**Nafngildi**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**Mældur sprengiþrýstingur**	6,25

24 Fr (8 mm) x 30 mm

(LOFTÞYNGD) Þrýstingur	**kPa**		**(mm) Blaðra**
6,0	600	**Nafngildi**	7,98 (24Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**Mældur sprengiþrýstingur**	8,46

24 Fr (8 mm) x 50 mm

(LOFTÞYNGD) Þrýstingur	kPa		(mm) Blaðra
6,0	600	**Nafngildi**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**Mældur sprengiþrýstingur**	8,54

30 Fr (10 mm) x 30 mm

(LOFTÞYNGD) Þrýstingur	kPa		(mm) Blaðra
6,0	600	**Nafngildi**	9,83 (30Fr)
8,0	800		10,09
10,0	1000	**Mældur sprengiþrýstingur**	10,29

30 Fr (10 mm) x 30 mm

(LOFTÞYNGD) Þrýstingur	kPa		(mm) Blaðra
6,0	600	**Nafngildi**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**Mældur sprengiþrýstingur**	10,44

Varúð: *Ekki ætti að fara yfir metinn sprengiþrýsting blöðru. Skoðið merkingu á vöru varðandi sprengiþrýsting. Uppblástur umfram metinn sprengiþrýsting getur valdið því að blaðran springi. Eigi sér stað þrýstingsfall innan blöðrunnar meðan á uppblæstri stendur eða springi blaðran við útvíkkun skal umsvifalaust hætta aðgerðinni. Hleypa þarf varlega úr blöðrunni og fjarlægja hana úr þvagrás. Ekki blása upp aftur.*

14.0 ÁBYRGÐ

Urotronic ábyrgist að eðlileg aðgæsla hefur verið höfð í frammi varðandi hönnun og framleiðslu þessarar vöru. Þessi ábyrgð kemur í stað og útilokar allar aðrar ábyrgðaryfirlýsingar sem ekki hafa verið sérstaklega settar fram hér, hvort sem þær eru beinar eða óbeinar, á grundvelli laga eða á annan hátt, þar á meðal en án þess að takamarkast við allar óbeinar ábyrgðaryfirlýsingar í sérstöku skyni. Meðferð, geymsla, þrif og sæfing þessa búnaðar sem og aðrir þættir sem tengjast sjúklingi, sjúkdómsgreiningu, meðferð, verklagi við skurðaðgerð og öðrum þáttum sem standa utan þess sem Urotronic getur haft áhrif á, hafa bein áhrif á búnað og niðurstöður sem fást vegna notkunar tækisins. Skuldbinding Urotronic samkvæmt ábyrgðaryfirlýsingu þessari takmarkast við viðgerð eða að skipt sé um búnað þennan og Urotronic skal ekki talið ábyrgt fyrir neinum tilfallandi eða afleiddum skaða, tjóni eða útgjöldum, sem leiðir beint eða óbeint af notkun þessa búnaðar. Urotronic gengst ekki undir neina ábyrgð varðandi búnað sem er endurnotaður, endurunninn, eða endursæfður og setur ekki fram neinar ábyrgðaryfirlýsingar, beinar eða óbeinar, þar á meðal en takmarkast ekki við sérstakan tilgang, að því er varðar slíkan búnað.

15.0 TÁKN SEM NOTUÐ ERU Á MERKIMIÐUM BÚNAÐAR

	Magn 1 í kassa
Rx only	Varúð: Alríkislög takmarka þennan búnað við sölu af hálfu eða samkvæmt fyrirmælum læknis.
	Tilgreinir dagsetningu þegar lækningatæki var framleitt.
	Má ekki endursæfa
	Má ekki endurnýta
	Má ekki nota ef umbúðir eru skemmdar
	Brotthætt
	Notist fyrir
	Haldið frá sólarljósi
	Haldið þurru
	Framleiðandi
LATEX	Inniheldur ekki latex
	Leyfilegt hitastig 15°C - 30°C
	Varúð: Lesið leiðbeiningar um hvernig nota eigi tækið
STERILE EO	Sæfið með etýlenoxíði
REF	Vörulistanúmer
LOT	Lotunúmer
CE 1434	CE-merking samkvæmt tilskipun Evrópusambandsins um lækningatæki 93/42/EEC (tilkynntur aðili númer 1434)
EC REP	Viðurkenndur fulltrúi Evrópusambandsins

Urotronic, Inc.
2495 Xenium Lane North
Minneapolis, MN 55441
USA

CE 1434

EC REP
MDSS GmbH
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OPTILUME®

LEGEMIDDELBELAGT URETHRALT BALLONGKATETER

Bruksanvisning

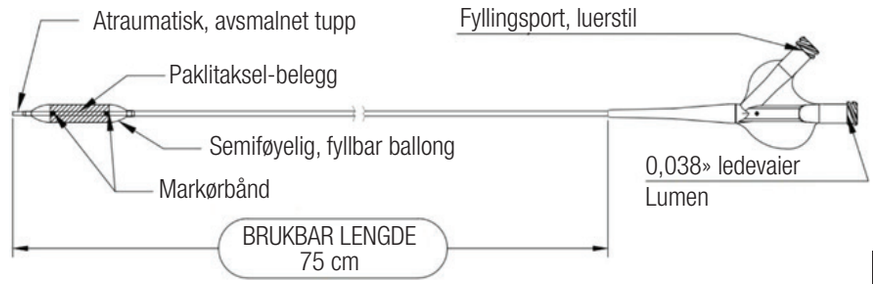
NORSK

Innholdsfortegnelse

1.0 BESKRIVELSE AV ENHETEN

1.1 Ballongkateter

Optilume legemiddelbelagt uretralt ballongdilateringskateter (DCB) er et over-vaieren-kateter (OTW) med dobbelt lumen og en avsmalnet, atraumatisk tupp, som er kompatibelt med en 0,97 mm (0,038") ledevaier og et fleksibelt cytoskop. DCB brukes til å påføre radial kraft for å dilatere trange urinrørssegmenter (strikturer). Kateterets distale ende har en semiføyelig, fyllbar ballong som er belagt med et proprietært belegg som inneholder virkestoffet paklitaksel. Legemiddelbelegget dekker arbeidslengden til ballongens hoveddel. Enheten har to røntgentette markørbånd som angir ballongens arbeidslengde.



Enheten er sterilisert med etylenoksid i en Tyvek-pose. Etter sterilisering blir kateteret i posen forseglet i en foliepose med tørkemiddel, og lukket inne i en eske med én enhet. Hvert DCB leveres i en beskyttelseshylse som dekker den legemiddelbelagte ballongdelen av kateteret. Et skjema med ballongens føyelighet finnes på etiketten på Tyvek-posen.

NORSK

1.2 Legemiddelbelegg

Legemiddelbelegget består av virkestoffet paklitaksel og hjelpestoffer. Legemiddelbelegget dekker arbeidslengden til kateterets ballongkomponent. Legemiddelbelegget er jevnt fordelt over hele ballongoverflaten, med en konsentrasjon på 3,5 µg/mm^2. Legemiddelbeleggets viktigste funksjonsegenskaper er å frigjøre paklitaksel til urotelet under fylling av ballongen.

Doseringsmatrise for DCB

Katalognummer	Diameter (Fr/mm)	Lengde (mm)	Paklitakseldose (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	30	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	30	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	30	5,5

2.0 TILTENKT BRUK

Optilume legemiddelbelagt uretralt ballongdilateringskateter (DCB) skal brukes til behandling av strikturer i det anteriore urinrøret hos voksne menn.

3.0 INDIKASJONER FOR BRUK

Optilume uretralt DCB-kateter brukes til å behandle menn ≥18 år med plagsomme urinveissymptomer forbundet med tilbakevendende anterior urinrørsstriktur. Det er utformet for å brukes som en dilateringsballong for en enkelt, tandem eller diffus anterior urinrørsstriktur på ≤3 cm i lengde, eller som tilleggsbehandling sammen med andre dilaterende enheter og/eller prosedyrer.

4.0 KONTRAINDIKASJONER

Det legemiddelbelagte ballongdilateringskateteret (DCB) er kontraindisert for bruk hos:

- pasienter med kjent overfølsomhet overfor paklitaksel eller strukturelt relaterte stoffer
- pasienter med lesjoner som ikke kan krysses med en 0,038” ledevaier

5.0 ADVARSLER

- Urethralt DCB leveres STERILT og er kun til engangsbruk. Må ikke reprosesseres eller resteriliseres. Reprosessering og resterilisering kan øke risikoen for pasientinfeksjon og risikoen for forringet enhetsytelse.
- Folieposen og den indre posens ytre overflate er IKKE-STERILE. INNHOLDET i den indre posen er STERILT. Brukes umiddelbart etter at folieposen er åpnet.
- Denne enheten må ikke brukes hvis det er infeksjon i urinrøret (UVI) eller blæren. Infeksjoner må ha opphørt før strikturen behandles med Optilume DCB.
- DCB skal bare brukes av leger med erfaring i og kunnskap om de kliniske og tekniske sidene ved urethral ballongdilatering.
- Før DCB brukes, skal leger lese og forstå bruksanvisningen. Dersom indikasjonene, kontraindikasjonene, begrensningene, advarslene og forsiktighetsreglene ikke følges, kan det føre til komplikasjoner.
- Må ikke brukes etter "Brukes innen"-datoen.
- DCB inneholder paklitaksel, et kjent gentoksin. Menn skal ha beskyttet sex (bruke kondom) i 30 dager etter behandling.
- Overvåk for tegn på anafylakse eller overfølsomhet overfor paklitaksel.
- Bruk aldri luft eller gass til å fylle DCB.
- Når DCB er i bruk, skal det manipuleres under direkte visualisering via cystoskopi eller fluoroskopisk observasjon av høy kvalitet.
- Ikke manipuler DCB når det er fylt.
- Hvis det møtes motstand på noe tidspunkt under innføringsprosedyren, skal det ikke fremtvinges passasje. Motstand kan forårsake skade på enheten eller lumenet. Trekk kateteret forsiktig tilbake.
- Menn med seksualpartnere i fertil alder bør bruke kondom i minst 90 dager etter behandling.
- Bivirkningsreaksjoner på paklitaksel og observerte symptomer stammer i hovedsak fra studier av intravenøs legemiddelinfusjon ved behandling av kreft og inkluderer
    - Kromosomavvik og kreftrisiko
    - Fosterskade når en gravid kvinne blir eksponert
    - Anafylaksi og overfølsomhet overfor paklitaksel
    - Svekket tilheling av urinrøret etter prosedyren
    - Myelosuppresjon, inkludert: nøytropeni, leukopeni, trombocytopeni, anemi
    - Arytmi
    - Perifer nevropati
    - Myalgi eller artralgi
    - Alopesi
    - Hypotensjon
    - Kvalme, brekninger eller diaré
    - Forhøyede verdier av bilirubin, ALP og ASAT
    - Potensiell effekt på lever og nyrer er ikke kjent og har ikke blitt undersøkt.

Mengden paklitaksel som leveres lokalt under Optilume DCB-prosedyren, er mye lavere enn en enkeltdose med systemisk kjemoterapi som gis til kreftpasienter, og stoffet ser i hovedsak ut til å forbli lokalisert i urinrøret.

6.0 FORSIKTIGHETSREGLER

- Fyll alltid med en steril væske (sterilt saltvann eller 50 % kontrastblanding). Fyll aldri med luft, karbondioksid eller annen gass. DCB skal ikke fylles over det nominelle sprengtrykket (RBP). Ikke overfyll ballongen.
- Ballongkatetre er ment for bruk av leger med opplæring og erfaring i teknikker for dilatering med ballongkateter.
- For å sikre riktig regulering av ballongtrykket anbefales det å bruke en ballongfyllingsenhet med trykkmåler.
- Aspirer ballongen fullstendig før enheten fjernes forsiktig fra urinrøret. Bruk av overdreven kraft for å trekke ut ballongen kan påføre skade på vevet.
- Undersøk DCB og emballasjen nøye før bruk. Ikke bruk kateteret hvis det er skadet, eller hvis størrelsen, formen eller tilstanden er uegnet for den tiltenkte prosedyren.
- Ikke nedsenk ballongdelen av DCB eller tørk av den med væske, ettersom integriteten til legemiddelbelegget kan bli skadet eller svekket. Bytt ut DCB hvis ballongen har kommet i kontakt med væske før bruk.
- Bruk tørre, sterile hansker eller tørre gaskompresser til å håndtere DCB før bruk. Pass på å minimere kontakt med den belagte ballongdelen av kateteret.
- Fyll aldri DCB utenfor kroppen eller før den når målstrikturen, da dette kan skade beleggets integritet.
- Ikke prøv å føre DCB gjennom et cystoskop med mindre French-størrelse enn det som er angitt på etiketten.
- DCBs arbeidslengde må dekke hele lengden til målstrikturen.

- For riktig levering av legemiddel til målstrikturen skal belegget hydreres i urinrøret i minst 60 sekunder før fylling, og fyllingen av DCB skal opprettholdes i minst 5 minutter. Etter legens skjønn kan lengre fyllingstider (> 5 minutter) brukes for å optimalisere dilatering av strikturen.
- Hvis produktet svikter før eller under fylling, skal DCB byttes ut og fylles i henhold til prosedyren. Hvis svikten oppstår etter fylling til nominelt sprengtrykk, skal ikke DCB-prosedyren gjentas.
- Etter bruk skal dette produktet behandles som potensielt biologisk farlig. Håndter og kasser i samsvar med akseptert medisinsk praksis og gjeldende lokale forskrifter.
- For å forebygge mulige allergiske reaksjoner hos pasienter som er allergiske overfor lateks, bør helsepersonell unngå å bruke latekshansker.
- Klargjøring av det urethrale lumenet i mållesjonen ved bruk av en egnet metode for lumenklargjøring som bestemmes av behandlende lege, er nødvendig før bruk av Optilume DCB.
- Lumenklargjøring med kun predilatering med et ubelagt ballongkateter eller DVIU er blitt undersøkt i den kliniske studien Robust I.
- I kliniske studier ble det brukt cystoskopi eller røntgenbilder av urinrøret for å visuelt bekrefte den signifikante strikturen (≤12F uretral diameter), og studieinkludering var begrenset til pasienter som hadde subjektive og objektive s symptomer på urinrørsstriktur (International Prostate Symptom Score [IPSS] >13, maksimal urinflow <15 ml/sek). Deltakerne hadde vært gjennom minst én tidligere endoskopisk behandling før de ble inkludert i de kliniske studiene.
- Data for sikkerhet og effekt har ikke blitt fastslått i den kliniske studien for å støtte behandling av strikturer hos pasienter med:
  - BPH
  - Radikal prostatektomi
  - Stråleskadet bekken
  - Botox-behandling
  - Mer enn 1 striktur
  - Tidligere uretroplastikk i anteriort urinrør
  - Bakteriell uretritt eller gonoré
  - Tilstedeværelse av penisimplantat, kunstig sfinkter eller urethral/prostatisk stent
  - Kjent nevrogen blære, unormal sfinktertilstand eller nedsatt funksjon i detrusormuskelen
  - Diagnostisert lichen sclerosus eller tidligere reparasjon av hypospadi
  - Anamnese med karsinom i blære eller prostata i løpet av de 5 siste årene
  - Striktur som skyldes balanitis xerotica obliterans (BXO)
  - Tumor i urethra eller peniskreft

7.0 BRUK HOS SPESIELLE PASIENTGRUPPER

Sikkerhet og effekt av urethralt DCB er ikke fastslått hos pediatriske pasienter (< 18 år) eller hos kvinner. Bruk av urethralt DCB hos pasienter ≥ 18 år og eldre skjer etter legens skjønn.

8.0 MULIGE KOMPLIKASJONER

Mulige komplikasjoner forbundet med bruk av Optilume DCB-kateter er tilsvarende komplikasjonene som er forbundet med standardprosedyrer for urinrørsdilatering. Mulige komplikasjoner kan inkludere, men er ikke begrenset til:

- smerte og ømhet
- blærespasmer grunnet plassering av Foley-kateter
- vevstraume i omkringliggende strukturer, inkludert urethral skade
- hematuri
- legemiddelreaksjoner, allergisk reaksjon overfor kontrastmiddel som brukes under diagnostisk urethrogram
- urinveisinfeksjon
- vevsperforering
- tilbakevending av striktur, som krever ytterligere kirurgi
- inkontinens
- dysuri
- feber
- urinretensjon

9.0 LEGEMIDDELINFORMASJON

o VIRKNINGSMEKANISME

Belegget på urethralt DCB inneholder paklitaksel, et antimiotisk legemiddel som spesifikt bindes til og stabiliserer mikrotubuli. Paklitaksel har vært rapportert å hemme proliferasjon og migrasjon av glatte muskelceller og fibroblaster samt utsondring av ekstracellulær matriks. Kombinasjonen av disse effektene kan føre til hemming av hyperplasi i urotelet, og derved tilbakevending av striktur.

o LEGEMIDDELINTERAKSJONER

Det er ikke utført formelle studier av legemiddelinteraksjoner for urethralt DCB. Derfor skal de respektive bruksanvisningene for alle legemidler som brukes sammen med DCB, konsulteres for interaksjoner med paklitaksel.

Potensialet for systemiske og lokale legemiddelinteraksjoner i urinrøret skal vurderes for pasienter som tar et legemiddel med kjente interaksjoner med paklitaksel, eller når det avgjøres å starte opp legemiddelbehandling av en pasient som har fått behandling med DCB. Metabolismen til paklitaksel katalyseres av cytokrom P450-isoenzymene CYP2C8 og CYP3A4, og det er et substrat av P-glykoprotein. Potensielle legemiddelinteraksjoner kan oppstå med ethvert legemiddel som påvirker disse isoenzymene. Ved fravær av formelle studier av legemiddelinteraksjoner skal det utvises forsiktighet når paklitaksel administreres.

o KARSINOGENITET, GENTOKSISITET OG REPRODUKSJONSTOKSIKOLOGI

Ingen langsiktige studier har blitt utført for å evaluere det karsinogene potensialet til legemidlet paklitaksel eller til Optilume DCB, og det finnes ingen tilstrekkelige og godt kontrollerte publiserte studier om gravide kvinner eller om menn som planlegger å bli far. Paklitaksel hemmer cellespredning ved å interagere med mikrotubuli, og én konsekvens er tap av hele kromosomer under celledeling.

NORSK

Denne indirekte virkningen er konsistent med positive responser i mikronukleusbaserte gentoksisitetsanalyser in vitro og in vivo, som påviser DNA-fragmenter. Positive resultater har også blitt rapportert for unormale endringer i kromosomer i primære humane lymfocytter. Det er ikke kjent om paklitaksel har en separat direkte virkning på DNA ved generering av DNA-trådbrudd eller -fragmenter. Det er negativt i analyser for genmutasjon, inkludert salmonella og CHO/HPRT.

Studier utført på rotter og kaniner som mottok i.v. paklitaksel under organogenese, avdekket evidens for maternal toksisitet, embryotoksisitet og føtotoksisitet ved doser på henholdsvis 1 og 3 mg/kg (ca. 13 og 39 ganger dosen som leveres av Optilume DCB belagt med 5,5 mg paklitaksel (10 mm x 50 mm ballong) justert for kroppsvekt). Ingen teratogenisitet ble observert hos drektige rotter som mottok daglige i.v. paklitakseldoser på 1 mg/kg (en daglig dose på omtrent 13 ganger dosen til Optilume DCB (10 mm x 50 mm), justert for kroppsvekt).

Den behandlende legen skal veie den potensielle medisinske nytten ved Optilume DCB-kateteret opp mot disse gentoksiske og reproduktive risikoene. ADVARSEL: Det urethrale DCB inneholder paklitaksel, et kjent gentoksin. Menn skal ha beskyttet sex (bruke kondom) i 30 dager etter behandling.

10.0 HVORDAN DET LEVERES

Optilume DCB-kateteret leveres STERILT og er kun til engangsbruk (sterilisert med etylenoksid). DCB-kateteret ligger i et emballasjesystem med to poser (folie- og Tyvek-pose) i en eske med én enkelt enhet.

11.0 OPPBEVARING

Det urethrale DCB-kateteret skal oppbevares i romtemperatur på et tørt sted, i originalemballasjen. Enheten skal brukes før "Brukes innen"-datoen på emballasjen.

12.0 ANBEFALT UTSTYR

Klargjør følgende utstyr ved bruk av steril teknikk:

- Ledevaier av egnet størrelse med fleksibel tupp (se produktetiketten)
- Cystoskop (fortrinnsvis fleksibelt)
- Sterilt saltvann
- 10 ml sprøyte
- Toveis stoppekran
- Fyllingsenhet med manometer
- Kontrastmiddel – Merk: Valgfritt for bruk med prosedyrer veiledet med fluoroskopi

13.0 BRUKSANVISNING

13.1 FØR BRUK

Periprosedyre-medisinering

Det anbefales at leger følger retningslinjer for preprosedyre-medisinering og forberedelser før en endoskopisk prosedyre, inkludert administrering av et preprosedyre-antibiotikum etter behov. Det anbefales også å gi perorale NSAID før prosedyren.

Hvis en urinveisinfeksjon (UVI) er til stede på behandlingstidspunktet, må pasienten behandles inntil infeksjonen er kurert, før behandlingsprosedyren kan finne sted.

13.2 KLARGJØRING AV MÅLSTRIKTUR

Urethral predilatering av målstrikturen ved bruk av en egnet klargjøringsmetode fastsatt av behandlende lege (ubelagt dilateringsballong eller DVIU), anbefales for strikturer med høy grad av stenose eller som vanskelig kan passeres, før bruk av Optilume DCB. Utfør en predilatering for å «utvide» strikturen. Dette er definert som en diameter på den dilaterte strikturens lumen > 20F eller > 50 % større enn den ikke-dilaterte strikturens lumen.

13.3 ENHETENS STØRRELSE

Kontroller at diameteren til valgt DCB-ballong ved nominelt trykk er den samme som, eller litt større enn, diameteren til det friske urinrøret som grenser opp mot den distale kanten av strikturen. Ballongdiameteren delt på det distale, friske, tilstøtende urinrøret defineres som strekkforholdet.

Størrelse på bulbært urinrør
For bulbære strikturer må strekkforholdet mellom ballongdiameteren og det distale, friske urinrøret ikke overskride 1,3. Hvis størrelsen på urinrøret faller mellom tilgjengelige enhetsstørrelser, bruker du den største størrelsen forutsatt at strekkforholdet er mindre enn eller lik 1,3. Hvis den neste større størrelsen gir et strekkforhold som er større enn 1,3, bruker du den minste størrelsen.

Størrelse på penilt urinrør
For penile urinrørsstrikturer velger du ballongdiameteren som passer best til det distale, friske urinrøret. Strekkforholdet til det penile urinrøret må ikke overskride 1:1. Hvis størrelsen på urinrøret faller mellom tilgjengelige ballongstørrelser, velger du den minste ballongstørrelsen. Strekkforholdet på 1:1 MÅ IKKE OVERSKRIDES.

For både det penile og bulbære urinrøret må lengden på DCB-ballongen være lenger enn lengden på strikturen som skal behandles. Ballonglengden må være omtrent 0,5–1 cm lenger enn strikturen på begge sider. Hvis strikturlengden for eksempel er 2 cm, velger du en DCB-ballong som er 3 cm.

13.4 KLARGJØRING AV BALLONGKATETER

Tøm ut luft fra DCB-kateteret. Kateterets ballonglumen inneholder luft. Denne luften må fjernes for å sikre at ballongen bare fylles med væske når kateteret er inne i urinrøret.

1. Fest stoppekranen i åpen stilling til ballongens fyllingskobling.
2. Fest en sprøyte halvfull med saltvann til stoppekranen.

3. Hold sprøytespissen ned og trekk tilbake stempelet til sprøytens fulle volum (dette danner maksimalt undertrykk), og hold til det ikke lenger kommer luftbobler ut av saltvannet i sprøyten. Gjenta etter behov for å tømme luften fra kateteret og bytte det ut med saltvann. Hold stempelet tilbake, vri på stop pekranen for å opprettholde vakuum, og fjern sprøyten. Fyll en fyllingsenhet halv full med fysiologisk saltvann eller 1:1 kontrast:saltvann hvis det brukes fluoroskopi, og tøm luften fra slangen.
4. Fest fyllingsenheten til stoppekranen på ballongkateteret, vri på stoppekranen, og trekk vakuum inn i fyllingsenheten.

13.5 INNFØRING AV OPTILUME DCB

1. Plasser en 0,97 mm (0,038") ledevaier med den fleksible tuppen kveilet opp i blæren ved hjelp av et cystoskop.
2. Fjern ballongbeskyttelsen fra tuppen av DCB-kateteret.

   Forsiktig: *Vær forsiktig når en ballong belagt med paklitaksel føres gjennom ethvert cystoskopsystem. Minimer håndteringen og ikke berør ballongen. Ikke tørk av ballongen med tørt, vått eller smurt gasbind eller noe løsemiddel som kan skade integriteten til den legemiddelbelagte ballongen.*
3. Før frem DCB-kateteret i cystoskopets arbeidskanal. Alternativt kan ledevaieren og ballongkateteret plasseres atskilt fra cystoskopets arbeidskanal for plassering side ved side.
4. Bruk cystoskopet til å veilede plasseringen av DCB. DCB kan også plasseres med fluoroskopi ved bruk av de røntgentette markørene som befinner seg under overgangen der ballongens hoveddel blir kjegleformet.

   Forsiktig: *Ikke før frem ledevaieren eller ballongdilateringskateteret hvis du møter motstand, uten først å fastslå årsaken til motstanden og iverksette egnede tiltak.*

13.6 FYLLING AV OPTILUME DCB

Forsiktig: *Fyllingsenheter kan oppnå svært høyt trykk med minimal innsats. Det anbefales sterkt å bruke en fyllingsenhet med høytrykksmåler for å optimalisere dilateringskraften slik at urinrørsstrikturen kan overkommes og legemiddel kan trenge inn i det utvidede urotelet.*

1. Sørg for at urinrøret er skylt med saltvann.
2. Plasser DCB tvers over strikturen med cystoskopet distalt for ballongen (bort fra blæren) for å visualisere at ballongen får riktig plassering over strikturen. Hold ballongen i posisjon uten fylling i minst 1 minutt før fylling. Kontroller ved hjelp av fluoroskopi at ballongens røntgentette markører er i riktig posisjon.
3. Fyll ballongen til det nominelle sprengtrykket ved hjelp av fyllingsenheten. Ikke overskrid ballongens nominelle sprengtrykk (RBP). Opprettholdtrykket i minst 5 minutter, eller til ønsket dilatering er oppnådd.
4. Tøm ballongen ved å påføre vakuum på ballongen med fyllingsenheten. Når ballongen er helt tømt, trekkes ledevaieren og DCB langsomt ut. Hvis det møtes lett motstand når ballongen fjernes, skal kateteret roteres forsiktig for å hjelpe ballongen med å folde seg rundt kateterskaftet og forenkle uttrekkingen.

   Forsiktig: *Hvis det møtes motstand når en ledevaier fjernes gjennom et kateter gjennom et cystoskop, skal du STOPPE og fjerne dem samlet, på samme tid, som en komplett enhet for å unngå skade på ledevaieren, kateteret eller pasientanatomien.*
5. Hvis produktet svikter før eller under fylling (men ved mindre enn RBP), skal DCB byttes ut og fylles i henhold til prosedyren. Hvis svikten oppstår etter fylling til nominelt sprengtrykk, skal ikke DCB-prosedyren gjentas.
6. Sett inn et 12–14 Fr glatt Foley-kateter, og la det være på plass i minst 2 dager eller ifølge standardbehandling, avhengig av hva som er lengst.

13.7 FØYELIGHETSSKJEMA

18 Fr (6 mm) x 30 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**RBP**	8,54

30Fr (10 mm) x 30 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30Fr (10 mm) x 50 mm

(ATM) Trykk	kPa		(mm) Ballong
6,0	600	**Nominelt**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**RBP**	10,44

Forsiktig: *Det nominelle sprengtrykket må ikke overskrides. Se produktetiketten for nominelle sprengtrykk. Fylling over det nominelle sprengtrykket kan gjøre at ballongen sprekker. Hvis trykket i ballongen minker under fylling, eller hvis ballongen sprekker under dilatering, skal prosedyren avbrytes umiddelbart. Tøm ballongen forsiktig og trekk den ut av urinrøret. Ikke fyll den på nytt.*

14.0 GARANTI

Urotronic garanterer at det er utvist rimelig forsiktighet under utforming og produksjon av dette produktet. Garantien erstatter og utelukker alle andre garantier som ikke er uttrykkelig gitt i dette dokumentet, det være seg uttrykkelige eller underforståtte i kraft av lov eller på annen måte, inkludert, men ikke begrenset til, enhver underforstått garanti for et bestemt formål. Håndtering, oppbevaring, rengjøring og sterilisering av denne enheten samt andre faktorer vedrørende pasient, diagnose, behandling, kirurgiske prosedyrer og andre temaer utenfor Urotronics kontroll, berører enheten og resultater oppnådd ved bruk av enheten direkte. Urotronics forpliktelse etter denne garantien begrenser seg til å reparere eller bytte ut denne enheten. Urotronic skal ikke være ansvarlig for noe tilfeldig eller følgemessig tap, skade eller kostnad som direkte eller indirekte oppstår som følge av bruk av denne enheten. Urotronic påtar seg ikke noe ansvar for enheter som er gjenbrukt, reprosessert eller resterilisert, og gir ingen garantier, uttrykte eller underforståtte, inkludert, men ikke begrenset til, for et bestemt formål når det gjelder slike enheter.

15.0 SYMBOLER SOM BENYTTES PÅ ENHETSETIKETTENE

	Mengde med 1 per boks
	Forsiktig: Føderal lov begrenser denne enheten til salg av eller etter ordre fra en lege.
	Angir datoen da den medisinske enheten ble produsert.
	Må ikke resteriliseres
	Må ikke gjenbrukes
	Må ikke brukes hvis emballasjen er skadet
	Knuselig
	Brukes innen-dato
	Holdes unna sollys
	Holdes tørt
	Produsent
	Inneholder ikke lateks
	Temperaturgrense 15 °C–30 °C
	Forsiktig: Se bruksanvisningen
	Sterilisert med etylenoksid
	Katalognummer
	Lotnummer
	CE-merket i henhold til direktiv 93/42/EØF om medisinsk utstyr (meldt organ nr. 1434)
	Autorisert representant fra EU

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OPTILUME®

URETRAL LÄKEMEDELSBELAGD BALLONGKATETER

Bruksanvisning

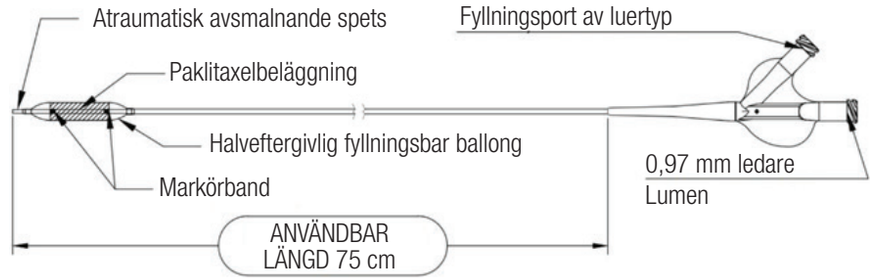
SVENSKA

Innehållsförteckning

1.0 PRODUKTBESKRIVNING

1.1 Ballongkateter

Optilume uretral, läkemedelsbelagd ballongkateter (DCB) är en ledare och flexibel cystoskopkompatibel over-the-wire-kateter (OTW) på 0,97 mm med dubbla lumen och avsmalnande atraumatisk spets. DCB-enheten förs in för att utöva radiell kraft i syfte att dilatera smala uretrala segment (strikturer). Kateterns distala ände är försedd med en halveftergivlig fyllningsbar ballong som är belagd med en egenutvecklad beläggning som innehåller den aktiva läkemedelssubstansen paklitaxel. Denna läkemedelsbeläggning täcker ballongens arbetslängd. Enheten har två röntgentäta markörband som indikerar ballongens arbetslängd.



Enheten har steriliserats med etylenoxid i en Tyvek-påse. Efter steriliseringen förseglas katetern i fodralet i en foliepåse med torkmedel och placeras i en enstyckskartong. Varje DCB-enhet levereras med ett skyddshölje som täcker kateterns läkemedelsbelagda ballongdel. Ett diagram över ballongens eftergivlighet finns på etiketten på Tyvek-påsen.

1.2 Läkemedelsbeläggning

Läkemedelsbeläggningen består av den aktiva läkemedelssubstansen paklitaxel samt hjälpämnen. Läkemedelsbeläggningen täcker hela arbetslängden på kateterns ballongkomponent. Läkemedelsbeläggningen är jämnt fördelad över ballongens yta med en koncentration på 3,5 µg/mm^2. Läkemedelsbeläggningens viktigaste funktion är att frisätta paklitaxel till urotelium under ballongvidgningen.

Doseringsmatris för DCB

Katalognummer	Diameter (Fr/mm)	Längd (mm)	Paklitaxeldos (mg)
1110-06030C	18,0/6,0	30	2,0
1110-06050C	18,0/6,0	50	3,3
1110-08030C	24,0/8,0	30	2,6
1110-08050C	24,0/8,0	50	4,4
1110-10030C	30,0/10,0	30	3,3
1110-10050C	30,0/10,0	50	5,5

SVENSKA

2.0 AVSEDD ANVÄNDNING

Optilume uretral, läkemedelsbelagd ballongkateter (DCB) är avsedd för behandling av strikturer i anterior uretra hos vuxna män.

3.0 ANVÄNDNINGSOMRÅDE

Optilume uretral DCB-kateter används för att behandla män ≥18 år med besvärande urinvägssymptom, förknippade med recidiverande, anterior uretrastriktur. Den är utformad för att användas som en dilatationsballong för en enkel, tandem eller diffus, anterior uretrastriktur med en längd på ≤3 cm, eller som en kompletterande behandling med andra dilatationsenheter och/eller ingrepp.

4.0 KONTRAINDIKATIONER

Den uretrala läkemedelsbelagda ballongvidgningskatetern (DCB) är kontraindicerad för användning hos

- Patienter med känd överkänslighet för paklitaxel eller strukturellt besläktade sammansättningar.
- Patienter med lesioner som inte kan korsas med en 0,97 mm ledare.

5.0 VARNINGAR

- Den uretrala DCB-enheten levereras steril och endast för engångsbruk. Den får ej upparbetas eller omsteriliseras. Upparbetning och omsterilisering kan öka risken för patientinfektion samt risken för äventyrad produktprestanda.
- Foliepåsen och utsidan på innerpåsen är ICKE-STERILA. INNEHÅLLET i innerpåsen är STERILT. Använd det omedelbart så snart foliepåsen har öppnats.
- Använd inte produkten om infektion föreligger i uretra (UTI) eller urinblåsan. Infektionen måste läkas innan strikturen behandlas med Optilume DCB.
- DCB-enheten får endast användas av läkare med erfarenhet och kännedom om de kliniska och tekniska aspekterna av uretral ballongvidgning.
- Innan DCB-enheten används ska läkaren läsa och förstå bruksanvisningen. Underlåtelse att följa indikationerna, kontraindikationerna, restriktionerna, varningarna och försiktighetsåtgärderna kan leda till komplikationer.
- Använd inte produkten efter sista användningsdag.
- DCB-enheten innehåller paklitaxel, ett känt gentoxin. Män ska ha skyddat sex (använda kondom) i 30 dagar efter behandlingen.
- Övervaka patienten för tecken på anafylaxi eller överkänslighet mot paklitaxel.
- Använd aldrig luft eller någon gasformigt medium för att fylla DCB-enheten.
- Under användningen ska DCB-enheten manipuleras under direkt visualisering via cystoskopi eller fluoroskopisk observation med hög kvalitet.
- Manipulera inte DCB-enheten i fyllt tillstånd.
- Om motstånd påträffas vid någon tidpunkt under insättningsförfarandet får passage inte tvingas fram. Motståndet kan orsaka skador på enheten eller dess lumen. Dra försiktigt tillbaka katetern.
- Män med sexpartners i fertil ålder, bör använda kondom i minst 90 dagar efter behandlingen.
- Biverkningar av paklitaxel och observerade symtom, som främst härrörde från IV-infusionsstudier av läkemedlet vid behandling av cancerpersoner, inkluderar
    - Kromosomavvikelser och risk för cancer
    - Fosterskada när en gravid kvinna exponeras
    - Anafylaxi och överkänslighet mot paklitaxel
    - Hämning av läkning av uretra efter ingreppet
    - Myelosuppression, inklusive: neutropeni, leukopeni, trombocytopeni, anemi
    - Arytmi
    - Perifer neuropati
    - Myalgi eller artralgi
    - Alopeci
    - Hypotension
    - Illamående, kräkningar eller diarré
    - Förhöjt bilirubin, ALP och AST
    - Den potentiella effekten på levern och njurarna är okänd och har inte studerats.

Mängden paklitaxel, som levererades lokalt under Optilume DCB-ingreppet, är mycket lägre än en enkel dos av systemisk kemoterapi, som ges till cancerpatienter, och läkemedlet verkar väsentligen vara kvar i uretra.

6.0 FÖRSIKTIGHETSÅTGÄRDER

- Fyll alltid ballongen med en steril vätska (steril koksaltlösning eller 50 % kontrastblandning). Fyll den aldrig med luft, koldioxid eller någon annan gas. DCB-enheten får inte fyllas utöver det angivna bristningstrycket (RBP). Överfyll inte ballongen.
- Ballongkatetrar är avsedda för användning av läkare med utbildning och erfarenhet av teknikerna för ballongkatetervidgning.
- För att säkerställa korrekt reglering av trycket i ballongen rekommenderas att en ballongfyllningsenhet och en tryckmätare används.
- Töm ballongen helt innan du försiktigt avlägsnar enheten från uretra. Att använda för stor kraft för att dra tillbaka ballongen kan åsamka trauma på vävnad.
- Inspektera noga DCB-enheten och förpackningen före användning. Använd inte katetern om den är skadad eller om dess storlek, form eller skick är olämpligt för det tilltänkta ingreppet.
- Sänk inte ned ballongdelen på DCB-enheten i, eller torka av den med, någon vätska eftersom läkemedelsbeläggningens integritet kan skadas eller äventyras. Byt ut en DCB-enhet där ballongen har kommit i kontakt med vätskor före användningen.
- Använd torra sterila handskar eller torra gasvävskompresser för att hantera DCB-enheten före användningen. Var försiktig och minimera kontakten med den belagda ballongdelen på enheten.
- Fyll aldrig DCB-enheten utanför kroppen eller innan den når målstrikturen, eftersom detta kan förstöra beläggningens integritet.
- Försök inte föra DCB-enheten genom ett cystoskop som har en mindre storlek i French än vad som anges på etiketten.
- DCB-enhetens arbetslängd måste täcka hela målstrikturens längd.

- För korrekt läkemedelstillförsel till målstrikturen ska beläggningen få hydrera i uretra i minst 60 sekunder före fyllning och DCB-enheten sedan hållas fylld i minst 5 minuter. För att optimera strikturdilatationen kan längre fyllningstider på >5 minuter användas enligt operatörens eget val.
- Om det blir något fel på produkten före eller under fyllningen, ska DCB-enheten bytas ut och ny fyllning utföras enligt beskrivet förfarande. Om felet uppstår efter fyllning till angivet bristningstryck (RBP) ska DCB-förfarandet inte upprepas.
- Efter användning kan denna produkt utgöra en potentiell biologisk risk. Hantera och kassera den i enlighet med vedertagen medicinsk praxis och gällande lokala föreskrifter.
- Vårdpersonalen bör inte använda latexhandskar för att undvika allergiska reaktioner hos patienter som är allergiska mot latex.
- Förberedelse av uretraöppningens mållesion, med användning av lämplig förberedelsemetod för lumen, enligt vad som bestämts av den behandlande läkaren, krävs före användning av Optilume DCB.
- Förberedelse av lumen, endast med användning av förutvidgning med en obelagd ballongkateter eller DVIU, studerades i Robust I kliniska studie.
- I kliniska studier krävdes visuell bekräftelse av signifikant striktur (≤12 F urinrörsdiameter) via cystoskopi eller urinrogram och registrering var begränsad till patienter som uppvisade subjektiva och objektiva symptom på uretrastriktur (International Prostate Symptom Score [IPSS] >13, maximal urinflödeshastighet <15 ml/sek). Patienterna hade genomgått minst en tidigare endoskopisk behandling innan de registrerades i de kliniska studierna.
- Säkerhets- och effektivitetsdata har inte fastställts under den kliniska studien för att stödja behandlingen av strikturer hos patienter med:
  - BPH
  - Radikal prostataektomi
  - Bäckenstrålning
  - Botoxbehandling
  - Mer än 1 striktur
  - Tidigare uretroplastik i anteriora uretra
  - Bakteriell uretrit eller gonorré
  - Närvaro av en artificiell sfinkter med penisimplantat eller uretra-/prostatastent
  - Känd neurogen blåsa, sfinkteravvikelser eller dålig detrusormuskelfunktion.
  - Diagnostiserad med Lichen-skleros, eller tidigare reparation av hypospadi.
  - Anamnes under de senaste 5 åren på cancer i urinblåsan eller prostata
  - Striktur på grund av balanitis xerotica obliterans (BXO)
  - Uretratumörer eller peniscancer

7.0 ANVÄNDNING I SÄRSKILDA POPULATIONER

Säkerheten och effekten av den uretrala DCB har inte fastställts hos barn (<18 år) eller hos kvinnor. Användning av den uretrala DCB hos patienter ≥18 år och äldre sker enligt läkarnas bedömning.

8.0 MÖJLIGA KOMPLIKATIONER

Möjliga komplikationer i samband med användningen av Optilume DCB-kateter liknar de som är förknippade med procedurer för uretradilatation av standardtyp. Möjliga komplikationer kan innefatta, men begränsas inte till

- smärta och ömhet
- blåsspasm från placeringen av Foley-katetern
- Vävnadstrauma i omgivande strukturer, inklusive uretraskada
- hematuri
- läkemedelsreaktioner, allergiska reaktioner mot det kontrastmedel som används under diagnostiskt uretrogram
- urinvägsinfektion
- vävnadsperforation
- återfall av striktur som kräver förnyat ingrepp
- inkontinens.
- Dysuri
- Feber
- Urinretention

9.0 LÄKEMEDELSINFORMATION

o VERKNINGSMEKANISM

Den uretrala DCB-beläggningen innehåller paklitaxel, en antimitotisk läkemedelssubstans som specifikt binds till och stabiliserar mikrotubuli. Paklitaxel har rapporterats hämma proliferering och migration av glatta muskelceller och fibroblastceller samt utsöndring av extracellulär matris. Dessa effekter i kombination kan resultera i hämning av uroteliumhyperplasi och därmed återfall av striktur.

o LÄKEMEDELSINTERAKTIONER

Inga formella studier på läkemedelsinteraktioner har genomförts för den uretrala DCB-enheten. Respektive bruksanvisningar för alla läkemedel som används i samband med DCB-enheten bör konsulteras för interaktioner med paklitaxel.

Hänsyn bör tas till risken för potentiella systemiska och lokala läkemedelsinteraktioner i uretra hos en patient som man vet tar ett läkemedel med kända interaktioner med paklitaxel eller när man fattar beslut om att sätta in läkemedelsterapi för en patient som har behandlats med DCB. Paklitaxels metabolism katalyseras av de cytokroma P450-isoenzymerna CYP2C8 och CYP3A4 och är ett substrat av P-glykoprotein. Potentiella läkemedelsinteraktioner kan ske med varje läkemedel som påverkar dessa isoenzymer. I brist på formella studier på läkemedelsinteraktioner bör försiktighet iakttas vid administrering av paklitaxel.

o KARCINOGENICITET, GENTOXICITET OCH REPRODUKTIONSTOXIKOLOGI

Inga långtidsstudier har utförts för att utvärdera den carcinogena potentialen för läkemedlet paklitaxel eller av Optilume DCB, och därför har inga adekvata och välkontrollerade studier publicerats för gravida kvinnor och män som ska bli fäder. Paklitaxel hämmar celltillväxt genom att interagera med mikrotubuli och en konsekvens är förlusten av hela kromosomer vid celldelning. Denna indirekta verkan överensstämmer med positiva resultat in vitro och in vivo för

SVENSKA

mikronukleära genotoxiska analyser, vilka detekterar DNA-fragment. Positiva resultat har också rapporterats för kromosomavvikelser hos primära, humana lymfocyter. Det är inte känt om paklitaxel har en separat, direkt verkan på DNA vid framställande av DNA-strängbrott eller fragment. Det är negativt vid analyser för genmutation, inklusive salmonella och CHO/HPRT.

Studier, som utförts på råttor och kaniner som fått IV paklitaxel under organutveckling, uppvisade bevis för förlossningstoxicitet, embryotoxicitet och fostertoxicitet vid doseringar på 1 respektive 3 mg/kg (cirka 13 och 39 gånger den dos som levererats av Optilume DCB, belagd med 5,5 mg paklitaxel (10 mm x 50 mm ballong) med justering för kroppsvikt). Ingen teratogenicitet observerades hos gravida råttor som dagligen mottog IV paklitaxel-doser med 1 mg/kg (en daglig dos som är cirka 13 gånger dosen från den största Optilume DCB (10 mm x 50 mm), justerad för kroppsvikt). Den behandlande läkaren bör väga de potentiella, medicinska fördelarna med Optilume DCB-katetern mot dessa genotoxiska och reproduktionsrisker. VARNING: Den uretrala DCB-enheten innehåller paklitaxel, ett känt gentoxin. Män ska ha skyddat sex (använda kondom) i 30 dagar efter behandlingen.

10.0 LEVERANSFORM

Optilume DCB-katetern levereras STERIL och är endast avsedd för engångsbruk (steriliserad med etylenoxid). DCB-enheten levereras i ett förpackningssystem med dubbla påsar (foliepåse och Tyvek-påse), inneslutna i en enstycksförpackning.

11.0 FÖRVARING

Den uretrala DCB-enheten bör förvaras vid rumstemperatur på en torr plats i sin originalförpackning. Enheten ska användas före den ”sista användningsdag” som anges på förpackningen.

12.0 REKOMMENDERADE ARTIKLAR

Förbered följande artiklar med steril teknik:

- Ledare av lämplig storlek med flexibel spets (se produktens märkning)
- Cystoskop (flexibelt är att föredra)
- Steril koksaltlösning
- 10 ml spruta
- Tvåvägskran
- Fyllningsanordning med manometer
- Kontrastmedel – Obs! Valfritt för användning med fluoroskopiskt guidade procedurer

13.0 ANVÄNDNINGSANVISNINGAR

13.1 FÖRE ANVÄNDNINGEN

Medicinering i samband med ingreppet

Det rekommenderas att läkare följer riktlinjerna för mediciner före ingreppet och förberedelser för ett endoskopiskt ingrepp, inklusive administrering av ett antibiotikum före ingreppet, i förekommande fall. Orala NSAID rekommenderas också att ges före ingreppet.

Om en urinvägsinfektion (UTI) förekommer vid behandlingstillfället, måste patienten behandlas tills infektionen botas innan behandlingsingreppet kan äga rum.

13.2 FÖRBEREDELSE AV MÅLSTRIKTUREN

Uretral förutvidgning av målstrikturen, med användning av lämplig förberedelsemetod, som bestämts av den behandlande läkaren (Obelagd utvidgningsballong eller DVIU), rekommenderas för strukturer med många stenoser och som är svåra att korsa, före användning av Optilume DCB. Genomför en förutvidgning för att ”få fram” strikturen. Detta definieras som den dilaterade strikturens lumendiameter >20 F eller >50 % större än det icke-dilaterade strikturlumenet.

13.3 DIMENSIONERING AV ENHETEN

Verifiera att den valda DCB-ballongens diameter vid nominellt tryck har samma eller något större diameter än den friska uretra, intill strikturens distala kant. Ballongens diameter dividerad med frisk närliggande distal uretra definieras som töjningskvoten.

Storleksbestämning av bulbär uretra

För bulbära strikturer som inte överstiger en töjningskvot på 1,3 mellan ballongens diameter och distal, frisk uretra. Om uretras storlek faller mellan tillgängliga enhetsstorlekar ska den större storleken användas, förutsatt att töjningskvoten är mindre än eller lika med 1,3. Om nästa större storlek ger en töjningskvot som överstiger 1,3 ska den mindre enheten användas.

Storleksbestämning av uretra i penis

För uretrastrikturer i penis ska den diameter på ballongen som bäst motsvarar distal, frisk uretra väljas. Töjningskvoten på uretra i penis får inte överstiga 1:1. Om uretras storlek faller mellan tillgängliga ballongstorlekar ska den mindre ballongstorleken väljas. ÖVERSKRID INTE en töjningskvot på 1:1.

För både uretra i penis och bulbär uretra ska DCB-ballongens längd inte vara längre än den striktur som ska behandlas. Ballonglängden måste sträcka sig ca 0,5–1 cm bortom strikturen på båda sidor. Exempel: Om strikturens längd är 2 cm, välj en DCB-ballong som är 3 cm.

13.4 FÖRBEREDELSE AV BALLONGKATETER

Töm luften ur DCB-katetern. Kateterns ballonglumen innehåller luft, och denna luft måste avlägsnas för att säkerställa att endast vätska fyller ballongen medan katetern befinner sig i uretra.

1. Anslut kranen i öppet läge till ballongfyllningskopplingen.
2. Anslut sprutan, till hälften fylld med koksaltlösning, till kranen.
3. Håll ned sprutspetsen och dra tillbaka kolven till sprutans fulla volym (detta skapar ett maximalt undertryck) och vänta sedan tills inga luftbubblor ses komma ut ur koksaltlösningen i sprutan. Upprepa vid behov för att tömma ut luften ur katetern, och ersätt den med saltlösning. Håll tillbaka kolven och vrid kranen för att bibehålla vakuum, och ta bort sprutan. Fyll en fyllningsanordning till hälften med normal koksaltlösning, eller kontrastmedel tillsammans med koksaltlösning till proportionerna 1:1 om fluoroskopi används, och töm slangen på luft.

4. Fäst uppblåsningsenheten på kranen på ballongkatetern, vrid kranen och dra vakuum på uppblåsningsenheten.

13.5 INFÖRANDE AV OPTILUM DCB

1. Placera ledaren på 0,97 mm med den flexibla spetsen hoprullad i urinblåsan, med hjälp av ett cytoskelett.
2. Avlägsna ballongskyddet från spetsen på DCB-katetern.

   Försiktighet: *Försiktighet bör iakttas när en ballong belagd med paklitaxel förs genom något cystoskopsystem. Minimera hanteringen och vidrör inte ballongen. Torka inte av ballongen med en torr eller våt kompress eller en kompress med glidmedel eller lösningsmedel som skulle kunna skada den läkemedelsbelagda ballongens integritet.*

3. För in DCB-katetern i cystoskopets arbetskanal. Alternativt kan ledaren och ballongkatetern placeras separat från cystoskopets arbetskanal för en placering sida vid sida.
4. Använd cystoskopet för att vägleda placeringen av DCB. Placera alternativt DCB med fluoroskopi genom att använda de röntgentäta markörerna belägna nedanför övergången mellan ballongen/konen.

   Försiktighet: *För inte in ledaren eller ballongvidgningskatetern om ett motstånd påträffas, utan att först fastställa orsaken till detta motstånd och vidta lämplig åtgärd.*

13.6 FYLLNING AV OPTILUM DCB

Försiktighet: *Fyllningsanordningar kan skapa mycket höga tryck med minimal ansträngning. Användning av en fyllningsanordning med högtrycksmätare rekommenderas starkt för att optimera vidgningskraften mot den uretrala strikturen och medge läkemedelspenetration in i det framtagna urotelium.*

1. Se till att uretra spolas med saltlösning.
2. Placera DCB över strikturen, med cystoskopet distalt om ballongen (på avstånd från urinblåsan), för att visualisera korrekt placering av ballongen över strikturen. Lämna ballongen på plats, ofylld, i minst 1 minut före fyllningen. Kontrollera att de röntgentäta markörerna på ballongen befinner sig i rätt position med hjälp av fluoroskopi.
3. Fyll ballongen till det angivna bristningstrycket med hjälp av fyllningsenheten. Överskrid inte ballongens angivna bristningstryck (RBP). Bibehåll trycket i minst 5 minuter eller tills önskad utvidgning har uppnåtts.
4. Töm ballongen genom att applicera vakuum på ballongen med fyllningsenheten. När ballongen är helt tömd ska ledaren och DCB-enheten långsamt dras tillbaka. Om ett lätt motstånd känns när ballongen tas bort, ska du försiktigt vrida på katetern för att hjälpa ballongen att vika sig runt kateterskaftet och underlätta utdragningen.

   Försiktighet: *Om ett motstånd påträffas när du avlägsnar en ledare genom en kateter i ett cystoskop, ska du STOPPA förfarandet och avlägsna dem tillsammans samtidigt som en enda enhet för att förhindra skada på ledaren, katetern eller patientens anatomi.*

5. Om det blir något fel på produkten före eller under fyllningen (men mindre än RBP), ska DCB-enheten bytas ut och ny fyllning utföras enligt beskrivet förfarande. Om felet uppstår efter fyllning till angivet bristningstryck (RBP) ska DCB-förfarandet inte upprepas.
6. För in en smörjd Foley-kateter på 12–14 Fr och lämna på plats i minst 2 dagar eller enligt vårdstandarden, beroende på vad som är störst.

13.7 DIAGRAM ÖVER BALLONGENS EFTERGIVLIGHET

18 Fr (6 mm) x 30 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	6,11 (18 Fr)
8,0	800		6,23
10,0	1000		6,34
12,0	1200	**RBP**	6,45

18 Fr (6 mm) x 50 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	5,87 (18 Fr)
8,0	800		6,03
10,0	1000		6,16
12,0	1200	**RBP**	6,25

24 Fr (8 mm) x 30 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	7,98 (24 Fr)
8,0	800		8,16
10,0	1000		8,32
12,0	1200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	8,00 (24 Fr)
8,0	800		8,20
10,0	1000		8,37
12,0	1200	**RBP**	8,54

30 Fr (10 mm) x 30 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	9,83 (30 Fr)
8,0	800		10,09
10,0	1000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Tryck	kPa		(mm) Ballong
6,0	600	**Nominellt**	9,98 (30 Fr)
8,0	800		10,23
10,0	1000	**RBP**	10,44

Försiktighet: *Angivet bristningstryck får inte överskridas. Se produktens etikett för angivna bristningstryck. Fyllning över angivet bristningstryck kan göra att ballongen brister. Om tryckfall inträffar i ballongen under fyllningen, eller om ballongen brister under fyllningen, ska ingreppet omedelbart avbrytas. Töm ballongen försiktigt och dra ut den ur uretra. Fyll den inte på nytt.*

14.0 GARANTI

Urotronic garanterar att rimlig omsorg har iakttagits vid utformning och tillverkning av denna produkt. Denna garanti gäller i stället för och utesluter alla andra garantier som inte uttryckligen anges här, oavsett om dessa är uttryckliga eller underförstådda enligt lag eller på annat sätt, inklusive, men inte begränsat till, eventuella underförstådda garantier om något visst ändamål. Hantering, förvaring, rengöring och sterilisering av denna enhet samt andra faktorer som rör patienten, diagnosen, behandlingen, de kirurgiska ingreppen och annat som är utom Urotronics kontroll påverkar enheten direkt och de resultat som uppnås genom dess användning. Urotronics skyldighet enligt denna garanti är begränsad till reparation eller utbyte av den här enheten, och Urotronic skall inte hållas ansvarigt för några oavsiktliga eller följdskador, förluster, skador eller kostnader som uppstår direkt eller indirekt till följd av användning av denna enhet. Urotronic påtar sig inget ansvar för enheter som återanvänts, upparbetats eller omsteriliserats, och lämnar inga garantier, vare sig uttryckliga eller underförstådda, inklusive, men inte begränsat till, för något visst syfte, vad gäller sådana enheter.

15.0 SYMBOLER SOM ANVÄNDS PÅ ENHETENS ETIKETTER

1	Antal om 1 per kartong
Rx only	Försiktighet: Enligt amerikansk federal lag får denna utrustning endast säljas till läkare eller på läkares ordination.
	Anger det datum då den medicinska enheten tillverkades.
	Får ej omsteriliseras
	Får inte återanvändas
	Får ej användas om förpackningen har skadats
	Ömtålig
	Utgångsdatum
	Skyddas från solljus
	Förvaras torrt
	Tillverkare
LATEX	Innehåller inte latex
	Temperaturgräns 15 °C till 30 °C
	Försiktighet: Se bruksanvisningen
STERILE EO	Steriliserad med etylenoxid
REF	Katalognummer
LOT	Lotnummer
CE 1434	CE-märkt enligt EU:s direktiv 93/42/EEG om medicintekniska produkter (Anmält organ nr 1434)
EC REP	Auktoriserad EU-representant

Urotronic, Inc.
2495 Xenium Lane North
Minneapolis, MN 55441
USA

CE 1434

EC REP
MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany

OPTILUME®

ΟΥΡΗΘΡΙΚΟΣ ΚΑΘΕΤΗΡΑΣ ΜΕ ΜΠΑΛΟΝΙ ΕΠΙΚΑΛΥΜΜΕΝΟ ΜΕ ΦΑΡΜΑΚΟ

Οδηγίες χρήσης

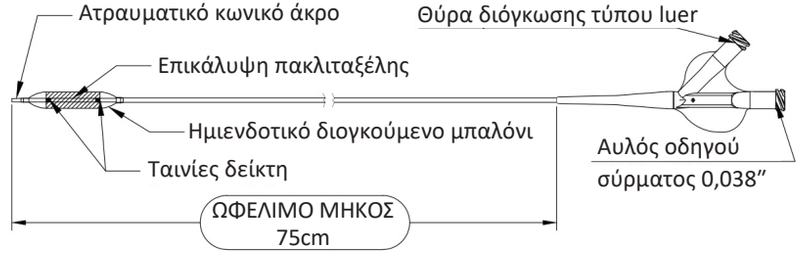
Ελληνικά

Πίνακας περιεχομένων

1.0 ΠΕΡΙΓΡΑΦΗ ΤΗΣ ΣΥΣΚΕΥΗΣ

1.1 Καθετήρας με μπαλόνι

Ο ουρηθρικός καθετήρας με μπαλόνι επικαλυμμένο με φάρμακο (DCB) Optilume είναι ένα οδηγό σύρμα 0,97 mm (0,038”) και ένας εύκαμπτος καθετήρας over-the-wire (OTW) συμβατός με κυστεοσκόπιο, ο οποίος διαθέτει σχεδιασμό διπλού αυλού και κωνικό ατραυματικό άκρο. Το DCB χρησιμοποιείται για τη διαστολή στενών τμημάτων της ουρήθρας (στενώσεων) ασκώντας πίεση ακτινικά. Το άπω άκρο του καθετήρα έχει ένα ημιενδοτικό διογκούμενο μπαλόνι το οποίο είναι επικαλυμμένο με μια αποκλειστική επικάλυψη που περιέχει τη δραστική φαρμακευτική ουσία, πακλιταξέλη. Η επικάλυψη φαρμάκου καλύπτει το μήκος εργασίας του σώματος του μπαλονιού. Η συσκευή έχει δύο ζώνες ακτινοσκιερών δεικτών που υποδεικνύουν το μήκος εργασίας του μπαλονιού.



Η συσκευή είναι αποστειρωμένη με αιθυλενοξείδιο μέσα σε θήκη Tyvek. Μετά την αποστείρωση, ο καθετήρας που βρίσκεται μέσα στη θήκη σφραγίζεται σε αλουμινένιο σακουλάκι μαζί με αποξηραντικό μέσο και συσκευάζεται μέσα σε ένα χαρτονένιο κουτί. Κάθε DCB παρέχεται με προστατευτικό θηκάρι το οποίο καλύπτει το επικαλυμμένο με φάρμακο τμήμα μπαλονιού του καθετήρα. Ένα διάγραμμα ενδοτικότητας του μπαλονιού βρίσκεται στην ετικέτα της θήκης Tyvek.

Ελληνικά

1.2 Επικάλυψη φαρμάκου

Η επικάλυψη φαρμάκου αποτελείται από το δραστικό φαρμακευτικό συστατικό, πακλιταξέλη και έκδοχα. Η επικάλυψη φαρμάκου καλύπτει το μήκος εργασίας του τμήματος μπαλονιού του καθετήρα. Η επικάλυψη φαρμάκου είναι ομοιόμορφα κατανεμημένη στην επιφάνεια του μπαλονιού σε συγκέντρωση 3,5 μg/mm^2. Το βασικό λειτουργικό χαρακτηριστικό της επικάλυψης φαρμάκου είναι ότι επιτρέπει την απελευθέρωση της πακλιταξέλης στο ουροθήλιο κατά τη διάρκεια της διόγκωσης του μπαλονιού.

Πίνακας δοσολογίας του DCB

Αριθμός καταλόγου	Διάμετρος (mm/Fr)	Μήκος (mm)	Δόση πακλιταξέλης (mg)
1110-06030C	18.0/6.0	30	2.0
1110-06050C	18.0/6.0	50	3.3
1110-08030C	24.0/8.0	30	2.6
1110-08050C	24.0/8.0	50	4.4
1110-10030C	30.0/10.0	30	3.3
1110-10050C	30.0/10.0	50	5.5

2.0 ΠΡΟΒΛΕΠΟΜΕΝΗ ΧΡΗΣΗ

Ο ουρηθρικός καθετήρας με μπαλόνι επικαλυμμένο με φάρμακο (DCB) Optilume προορίζεται για τη θεραπεία στενώσεων στην πρόσθια ουρήθρα σε ενήλικους άνδρες.

3.0 ΕΝΔΕΙΞΕΙΣ ΧΡΗΣΗΣ

Ο ουρηθρικός καθετήρας DCB Optilume χρησιμοποιείται για τη θεραπεία ανδρών ηλικίας ≥18 ετών με ενοχλητικά συμπτώματα κατά την ούρηση τα οποία σχετίζονται με υποτροπιάζουσα πρόσθια ουρηθρική στένωση. Έχει σχεδιαστεί για χρήση ως μπαλόνι διαστολής για μονή, διαδοχική ή διάχυτη πρόσθια ουρηθρική στένωση, μήκους ≤3 cm ή χρησιμοποιείται ως βοηθητική θεραπεία με άλλες συσκευές διαστολής ή/και άλλες επεμβάσεις.

4.0 ΑΝΤΕΝΔΕΙΞΕΙΣ

Ο ουρηθρικός καθετήρας διαστολής με μπαλόνι επικαλυμμένο με φάρμακο (DCB) αντενδείκνυται για χρήση σε:

- Ασθενείς με γνωστή υπερευαισθησία στην πακλιταξέλη ή σε δομικά σχετικές ενώσεις.
- Ασθενείς με αλλοιώσεις τις οποίες δεν μπορεί να διασχίσει ένα οδηγό σύρμα 0,038”.

5.0 ΠΡΟΕΙΔΟΠΟΙΗΣΕΙΣ

- Το ουρηθρικό DCB παρέχεται ΑΠΟΣΤΕΙΡΩΜΕΝΟ για μία χρήση μόνο. Μην επανεπεξεργάζεστε ή επαναποστειρώνετε. Η επανεπεξεργασία και η επαναποστείρωση θα μπορούσαν να αυξήσουν τον κίνδυνο λοίμωξης του ασθενούς και τον κίνδυνο να διακυβευτεί η απόδοση της συσκευής.
- Το αλουμινένιο σακουλάκι και η εξωτερική επιφάνεια της εσωτερικής θήκης είναι ΜΗ ΑΠΟΣΤΕΙΡΩΜΕΝΑ. Τα ΠΕΡΙΕΧΟΜΕΝΑ της εσωτερικής θήκης είναι ΑΠΟΣΤΕΙΡΩΜΕΝΑ. Χρησιμοποιήστε αμέσως μόλις ανοίξετε το αλουμινένιο σακουλάκι.
- Μη χρησιμοποιήσετε αυτήν τη συσκευή εάν υπάρχει λοίμωξη στην ουρήθρα (λοίμωξη του ουροποιητικού συστήματος - UTI) ή στην ουροδόχο κύστη. Η λοίμωξη πρέπει να αποκατασταθεί πριν από τη θεραπεία της στενώσεως με το Optilume DCB.
- Το DCB πρέπει να χρησιμοποιείται μόνο από ιατρούς που διαθέτουν εμπειρία και γνωρίζουν καλά τις κλινικές και τεχνικές πτυχές της διαστολής της ουρήθρας με μπαλόνι.
- Πριν από τη χρήση του DCB, οι ιατροί πρέπει να διαβάσουν και να κατανοήσουν τις οδηγίες χρήσης. Η μη τήρηση των ενδείξεων, των αντενδείξεων, των περιορισμών,
των προειδοποιήσεων και των προφυλάξεων μπορεί να οδηγήσει σε επιπλοκές.
- Μη χρησιμοποιείτε μετά την ημερομηνία λήξης.
- Το DCB περιέχει πακλιταξέλη, μια γνωστή γονοτοξίνη. Οι άνδρες θα πρέπει να λαμβάνουν τις απαραίτητες προφυλάξεις κατά τη σεξουαλική επαφή (να φορούν προφυλακτικό) για 30 ημέρες μετά τη θεραπεία.
- Παρακολουθείτε για ενδείξεις αναφυλαξίας ή υπερευαισθησίας στην πακλιταξέλη
- Ποτέ μη χρησιμοποιείτε αέρα ή οποιοδήποτε αέριο μέσο για να διογκώσετε το DCB.
- Κατά τη διάρκεια της χρήσης, οι χειρισμοί του DCB θα πρέπει να γίνονται υπό άμεση οπτική επαφή μέσω κυστεοσκόπησης ή ακτινοσκοπικής παρατήρησης υψηλής ποιότητας.
- Μην χειρίζεστε το DCB όταν βρίσκεται σε διογκωμένη κατάσταση.
- Εάν συναντήσετε αντίσταση οποιαδήποτε στιγμή κατά τη διάρκεια της διαδικασίας εισαγωγής, μην ασκείτε δύναμη για να επιτύχετε τη διέλευση. Η αντίσταση μπορεί να προκαλέσει ζημιά στη συσκευή ή στον αυλό. Αποσύρετε προσεκτικά τον καθετήρα.
- Άνδρες με ερωτικές συντρόφους που έχουν δυνατότητα τεκνοποίησης θα πρέπει να χρησιμοποιούν προφυλακτικό για 90 ημέρες τουλάχιστον μετά τη θεραπεία.
- Οι ανεπιθύμητες ενέργειες στην πακλιταξέλη και τα συμπτώματα που παρατηρήθηκαν προέρχονται κυρίως από μελέτες έγχυσης IV του φαρμάκου για τη θεραπεία ατόμων με καρκίνο και περιλαμβάνουν
    - Χρωμοσωμικές ανωμαλίες και κίνδυνο καρκίνου
    - Βλάβη στο έμβρυο όταν εκτίθεται γυναίκα που κυοφορεί
    - Αναφυλαξία και υπερευαισθησία στην πακλιταξέλη
    - Αναστολή της επούλωσης της ουρήθρας μετά την επέμβαση
    - Μυελοκαταστολή που περιλαμβάνει: ουδετεροπενία, λευκοπενία, θρομβοκυτταροπενία, αναιμία
    - Αρρυθμία
    - Περιφερική νευροπάθεια
    - Μυαλγία ή αρθραλγία
    - Αλωπεκίαση
    - Υπόταση
    - Ναυτία, έμετος ή διάρροια
    - Αυξημένη χολερυθρίνη, ALP και AST
    - Η πιθανή επίδραση στο ήπαρ και στα νεφρά είναι άγνωστη και δεν έχει μελετηθεί

Η ποσότητα της πακλιταξέλης που χορηγείται τοπικά κατά τη διάρκεια της διαδικασίας Optilume DCB είναι πολύ χαμηλότερη από μια εφάπαξ δόση συστηματικής χημειοθεραπείας που παρέχεται σε καρκινοπαθείς και το φάρμακο φαίνεται να παραμένει ουσιαστικά εντοπισμένο στην ουρήθρα.

6.0 ΠΡΟΦΥΛΑΞΕΙΣ

- Διογκώνετε πάντα με αποστειρωμένο υγρό (αποστειρωμένος φυσιολογικός ορός ή μείγμα 50% σκιαγραφικού). Ποτέ μη διογκώνετε με αέρα, διοξείδιο του άνθρακα ή οποιοδήποτε άλλο αέριο. Το DCB δεν πρέπει να διογκώνεται πέρα από την ονομαστική πίεση ρήξης (RBP). Μη διογκώνετε υπερβολικά το μπαλόνι.
- Οι καθετήρες με μπαλόνι προορίζονται για χρήση από ιατρούς που διαθέτουν εκπαίδευση και εμπειρία στις τεχνικές διαστολής καθετήρων με μπαλόνι.
- Για να διασφαλίσετε τη σωστή ρύθμιση της πίεσης του μπαλονιού, απαιτείται η χρήση συσκευής διόγκωσης μπαλονιού με μετρητή πίεσης.
- Αναρροφήστε πλήρως το μπαλόνι προτού αφαιρέσετε προσεκτικά τη συσκευή από την ουρήθρα. Η χρήση υπερβολικής δύναμης για την απόσυρση του μπαλονιού μπορεί να προκαλέσει τραύμα στον ιστό.
- Επιθεωρήστε προσεκτικά το DCB και τη συσκευασία πριν από τη χρήση. Μη χρησιμοποιείτε τον καθετήρα εάν έχει υποστεί ζημιά ή εάν το μέγεθος, το σχήμα ή η κατάσταση είναι ακατάλληλα για τη διαδικασία για την οποία προορίζεται.
- Μην εμβυθίζετε ή σκουπίζετε το τμήμα του μπαλονιού του DCB με οποιοδήποτε υγρό, καθώς μπορεί να καταστραφεί ή να κινδυνέψει η ακεραιότητα της επικάλυψης φαρμάκου. Αντικαταστήστε οποιοδήποτε DCB του οποίου το μπαλόνι έχει έρθει σε επαφή με υγρά πριν από τη χρήση

- Χρησιμοποιείτε στεγνά αποστειρωμένα γάντια ή στεγνά επιθέματα γάζας για να χειριστείτε το DCB πριν από τη χρήση. Απαιτείται προσοχή για να ελαχιστοποιηθεί η επαφή με το τμήμα της συσκευής που περιλαμβάνει το μπαλόνι με την επίστρωση.
- Ποτέ μη διογκώνετε το DCB έξω από το σώμα ή προτού φθάσει στη στοχευόμενη στένωση, καθώς μπορεί να διαταραχθεί η ακεραιότητα της επικάλυψης.
- Μην επιχειρήσετε να περάσετε το DCB διαμέσου κυστεοσκοπίου μικρότερου μεγέθους French από εκείνο που υποδεικνύεται στην ετικέτα.
- Το μήκος εργασίας του DCB πρέπει να καλύπτει ολόκληρο το μήκος της στοχευόμενης στένωσης.
- Για τη σωστή χορήγηση του φαρμάκου στη στοχευόμενη στένωση, αφήστε την επικάλυψη να ενυδατωθεί μέσα στην ουρήθρα για τουλάχιστον 60 δευτερόλεπτα πριν τη διόγκωση και διατηρήστε τη διόγκωση του DCB για τουλάχιστον 5 λεπτά. Για τη βελτίωση της διαστολής της στένωσης, μπορούν να χρησιμοποιηθούν μεγαλύτεροι χρόνοι διόγκωσης > 5 λεπτά κατά την κρίση του χειριστή.
- Εάν το προϊόν παρουσιάσει αστοχία πριν ή κατά τη διάρκεια της διόγκωσης, αντικαταστήστε το DCB και διογκώστε ανάλογα με τη διαδικασία. Εάν η αστοχία προκύψει μετά τη διόγκωση στην RBP, μην επαναλάβετε τη διαδικασία DCB.
- Μετά τη χρήση, αυτό το προϊόν μπορεί να αποτελεί πιθανό βιολογικό κίνδυνο. Ο χειρισμός και η απόρριψη πρέπει να γίνονται σύμφωνα με την αποδεκτή ιατρική πρακτική και τους ισχύοντες τοπικούς κανονισμούς.
- Οι επαγγελματίες υγείας πρέπει να αποφεύγουν τη χρήση γαντιών από λάτεξ για να αποτρέψουν πιθανές αλλεργικές αντιδράσεις σε ασθενείς οι οποίοι είναι αλλεργικοί στο λάτεξ.
- Απαιτείται προετοιμασία του ουρηθρικού αυλού της στοχευόμενης βλάβης με την κατάλληλη μέθοδο παρασκευής αυλού, όπως αυτή θα καθοριστεί από τον θεράποντα ιατρό πριν από τη χρήση του Optilume DCB.
- Στην κλινική μελέτη Robust I μελετήθηκε η προετοιμασία του αυλού με χρήση μόνο προ-διαστολής με μη επικαλυμμένο καθετήρα μπαλονιού ή DVIU.
- Στις κλινικές μελέτες, ήταν απαιτούμενη η οπτική επιβεβαίωση σημαντικής στένωσης (διάμετρος ουρήθρας ≤ 12F) μέσω κυστεοσκόπησης ή ουρηθρογραφίας και η ένταξη περιορίστηκε σε ασθενείς που επιδείκνυαν υποκειμενικά και αντικειμενικά συμπτώματα ουρηθρικής στένωσης (Διεθνής Βαθμολογία των Συμπτωμάτων του Προστάτη [International Prostate Symptoms Score, IPSS] > 13, μέγιστος ρυθμός ροής ούρων < 15 mL/sec). Οι συμμετέχοντες είχαν υποβληθεί σε τουλάχιστον μία προηγούμενη ενδοσκοπική θεραπεία πριν την ένταξη στις κλινικές μελέτες.
- Τα δεδομένα για την ασφάλεια και την αποτελεσματικότητα δεν έχουν τεκμηριωθεί κατά τη διάρκεια της κλινικής μελέτης για την υποστήριξη της θεραπείας των στενώσεων σε ασθενείς με:
    - o BPH
    - o Ριζική προστατεκτομή
    - o Πυελική ακτινοβολία
    - o Θεραπεία Botox
    - o Περισσότερες από 1 στενώσεις
    - o Προηγούμενη ουρηθροπλαστική στην πρόσθια ουρήθρα
    - o Βακτηριακή ουρηθρίτιδα ή γονόρροια
    - o Παρουσία εμφυτεύματος τεχνητού σφιγκτήρα πέους ή στεντ ουρήθρας προστάτη
    - o Γνωστές νευρογενείς κύστεις, ανωμαλίες του σφιγκτήρα ή κακή λειτουργία του εξωστήρα μυός.
    - o Διάγνωση σκληρυντικού λειχήνα ή προηγούμενη επιδιόρθωση υποσπαδία.
    - o Ιστορικό καρκινώματος της ουροδόχου κύστης ή του προστάτη τα τελευταία 5 έτη
    - o Στένωση λόγω σκληροατροφικού λειχήνα (BXO)
    - o Όγκοι ουρήθρας ή καρκίνος του πέους

7.0 ΧΡΗΣΗ ΣΕ ΕΙΔΙΚΟΥΣ ΠΛΗΘΥΣΜΟΥΣ

Η ασφάλεια και η αποτελεσματικότητα του ουρηθρικού DCB δεν έχει τεκμηριωθεί σε παιδιατρικούς ασθενείς (ηλικίας < 18 ετών) ή σε γυναίκες. Η χρήση του ουρηθρικού DCB σε ασθενείς ηλικίας ≥ 18 ετών και άνω είναι στη διακριτική ευχέρεια του ιατρού.

8.0 ΠΙΘΑΝΕΣ ΕΠΙΠΛΟΚΕΣ

Οι πιθανές επιπλοκές που συσχετίζονται με τη χρήση του καθετήρα DCB Optilume είναι παρόμοιες με εκείνες που συσχετίζονται με τις τυπικές διαδικασίες διαστολής της ουρήθρας. Οι πιθανές επιπλοκές μπορεί ενδεικτικά να περιλαμβάνουν:

- Πόνο και ευαισθησία
- Σπασμό της κύστης από την τοποθέτηση καθετήρα Foley
- Τραύμα ιστών σε περιβάλλουσες δομές, συμπεριλαμβανομένης της ουρηθρικής βλάβης
- Αιματουρία
- Αντιδράσεις στο φάρμακο, αλλεργική αντίδραση στο σκιαγραφικό μέσο που χρησιμοποιείται κατά τη διάρκεια διαγνωστικού ουρηθρογράμματος
- Λοίμωξη του ουροποιητικού συστήματος
- Διάτρηση ιστού
- Επανεμφάνιση της στένωσης που επιβάλλει τη διεξαγωγή περαιτέρω χειρουργικής επέμβασης
- Ακράτεια
- Δυσουρία
- Πυρετός
- Κατακράτηση ούρων

9.0 ΠΛΗΡΟΦΟΡΙΕΣ ΓΙΑ ΤΟ ΦΑΡΜΑΚΟ

o ΜΗΧΑΝΙΣΜΟΣ ΔΡΑΣΗΣ

Η επικάλυψη του ουρηθρικού DCB περιέχει πακλιταξέλη, η οποία είναι μια αντιμιτωτική φαρμακευτική ουσία που συνδέεται ειδικά στους μικροσωληνίσκους και τους σταθεροποιεί. Η πακλιταξέλη έχει αναφερθεί ότι αναστέλλει τον πολλαπλασιασμό και τη μετανάστευση των λείων μυϊκών κυττάρων και των ινοβλαστών, καθώς και την έκκριση της εξωκυττάριας θεμέλιας ουσίας. Ο συνδυασμός αυτών των επιδράσεων μπορεί να έχει ως αποτέλεσμα την αναστολή της υπερπλασίας του ουροθηλίου και ως εκ τούτου η στένωση δεν επανεμφανίζεται.

o ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ ΦΑΡΜΑΚΩΝ

Δεν έχουν διενεργηθεί επίσημες μελέτες αλληλεπιδράσεων φαρμάκων για το ουρηθρικό DCB. Για τις αλληλεπιδράσεις με την πακλιταξέλη θα πρέπει να συμβουλευτείτε τις αντίστοιχες οδηγίες χρήσης των φαρμάκων που χρησιμοποιούνται σε συνδυασμό με το DCB.

Θα πρέπει να λαμβάνεται υπόψη η πιθανότητα συστηματικών και τοπικών αλληλεπιδράσεων φαρμάκων στην ουρήθρα σε έναν ασθενή που λαμβάνει ένα φάρμακο με γνωστές αλληλεπιδράσεις με την πακλιταξέλη ή όταν αποφασίζεται

η έναρξη φαρμακευτικής θεραπείας σε έναν ασθενή που έχει υποβληθεί σε θεραπεία με το DCB.

Ο μεταβολισμός της πακλιταξέλης καταλύεται από τα ισοένζυμα CYP2C8 και CYP3A4 του κυτοχρώματος P450 και είναι υπόστρωμα της Ργλυκοπρωτεΐνης. Πιθανές αλληλεπιδράσεις φαρμάκων μπορεί να προκύψουν με οποιοδήποτε φάρμακο επηρεάζει αυτά τα ισοένζυμα. Όταν απουσιάζουν επίσημες μελέτες για την αλληλεπίδραση φαρμάκων, απαιτείται προσοχή κατά τη χορήγηση της πακλιταξέλης.

- **ΚΑΡΚΙΝΟΓΕΝΕΣΗ, ΓΟΝΟΤΟΞΙΚΟΤΗΤΑ ΚΑΙ ΑΝΑΠΑΡΑΓΩΓΙΚΗ ΤΟΞΙΚΟΤΗΤΑ**

  Δεν έχουν πραγματοποιηθεί μακροχρόνιες μελέτες για την αξιολόγηση της καρκινογόνου δράσης της φαρμακευτικής ουσίας, πακλιταξέλη, ή του Optilume DCB και δεν υπάρχουν δημοσιευμένες επαρκείς και καλά ελεγχόμενες μελέτες σε εγκύους γυναίκες ή σε άνδρες που σκοπεύουν να αποκτήσουν παιδιά. Η πακλιταξέλη αναστέλλει τον πολλαπλασιασμό των κυττάρων μέσω της αλληλεπίδρασης με μικροσωληνίσκους, προκαλώντας έτσι μεταξύ άλλων απώλεια ολόκληρων χρωμοσωμάτων στη διάρκεια της κυτταρικής διαίρεσης. Αυτή η έμμεση δράση είναι σύμφωνη με θετικές αποκρίσεις in vitro και in vivo προσδιορισμούς γονοτοξικότητας μικροπυρήνων, οι οποίοι ανιχνεύουν θραύσματα DNA. Έχουν επίσης αναφερθεί θετικά αποτελέσματα για χρωμοσωμικές εκτροπές σε ανθρώπινα πρωτογενή λεμφοκύτταρα. Δεν είναι γνωστό εάν η πακλιταξέλη έχει ξεχωριστή άμεση δράση στο DNA κατά τη δημιουργία σχάσεων ή θραυσμάτων κλώνων του DNA. Εμφανίζεται αρνητική σε αναλύσεις για γονιδιακή μετάλλαξη, συμπεριλαμβανομένων των αναλύσεων σαλμονέλας και των μεταλλάξεων HPRT σε κύτταρα ωοθηκών κινεζικού κρικητού (CHO).

  Μελέτες που πραγματοποιήθηκαν σε αρουραίους και κουνέλια που έλαβαν IV πακλιταξέλη κατά τη διάρκεια της οργανογένεσης αποκάλυψαν στοιχεία μητρικής τοξικότητας, εμβρυοτοξικότητας και εμβρυοτοξικότητας σε δόσεις 1 και 3 mg/kg, αντίστοιχα [περίπου 13 και 39 φορές πάνω από τη δόση που παρέχεται από το Optilume DCB το οποίο επικαλύπτεται με 5,5 mg πακλιταξέλης (μπαλόνι 10mm x 50mm) με προσαρμογή ανάλογα με το βάρος του σώματος]. Δεν παρατηρήθηκε τερατογένεση σε κυοφορούντες αρουραίους που έλαβαν ημερήσιες δόσεις πακλιταξέλης IV 1 mg/kg [ημερήσια δόση περίπου 13 φορές πάνω από τη δόση του Optilume DCB (10mm x 50mm), με προσαρμογή ανάλογα με το σωματικό βάρος].

  Ο θεράπων ιατρός πρέπει να εξισορροπήσει τα πιθανά ιατρικά οφέλη του καθετήρα Optilume DCB έναντι αυτών των γονοτοξικών και αναπαραγωγικών κινδύνων. ΠΡΟΕΙΔΟΠΟΙΗΣΗ: Το ουρηθρικό DCB περιέχει πακλιταξέλη, μια γνωστή γονοτοξίνη. Οι άνδρες θα πρέπει να λαμβάνουν τις απαραίτητες προφυλάξεις κατά τη σεξουαλική επαφή (να φορούν προφυλακτικό) για 30 ημέρες μετά τη θεραπεία.

10.0 ΤΡΟΠΟΣ ΠΑΡΟΧΗΣ

Ο καθετήρας Optilume DCB παρέχεται ΑΠΟΣΤΕΙΡΩΜΕΝΟΣ μόνο για μία χρήση (αποστείρωση με αιθυλενοξείδιο). Ο καθετήρας DCB βρίσκεται σε σύστημα συσκευασίας με διπλό σακουλάκι (αλουμινένιο σακουλάκι και θήκη Tyvek) που περιέχεται μέσα σε ένα κουτί.

11.0 ΑΠΟΘΗΚΕΥΣΗ

Το ουρηθρικό DCB πρέπει να αποθηκεύεται σε θερμοκρασία δωματίου σε ξηρό μέρος μέσα στην αρχική του συσκευασία. Η συσκευή πρέπει να χρησιμοποιείται πριν την ημερομηνία λήξης που αναφέρεται πάνω στη συσκευασία.

12.0 ΣΥΝΙΣΤΩΜΕΝΑ ΕΙΔΗ

Προετοιμάστε τα ακόλουθα είδη χρησιμοποιώντας άσηπτη τεχνική:

- Οδηγό σύρμα κατάλληλου μεγέθους με εύκαμπτο άκρο (ανατρέξτε στην επισήμανση του προϊόντος)
- Κυστεοσκόπιο (κατά προτίμηση εύκαμπτο)
- Αποστειρωμένος φυσιολογικός ορός
- Σύριγγα 10 cc
- Δίοδη στρόφιγγα
- Συσκευή διόγκωσης με μανόμετρο
- Σκιαγραφικό μέσο – Σημείωση: Προαιρετικά για χρήση με ακτινοσκοπικά καθοδηγούμενες διαδικασίες

13.0 ΟΔΗΓΙΕΣ ΧΡΗΣΗΣ

13.1 ΠΡΙΝ ΑΠΟ ΤΗ ΧΡΗΣΗ

Φαρμακευτική αγωγή κατά την περιεγχειρητική περίοδο

Συνιστάται οι γιατροί να ακολουθούν τις κατευθυντήριες οδηγίες για τη φαρμακευτική αγωγή που χορηγείται πριν από την επέμβαση και την προετοιμασία για την ενδοσκοπική διαδικασία, συμπεριλαμβανομένης της χορήγησης αντιβίωσης πριν από την επέμβαση, ανάλογα με την περίπτωση. Συνιστάται επίσης η χορήγηση από του στόματος ΜΣΑΦ πριν από την επέμβαση.

Εάν έχει εκδηλωθεί λοίμωξη του ουροποιητικού συστήματος (UTI) κατά το χρόνο της θεραπείας, ο ασθενής πρέπει να υποβληθεί σε θεραπεία έως ότου η λοίμωξη θεραπευτεί πριν λάβει χώρα η θεραπευτική επέμβαση.

13.2 ΠΡΟΕΤΟΙΜΑΣΙΑ ΤΗΣ ΣΤΟΧΕΥΟΜΕΝΗΣ ΣΤΕΝΩΣΗΣ

Για εξαιρετικά στενωμένες και δύσβατες στενώσεις, πριν από τη χρήση του Optilume DCB συνιστάται προ-διαστολή της στοχευόμενης στένωσης στην ουρήθρα χρησιμοποιώντας την κατάλληλη μέθοδο προετοιμασίας, όπως αυτή θα καθοριστεί από τον θεράποντα ιατρό (μπαλόνι διαστολής χωρίς επικάλυψη ή DVIU). Η προ-διαστολή αποσκοπεί στην υποχώρηση της στένωσης. Αυτό επιτυγχάνεται όταν η διάμετρος του αυλού της διεσταλμένης στένωσης είναι > 20F ή> 50% μεγαλύτερη από τον αυλό της μη διεσταλμένης στένωσης.

13.3 ΥΠΟΛΟΓΙΣΜΟΣ ΜΕΓΕΘΟΥΣ ΤΗΣ ΣΥΣΚΕΥΗΣ

Βεβαιωθείτε ότι η διάμετρος του μπαλονιού του επιλεγμένου DCB σε ονομαστική πίεση είναι ίδια ή ελαφρώς μεγαλύτερη από τη διάμετρο της υγιούς ουρήθρας που βρίσκεται κοντά στο περιφερικό άκρο της στένωσης. Ως λόγος τάνυσης ορίζεται η διάμετρος του μπαλονιού δια της περιφερικής υγιούς παρακείμενης ουρήθρας.

Υπολογισμός μεγέθους για τη βολβική ουρήθρα
Για στενώσεις που βρίσκονται στη βολβική ουρήθρα, μην υπερβαίνετε το λόγο τάνυσης 1,3 της διαμέτρου του μπαλονιού προς την περιφερική υγιή ουρήθρα. Εάν το μέγεθος της ουρήθρας κυμαίνεται μεταξύ των διαθέσιμων μεγεθών της συσκευής, χρησιμοποιήστε το μεγαλύτερο μέγεθος με την προϋπόθεση ότι ο λόγος τάνυσης είναι χαμηλότερος από ή ίσος με 1,3. Εάν το επόμενο μεγαλύτερο μέγεθος παράγει λόγο τάνυσης υψηλότερο από 1,3, χρησιμοποιήστε τη μικρότερη συσκευή.

Υπολογισμός μεγέθους για την πεϊκή ουρήθρα
Για στενώσεις που βρίσκονται στην πεϊκή ουρήθρα, επιλέξτε τη διάμετρο του μπαλονιού που ταιριάζει καλύτερα στην περιφερική υγιή ουρήθρα. Ο λόγος τάνυσης

της πεϊκής ουρήθρας δεν πρέπει να υπερβαίνει το 1:1. Εάν το μέγεθος της ουρήθρας κυμαίνεται μεταξύ των διαθέσιμων μεγεθών μπαλονιού, επιλέξτε το μικρότερο μέγεθος μπαλονιού. ΜΗΝ ΥΠΕΡΒΑΙΝΕΤΕ το λόγο τάνυσης 1:1.

Τόσο για την πεϊκή όσο και για τη βολβική ουρήθρα, το μήκος του μπαλονιού του καθετήρα DCB πρέπει να είναι μεγαλύτερο από το μήκος της υπό θεραπεία στένωσης. Το μήκος του μπαλονιού πρέπει να εκτείνεται κατά 0,5-1 cm περίπου πέρα από τη στένωση και στις δύο πλευρές. Για παράδειγμα, εάν το μήκος της στένωσης είναι 2 cm, επιλέξτε ένα μπαλόνι DCB που είναι 3 cm.

13.4 ΠΡΟΕΤΟΙΜΑΣΙΑ ΤΟΥ ΚΑΘΕΤΗΡΑ ΜΕ ΜΠΑΛΟΝΙ

Απομακρύνετε τον αέρα από τον καθετήρα DCB. Ο αυλός μπαλονιού του καθετήρα περιέχει αέρα και ο αέρας πρέπει να εκτοπιστεί για να διασφαλιστεί ότι το μπαλόνι γεμίζει μόνο με υγρό για όσο διάστημα ο καθετήρας βρίσκεται μέσα στην ουρήθρα.

1. Συνδέστε τη στρόφιγγα στην ανοιχτή θέση με το σύνδεσμο διόγκωσης του μπαλονιού.
2. Συνδέστε τη σύριγγα γεμάτη κατά το ήμισυ με φυσιολογικό ορό στη στρόφιγγα.
3. Με το άκρο της σύριγγας προς τα κάτω, τραβήξτε προς τα πίσω το έμβολο ώστε η σύριγγα να γεμίσει πλήρως (παράγοντας έτσι μέγιστη αρνητική πίεση) και κρατήστε το μέχρι να πάψουν να βγαίνουν φυσαλίδες αέρος από τον φυσιολογικό ορό που περιέχεται στη σύριγγα. Επαναλάβετε εφόσον χρειάζεται για να εκκενώσετε τον καθετήρα από τον αέρα και να τον αντικαταστήσετε με φυσιολογικό ορό. Κρατήστε το έμβολο προς τα πίσω, γυρίστε τη στρόφιγγα για να διατηρήσετε το κενό και αφαιρέστε τη σύριγγα. Γεμίστε κατά το ήμισυ μια συσκευή διόγκωσης με φυσιολογικό ορό ή με σκιαγραφικό μέσο: φυσιολογικό ορό σε αναλογία 1:1, εάν χρησιμοποιείται ακτινοσκόπηση, και απομακρύνετε τον αέρα από τη γραμμή.
4. Συνδέστε τη συσκευή διόγκωσης στη στρόφιγγα του καθετήρα μπαλονιού, γυρίστε τη στρόφιγγα και αναρροφήστε κενό με τη συσκευή διόγκωσης.

13.5 ΕΙΣΑΓΩΓΗ ΤΟΥ OPTILUME DCB

1. Με τη βοήθεια ενός κυστεοσκοπίου, τοποθετήστε ένα οδηγό σύρμα 0,038” με το εύκαμπτο άκρο περιελιγμένο στην ουροδόχο κύστη.
2. Αφαιρέστε το προστατευτικό του μπαλονιού από το άκρο του καθετήρα DCB.

   Προσοχή: *Απαιτείται προσοχή κατά τη διέλευση ενός μπαλονιού με επικάλυψη πακλιταξέλης διαμέσου οποιουδήποτε συστήματος κυστεοσκοπίου.Χρησιμοποιήστε όσο το δυνατόν λιγότερους ελιγμούς και μην αγγίζετε το μπαλόνι. Μη σκουπίζετε το μπαλόνι με στεγνή, υγρή ή λιπασμένη γάζα ή οποιονδήποτε διαλύτη που θα μπορούσε να καταστρέψει την ακεραιότητα του επικαλυμμένου με φάρμακο μπαλονιού.*

3. Προωθήστε τον καθετήρα DCB εντός του καναλιού εργασίας του κυστεοσκοπίου. Εναλλακτικά, τοποθετήστε το οδηγό σύρμα και τον καθετήρα με μπαλόνι ξεχωριστά από το κανάλι εργασίας του κυστεοσκοπίου για τοποθέτηση το ένα δίπλα στο άλλο.
4. Χρησιμοποιήστε το κυστεοσκόπιο για να καθοδηγήσετε την τοποθέτηση του DCB. Εναλλακτικά, τοποθετήστε το DCB με φθοροσκόπηση χρησιμοποιώντας τους ακτινοσκιερούς δείκτες που βρίσκονται κάτω από το σημείο μετάβασης σώματος/κώνου του μπαλονιού.

   Προσοχή: *Μην προωθείτε το οδηγό σύρμα ή τον καθετήρα διαστολής με μπαλόνι εάν συναντήσετε αντίσταση, χωρίς να προσδιορίσετε πρώτα την αιτία της αντίστασης και να λάβετε διορθωτικά μέτρα.*

13.6 ΔΙΟΓΚΩΣΗ ΤΟΥ OPTILUME DCB

Προσοχή: *Οι συσκευές διόγκωσης έχουν τη δυνατότητα να επιτύχουν πολύ υψηλές πιέσεις με ελάχιστη προσπάθεια. Συνιστάται ιδιαίτερα η χρήση συσκευής διόγκωσης με μετρητή υψηλής πίεσης για τη βελτιστοποίηση της ισχύος διαστολής έτσι ώστε να υποχωρήσει η στένωση της ουρήθρας και να είναι εφικτή η διείσδυση του φαρμάκου στις μικρορρήξεις του ουροθηλίου.*

1. Βεβαιωθείτε ότι η ουρήθρα έχει ξεπλυθεί με φυσιολογικό ορό.
2. Τοποθετήστε το DCB κατά μήκος της στένωσης με το κυστεοσκόπιο περιφερικά προς το μπαλόνι (μακριά από την ουροδόχο κύστη) για να απεικονίσετε τη σωστή τοποθέτηση του μπαλονιού κατά μήκος της στένωσης. Αφήστε το μπαλόνι στη θέση του χωρίς να είναι φουσκωμένο για 1 λεπτό τουλάχιστον πριν από τη διόγκωση. Με χρήση ακτινοσκόπησης ελέγξτε εάν οι ακτινοσκιεροί δείκτες του μπαλονιού βρίσκονται στη σωστή θέση.
3. Φουσκώστε το μπαλόνι μέχρι την τιμή της ονομαστικής πίεσης ρήξης χρησιμοποιώντας τη συσκευή διόγκωσης. Μην υπερβαίνετε την ονομαστική πίεση ρήξης (RBP) του μπαλονιού. Διατηρήστε την πίεση για 5 λεπτά τουλάχιστον ή μέχρι να επιτευχθεί η επιθυμητή διαστολή.
4. Ξεφουσκώστε το μπαλόνι εφαρμόζοντας κενό στο μπαλόνι με τη συσκευή διόγκωσης. Όταν το μπαλόνι ξεφουσκώσει πλήρως, αποσύρετε αργά το οδηγό σύρμα και το DCB. Εάν συναντήσετε ελαφριά αντίσταση καθώς αφαιρείτε αργά το μπαλόνι, περιστρέψτε τον καθετήρα για να βοηθήσετε το μπαλόνι να αναδιπλωθεί γύρω από το στέλεχος του καθετήρα και να διευκολύνετε την απόσυρση.

   Προσοχή: *Εάν συναντήσετε αντίσταση κατά την αφαίρεση ενός οδηγού σύρματος διαμέσου ενός καθετήρα μέσω κυστεοσκοπίου, ΣΤΑΜΑΤΗΣΤΕ και αφαιρέστε τα μαζί ταυτόχρονα ως μία ενιαία μονάδα για να αποφύγετε την πρόκληση ζημιάς στο οδηγό σύρμα, τον καθετήρα ή την ανατομία του ασθενούς.*

5. Εάν το προϊόν εμφανίσει αστοχία πριν από ή κατά τη διάρκεια της διόγκωσης (αλλά χαμηλότερη από την τιμή RBP), αντικαταστήστε το DCB και διογκώστε ανάλογα με τη διαδικασία. Εάν η αστοχία προκύψει μετά τη διόγκωση στην RBP, μην επαναλάβετε τη διαδικασία DCB.
6. Τοποθετήστε έναν λιπαντικό καθετήρα Foley, 12-14 Fr και αφήστε τον στη θέση του για 2 ημέρες τουλάχιστον ή με βάση το πρότυπο φροντίδας, όποιο από τα δύο είναι μεγαλύτερο.

13.7 ΔΙΑΓΡΑΜΜΑ ΕΝΔΟΤΙΚΟΤΗΤΑΣ

18 Fr (6 mm) x 30 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	6,11 (18 Fr)
8,0	800		6,23
10,0	1.000		6,34
12,0	1.200	**RBP**	6,45

Ελληνικά

18 Fr (6 mm) x 50 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	5.87 (18 Fr)
8,0	800		6.03
10,0	1.000		6.16
12,0	1.200	**RBP**	6.25

24 Fr (8 mm) x 30 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	7,98 (24 Fr)
8,0	800		8,16
10,0	1.000		8,32
12,0	1.200	**RBP**	8,46

24 Fr (8 mm) x 50 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	8.00 (24 Fr)
8,0	800		8.20
10,0	1.000		8.37
12,0	1.200	**RBP**	8.54

30 Fr (10 mm) x 30 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	9,83 (30 Fr)
8,0	800		10,09
10,0	1.000	**RBP**	10,29

30 Fr (10 mm) x 50 mm

(ATM) Πίεση	kPa		(mm) Μπαλόνι
6,0	600	**Ονομαστική**	9.98 (30 Fr)
8,0	800		10.23
10,0	1.000	**RBP**	10.44

Προσοχή: *Δεν πρέπει να γίνεται υπέρβαση της ονομαστικής πίεσης ρήξης. Ανατρέξτε στην ετικέτα του προϊόντος για τις τιμές ονομαστικής πίεσης ρήξης. Τυχόν διόγκωση πέρα από την ονομαστική πίεση ρήξης μπορεί να προκαλέσει ρήξη του μπαλονιού. Εάν υπάρξει απώλεια πίεσης εντός του μπαλονιού κατά τη διάρκεια της διόγκωσης ή ρήξη του μπαλονιού κατά τη διάρκεια της διαστολής, διακόψτε αμέσως τη διαδικασία. Ξεφουσκώστε προσεκτικά το μπαλόνι και αφαιρέστε το από την ουρήθρα. Μην το διογκώσετε εκ νέου.*

14.0 ΕΓΓΥΗΣΗ

Η Urotronic εγγυάται ότι έχει δοθεί εύλογη φροντίδα κατά τον σχεδιασμό και την κατασκευή αυτού του προϊόντος. Η παρούσα εγγύηση αντικαθιστά και αποκλείει όλες τις άλλες εγγυήσεις που δεν αναφέρονται ρητά στο παρόν, είτε ρητές είτε σιωπηρές αυτοδικαίως ή άλλως, συμπεριλαμβανομένων, ενδεικτικά, οποιωνδήποτε σιωπηρών εγγυήσεων για έναν συγκεκριμένο σκοπό. Ο χειρισμός, η αποθήκευση, ο καθαρισμός και η αποστείρωση αυτής της συσκευής, όπως επίσης και άλλοι παράγοντες που σχετίζονται με τον ασθενή, τη διάγνωση, τη θεραπεία, τις χειρουργικές διαδικασίες και άλλα ζητήματα πέρα από τον έλεγχο της Urotronic, επηρεάζουν άμεσα τη συσκευή και τα αποτελέσματα που λαμβάνονται από τη χρήση της. Η υποχρέωση της Urotronic στα πλαίσια της παρούσας εγγύησης περιορίζεται στην επισκευή ή αντικατάσταση αυτής της συσκευής και η Urotronic δεν φέρει καμία ευθύνη για οποιαδήποτε συμπτωματική ή παρεπόμενη απώλεια, ζημία ή δαπάνη, που θα μπορούσε να προκύψει άμεσα ή έμμεσα από τη χρήση αυτής της συσκευής. Η Urotronic δεν αναλαμβάνει καμία ευθύνη όσον αφορά συσκευές που έχουν επαναχρησιμοποιηθεί, υποβληθεί σε επανεπεξεργασία ή επαναποστειρωθεί και δεν παρέχει καμία εγγύηση, ρητή ή σιωπηρή, συμπεριλαμβανομένων, ενδεικτικά, για ένα συγκεκριμένο σκοπό όσον αφορά τέτοιες συσκευές.

15.0 ΣΥΜΒΟΛΑ ΠΟΥ ΧΡΗΣΙΜΟΠΟΙΟΥΝΤΑΙ ΣΤΙΣ ΕΤΙΚΕΤΕΣ ΤΗΣ ΣΥΣΚΕΥΗΣ

1	Ποσότητα 1 τεμ. ανά κουτί
Rx only	Προσοχή: Η ομοσπονδιακή νομοθεσία επιτρέπει την πώληση αυτής της συσκευής μόνο από ιατρό ή κατόπιν εντολής ιατρού.
	Υποδεικνύει την ημερομηνία κατασκευής της ιατρικής συσκευής.
	Μην επαναποστειρώνετε
	Μην επαναχρησιμοποιείτε
	Μην το χρησιμοποιείτε εάν η συσκευασία έχει υποστεί ζημιά
	Εύθραυστο
	Ημερομηνία λήξης
	Να φυλάσσεται μακριά από ηλιακή ακτινοβολία
	Να διατηρείται στεγνό
	Κατασκευαστής
LATEX	Δεν περιέχει λάτεξ
	Όριο θερμοκρασίας 15 °C - 30 °C
	Προσοχή: Συμβουλευτείτε τις οδηγίες χρήσης
STERILE EO	Αποστειρωμένο με αιθυλενοξείδιο
REF	Αριθμός καταλόγου
LOT	Αριθμός παρτίδας
CE 1434	Με σήμανση CE σύμφωνα με την οδηγία για τα ιατροτεχνολογικά προϊόντα 93/42/ΕΟΚ της Ευρωπαϊκής Ένωσης (κοινοποιημένος οργανισμός αριθ. 1434)
EC REP	Εξουσιοδοτημένος αντιπρόσωπος στην Ευρωπαϊκή Ένωση

Urotronic, Inc.
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USA

EC REP
MDSS GmbH
Schiffgraben 41
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CE 1434

OPTILUME®

قسطرة البالون المغلف بالدواء الإحليلية

تعليمات الاستخدام

عربي

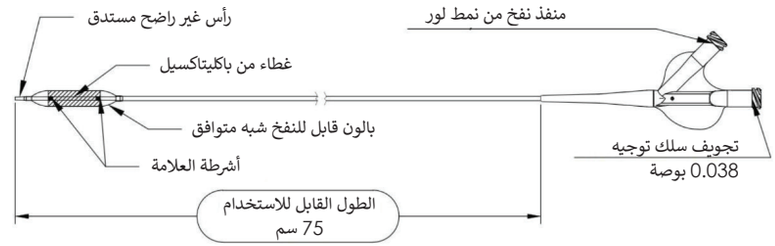
Rev D 002-1111

جدول المحتويات

1.0 وصف الجهاز

1.1 القسطرة البالونية

قسطرة البالون المغلف بالدواء الإحليلية Optilume (DCB) عبارة عن سلك توجيه مقاس 0.038 بوصة (0.97 مم) وقسطرة منظار المثانة المرنة المتوافقة فوق السلك (OTW) بتصميم مزدوج التجويف ورأس غير راضح مستدق. يحتوي الطرف البعيد للقسطرة على بالون قابل للنفخ شبه متوافق ومغطى بطبقة خاصة تحتوي على باكليتاكسيل صيدلاني نشط. يغطي غلاف الدواء طول فترة العمل لجسم البالون. يحتوي الجهاز على شريطين للعلامة معتمة الإشعاع يشيران إلى طول عمل البالون.



يتم تعقيم الجهاز باستخدام أكسيد الإيثيلين في كيس Tyvek. بعد التعقيم، يتم إغلاق القسطرة المكيسة في كيس من الرقائق المعدنية مع مادة مجففة وتوضع داخل عبوة تحتوي على وحدة واحدة. يتم تزويد كل DCB بغطاء واقٍ يغطي جزء البالون المغلف بالدواء من القسطرة. يوجد مخطط توافق البالون على ملصق الكيس Tyvek.

1.2 تغليف الدواء

يتكون غلاف الدواء من المكون الصيدلاني النشط باكليتاكسيل وسواغات. يغطي غلاف الدواء طول العمل لمكون بالون القسطرة. يتم توزيع غلاف الدواء بالتساوي عبر سطح البالون بتركيز 3.5 ميكروجرامات/مم^2. تتمثل السمة الوظيفية الرئيسية لغلاف الدواء في السماح بإطلاق باكليتاكسيل إلى الظهارة البولية أثناء نفخ البالون.

مصفوفة جرعات DCB

رقم الكتالوج	القطر (Fr/مم)	الطول (مم)	جرعة باكليتاكسيل (مجم)
06030C-1110	6.0/18.0	30	2.0
06050C-1110	6.0/18.0	50	3.3
08030C-1110	8.0/24.0	30	2.6
08050C-1110	8.0/24.0	50	4.4
10030C-1110	10.0/30.0	30	3.3
10050C-1110	10.0/30.0	50	5.5

2.0 الغرض من الاستخدام

تُستخدم قسطرة البالون المغلف بالدواء الإحليلية Optilume (DCB)لعلاج التضيق في الإحليل الأمامي ع البالغين.

3.0 دواعي الاستعمال

تُستخدم قسطرة Optilume DCB الإحليلية لعلاج الذكور من عمر 18 عامًا أو أقل الذين يعانون من أعراض بولية مزعجة مرتبطة بتضيق الإحليل الأمامي المتكرر. فهي مصممة لتُستخدم كبالون توسيع لتضيق إحليل أمامي واحد ترادفي أو منتشر بطول أكبر من أو يساوي 3 سم أو تُستخدم كعلاج مساعد مع أجهزة و/أو عمليات توسيع أخرى.

4.0 موانع الاستعمال

يمنع استخدام قسطرة توسيع البالون المغلف بالدواء الإحليلية (DCB) في الحالات التالية:

- المرضى الذين يعانون من فرط الحساسية تجاه باكليتاكسيل أو المركبات ذات الصلة من الناحية التركيبية.
- المرضى الذين يعانون من آفات لا يمكن إدخال سلك توجيه مقاس 0.038 بوصة عبرها.

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- القسطرة البالونية مخصصة للاستخدام من قبل الأطباء المدربين وذوي الخبرة في تقنيات توسيع القسطرة البالونية.
- لضمان التنظيم الصحيح لضغط البالون، يوصى باستخدام جهاز نفخ البالون مع مقياس الضغط.
- اشفط البالون بالكامل قبل إزالة الجهاز برفق من الإحليل. يمكن أن يتسبب استخدام القوة المفرطة لسحب البالون في حدوث صدمة للأنسجة.
- افحص بالون DCB والعبوة بعناية قبل الاستخدام. لا تستخدم القسطرة إذا كانت تالفة أو إذا كان الحجم أو الشكل أو الحالة غير مناسبة للعملية المقصودة.
- لا تغمس قسم البالون من DCB أو تمسحه بأي سائل لأن غلاف الدواء قد يتلف أو يتعرض للخطر. استبدل أي DCB عند تلامس البالون مع السوائل قبل الاستخدام.
- استخدم قفازات معقمة جافة أو شاشًا جافًا للتعامل مع DCB قبل الاستخدام. يجب توخي الحذر لتقليل التلامس مع جزء البالون المغطى بالجهاز.
- لا تقم أبدًا بنفخ بالون DCB خارج الجسم أو قبل الوصول إلى التضيق المستهدف لأنه قد يعطل سلامة الغلاف.
- لا تحاول تمرير بالون DCB من خلال منظار المثانة ذي الحجم الفرنسي الأصغر من الموضح على الملصق.
- يجب أن يغطي طول عمل DCB طول التضيق الهدف بأكمله.
- لتوصيل الدواء المناسب إلى التضيق الهدف، اسمح للغلاف بالترطيب في الإحليل لمدة 60 ثانية على الأقل قبل النفخ وحافظ على نفخ DCB لمدة لا تقل عن 5 دقائق. لتحسين توسيع التضيق، يمكن تنفيذ أوقات نفخ أطول > 5 دقائق حسب تقدير القائم بالعملية.
- إذا كان المنتج يعاني من فشل قبل النفخ أو في أثنائه، فاستبدل بالون DCB وانفخ وفقًا للعملية. إذا كان الفشل بعد النفخ إلى RBP، فلا تكرر عملية DCB.
- بعد الاستخدام، قد يمثل هذا المنتج خطرًا بيولوجيًا محتملاً. تعامل معه وتخلص منه وفقًا للممارسة الطبية المقبولة واللوائح المحلية السارية.
- يجب على ممارسي الرعاية الصحية تجنب استخدام قفازات اللاتكس لمنع الحساسية المحتملة من قبل المرضى الذين لديهم حساسية من اللاتكس.
- يلزم إعداد تجويف الإحليل من الإصابة المستهدفة، باستخدام طريقة تحضير التجويف المناسبة كما يحددها الطبيب المعالج، قبل استخدام Optilume DCB.
- تمت دراسة تحضير التجويف باستخدام التوسيع المسبق فقط باستخدام قسطرة البالون غير المغطاة أو DVIU في الدراسة السريرية القوية 1.
- في الدراسات السريرية، كان التأكيد البصري للتضيق كبير الحجم (قطر الإحليل أكبر من F12) مطلوبًا عبر إجراء تنظير المثانة أو مخطط الإحليل، وكان التسجيل مقصورًا على المرضى الذين يظهرون أعراضًا شخصية وموضوعية لتضيق الإحليل (المقياس العالمي لأعراض البروستات [IPSS] أقل من 13 ومعدل ذروة جريان البول أكثر من 15 مل/ثانية). وقد خضع المرضى للعلاج بالتنظير الداخلي مرة واحدة على الأقل قبل التسجيل في الدراسات السريرية.
- لم يتم إنشاء بيانات السلامة والفعالية خلال الدراسة السريرية لدعم علاج التضيق في المرضى الذين يعانون من:
  - BPH
  - استئصال البروستاتا
  - الإشعاع الحوضي
  - العلاج بالبوتكس
  - أكثر من تضيق واحد
  - رأب الإحليل السابق داخل الإحليل الأمامي
  - التهاب الإحليل البكتيري أو السيلان
  - وجود مصرة اصطناعية لزرع القضيب أو دعامة الإحليل/البروستاتا
  - المثانة العصبية المعروفة أو اختلالات المصرة أو ضعف وظيفة العضلة النافضة.
  - تم تشخيصهم بمرض الحزاز الجلدي المتصلب، أو إصلاح الإحليل التحتاني السابق.
  - تاريخ من سرطان المثانة أو البروستاتا خلال السنوات الخمس الأخيرة
  - التضيق بسبب التهاب الحشفة الجفافي المُسِد (BXO)
  - أورام الإحليل أو سرطان القضيب

5.0 تحذيرات

- يتم توفير بالون DCB الإحليلي معقمًا للاستخدام مرة واحدة فقط. لا تعد معالجته أو تعقيمه. يمكن أن تؤدي إعادة المعالجة وإعادة التعقيم إلى زيادة خطر انتقال عدوى للمريض وتعرض أداء الجهاز للخطر.
- الكيس المصنوع من رقائق معدنية والسطح الخارجي للكيس الداخلي غير معقمين. محتويات الكيس الداخلي معقمة. تُستخدم فور فتح الكيس المصنوع من الرقائق المعدنية.
- لا تستخدم هذا الجهاز إذا كانت هناك عدوى في الإحليل (UTI) أو المثانة. يجب التخلص من العدوى قبل معالجة التضيق باستخدام Optilume DCB.
- يجب استخدام بالون DCB فقط من قبل الأطباء ذوي الخبرة والمعرفة بالجوانب السريرية والفنية لتوسيع بالون الإحليل.
- قبل استخدام بالون DCB، يجب على الأطباء قراءة تعليمات الاستخدام وفهمها. قد يؤدي عدم اتباع دواعي الاستعمال وموانع الاستعمال والقيود والتحذيرات والاحتياطات إلى حدوث مضاعفات.
- لا تستخدمه بعد تاريخ "تُستخدم قبل".
- يحتوي بالون DCB على باكليتاكسيل، وهو مادة سامة جينيًا معروفة. يجب أن يمارس الرجال الجنس المحمي (ارتداء الواقي الذكري) لمدة 30 يومًا بعد العلاج.
- راقب علامات العوار أو فرط الحساسية للباكليتاكسيل
- لا تستخدم أبدًا الهواء أو أي وسيط غازي لنفخ بالون DCB.
- عند الاستخدام، يجب معالجة بالون DCB تحت التصور المباشر عن طريق تنظير المثانة أو الملاحظة بالكاشف الفلوري عالي الجودة.
- لا تعبث في بالون DCB بعد نفخه.
- إذا واجهت مقاومة في أي وقت أثناء إجراء الإدخال، فلا تدفعه بالقوة للمرور. قد تتسبب المقاومة في تلف الجهاز أو التجويف. اسحب القسطرة بعناية.
- يجب على الرجال الذين لديهم شركاء جنسيون لديهم إمكانية الحمل استخدام الواقي الذكري لمدة 90 يومًا على الأقل بعد العلاج.
- ردود الفعل العكسية على باكليتاكسيل والأعراض التي لوحظت مستمدة في المقام الأول من دراسات التسريب الوريدي للدواء في علاج مرضى السرطان تشمل
  - اختلالات الكروموسومات وخطر الإصابة بالسرطان
  - إلحاق الضرر بالجنين عند تعرض المرأة الحامل
  - العوار وفرط الحساسية لباكليتاكسيل
  - تثبيط شفاء ما بعد عملية الإحليل
  - كبت النقي بما في ذلك: قلة العدلات، ونقص الكريات البيضاء، ونقص الصفيحات، وفقر الدم
  - اضطراب نبض القلب
  - اعتلال الأعصاب
  - الألم العضلي
  - داء الثعلبة
  - نقص ضغط الدم
  - الغثيان أو القيء أو الإسهال
  - البيليروبين المرتفع، وALP، وAST
  - التأثير المحتمل على الكبد والكليتين غير معروف ولم تتم دراسته. إن كمية باكليتاكسيل التي يتم توصيلها داخليًا أثناء عملية Optilume DCB أقل بكثير من جرعة واحدة من العلاج الكيميائي الجهازي الذي يتم توفيره لمرضى السرطان ويبدو أن الدواء يظل موضعيًا بشكل أساسي في الإحليل.

6.0 الاحتياطات

- يتم النفخ دائمًا بسائل معقم (محلول ملحي معقم أو 50% من خليط التباين). لا يُنفخ أبدًا بالهواء أو ثاني أكسيد الكربون أو أي غاز آخر. يجب ألا يتم نفخ بالون DCB إلى مستوى يتجاوز ضغط الانفجار المقنن (RBP). لا تفرط في نفخ البالون.

- **التداخلات الدوائية**

لم يتم إجراء دراسات رسمية للتفاعلات الدوائية لـ DCB الإحليلي. يجب الرجوع إلى التعليمات ذات الصلة للاستخدام لجميع الأدوية المستخدمة مع DCB للتعرف على التداخلات مع باكليتاكسيل.

يجب مراعاة إمكانات التفاعلات الدوائية الجهازية والداخلية في الإحليل في مريض يتناول دواءً ذا تفاعلات معروفة مع باكليتاكسيل أو عند اتخاذ قرار ببدء العلاج الدوائي في مريض تم علاجه باستخدام DCB. يتم تحفيز عملية التمثيل الغذائي للباكليتاكسيل بواسطة إنزيمي السيتوكروم P450 المتماثلين CYP2C8 وCYP3A4 وهما يمثلان معًا ركيزة من البروتين السكري-P. قد تحدث تداخلات دوائية محتملة مع أي دواء يؤثر على هذين الإنزيمين المتماثلين. في حالة عدم وجود دراسات رسمية للتفاعلات الدوائية، يجب توخي الحذر عند إعطاء باكليتاكسيل.

- **السرطنة والتسمم الجيني والسموم التناسلية**

لم يتم إجراء دراسات طويلة الأمد لتقييم الاحتمالات المسببة للسرطان لدواء باكليتاكسيل أو Optilume DCB، ولا توجد دراسات كافية وذات شواهد جيدة منشورة في النساء الحوامل أو في الرجال الذين ينوون إنجاب أطفال. يثبط باكليتاكسيل تكاثر الخلايا من خلال التفاعل مع الأنيبوبات الميكروية، والنتيجة الوحيدة تتمثل في فقدان الكروموسومات الكاملة أثناء انقسام الخلايا. يتوافق هذا الإجراء غير المباشر مع الاستجابات الإيجابية في فحوصات السمية الجينية في المختبر وفي الجسم الحي، والتي تكتشف أجزاء الحمض النووي. كما تم رصد نتائج إيجابية لزيغ الكروموسومات في الخلايا الليمفاوية الأولية البشرية. من غير المعروف ما إذا كان باكليتاكسيل له تأثير مباشر منفصل على الحمض النووي في توليد فواصل مجدولة أو أجزاء من الحمض النووي. إنه سلبي في فحوصات الطفرة الجينية، بما في ذلك السالمونيلا وCHO/HPRT.

كشفت الدراسات التي أجريت على الفئران والأرانب التي تلقت باكليتاكسيل بالحقن الوريدي أثناء تخلق الأعضاء دليلاً على سمية الأم، والسمية الجنينية، وسمية الأجنة بجرعات 1 و3 مجم/كجم، على التوالي (حوالي 13 و39 ضعف الجرعة التي يوفرها Optilume DCB المغلف بـ 5.5 مجم من باكليتاكسيل (بالون مقاس 10 مم × 50 مم) يتم تعديله وفقًا لوزن الجسم). لم يُلاحظ أي تشوه في الفئران الجاذبة التي تتلقى جرعات باكليتاكسيل بالحقن الوريدي اليومي من 1 مجم/كجم (جرعة يومية تقارب 13 ضعف جرعة Optilume DCB (10 مم × 50 مم)، معدلة حسب وزن الجسم).

يجب على الطبيب المعالج أن يوازن بين الفوائد الطبية المحتملة لقسطرة Optilume DCB وبين مخاطر السمية الجينية والمخاطر التناسلية هذه. تحذير: يحتوي بالون DCB الإحليلي على باكليتاكسيل، وهو مادة سامة جينيًا معروفة. يجب أن يمارس الرجال الجنس المحمي (ارتداء الواقي الذكري) لمدة 30 يومًا بعد العلاج.

10.0 كيفية توفيره

يتم توفير قسطرة Optilume DCB في حالة معقمة للاستخدام مرة واحدة فقط (تعقيم بأكسيد الإيثيلين). يوجد DCB في نظام تعبئة مزدوج الكيس (أكياس من الرقائق المعدنية وأكياس Tyvek) متضمنًا في عبوة تضم وحدة واحدة.

11.0 التخزين

يجب تخزين DCB الإحليلي في درجة حرارة الغرفة في مكان جاف في عبوته الأصلية. يجب استخدام الجهاز قبل تاريخ "تُستخدم قبل" المدون على العبوة.

7.0 الاستخدام في مجموعات سكانية خاصة

لم تثبت سلامة وفعالية DCB الإحليلي في المرضى الأطفال (أقل من 18 سنة) أو في النساء. يخضع استخدام Urethral DCB في المرضى الذين تقل أعمارهم عن 18 عامًا لتقدير الطبيب.

8.0 المضاعفات المحتملة

تتشابه المضاعفات المحتملة المرتبطة باستخدام قسطرة Optilume DCB مع تلك المرتبطة بعمليات توسيع الإحليل القياسية. قد تشمل المضاعفات المحتملة، على سبيل المثال لا الحصر:

- الألم والمضض
- تشنج المثانة من وضع قسطرة فولي
- صدمة الأنسجة في الهياكل المحيطة، بما في ذلك تلف الإحليل
- البيلة الدموية
- التفاعلات الدوائية، ورد الفعل التحسسي تجاه وسط التباين المستخدم أثناء مخطط الإحليل التشخيصي
- التهاب المسالك البولية
- ثقب الأنسجة
- تكرار التضيق الذي يتطلب المزيد من الجراحة
- سلس البول
- عسر البول
- الحمى
- احتباس البول

9.0 معلومات الدواء

- **آلية العمل**

يحتوي غلاف Urethral DCB على باكليتاكسيل، وهو عامل صيدلاني مضاد للانقسام يرتبط بشكل خاص بالأنيبوبات الميكروية ويستقر فيها. تم رصد حالات تسبب فيها باكليتاكسيل في منع خلايا العضلات الملساء وانتشار الأرومة الليفية والهجرة وكذلك إفراز المصفوفة خارج الخلية. قد يؤدي الجمع بين هذه التأثيرات إلى تثبيط فرط تنسج الظهارة البولية وبالتالي عودة التضيق.

- **التداخلات الدوائية**

لم يتم إجراء دراسات رسمية للتفاعلات الدوائية لـ DCB الإحليلي. يجب الرجوع إلى التعليمات ذات الصلة للاستخدام لجميع الأدوية المستخدمة مع DCB للتعرف على التداخلات مع باكليتاكسيل.

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- **السرطنة والتسمم الجيني والسموم التناسلية**

لم يتم إجراء دراسات طويلة الأمد لتقييم الاحتمالات المسببة للسرطان لدواء باكليتاكسيل أو Optilume DCB، ولا توجد دراسات كافية وذات شواهد جيدة منشورة في النساء الحوامل أو في الرجال الذين ينوون إنجاب أطفال. يثبط باكليتاكسيل تكاثر الخلايا من خلال التفاعل مع الأنيبوبات الميكروية، والنتيجة الوحيدة تتمثل في فقدان الكروموسومات الكاملة أثناء انقسام الخلايا. يتوافق هذا الإجراء غير المباشر مع الاستجابات الإيجابية في فحوصات السمية الجينية في المختبر وفي الجسم الحي، والتي تكتشف أجزاء الحمض النووي. كما تم رصد نتائج إيجابية لزيغ الكروموسومات في الخلايا الليمفاوية الأولية البشرية. من غير المعروف ما إذا كان باكليتاكسيل له تأثير مباشر منفصل على الحمض النووي في توليد فواصل مجدولة أو أجزاء من الحمض النووي. إنه سلبي في فحوصات

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13.4 إعداد القسطرة البالونية

قم بتفريغ الهواء من قسطرة DCB. يحتوي تجويف بالون القسطرة على الهواء ويجب إزاحة الهواء للتأكد من أن السائل فقط يملأ البالون أثناء وجود القسطرة في الإحليل.

1. اربط المحبس في الوضع المفتوح لموصل نفخ البالون.
2. أرفق محقنة مملوءة حتى النصف بمحلول ملحي في المحبس.
3. مع توجيه طرف المحقنة إلى الأسفل، اسحب المكبس إلى الحجم الكامل للمحقنة (وهذا يخلق ضغطًا سلبيًا أقصى) واستمر حتى لا تظهر أي فقاعات هواء تخرج من المحلول الملحي في المحقنة. كرر حسب الحاجة لتنقية الهواء من القسطرة واستبداله بمحلول ملحي. حافظ على المكبس في الوضع الخلفي، وقم بتدوير المحبس للحفاظ على التفريغ وأزل المحقنة. املأ جهاز النفخ حتى النصف بمحلول ملحي عادي أو بنسبة تباين 1:1: محلول ملحي إذا كنت تستخدم التنظير الفلوري، وقم بتطهير الهواء من الخط.
4. قم بتوصيل جهاز النفخ في المحبس الموجود في القسطرة البالونية، وقم بتدوير المحبس السحب وسحب الفراغ من جهاز النفخ.

13.5 إدخال OPTILUME DCB

1. ضع سلكًا توجيهيًا يبلغ 0.038 بوصة مع الطرف المرن الملفوف في المثانة بمساعدة منظار المثانة.
2. أزِل واقي البالون من طرف قسطرة DCB.

تنبيه: *يجب توخي الحذر عند تمرير بالون مغلف بباكليتاكسيل من خلال أي نظام من أنظمة منظار المثانة. قلل من الاستخدام المفرط ولا تلمس البالون. لا تمسح البالون بشاش جاف أو مبلل أو مشحم أو أي مذيب يمكن أن يضر بسلامة البالون المغلف بالدواء.*

3. ادفع قسطرة DCB داخل قناة عمل منظار المثانة. بالتناوب، ضع سلك التوجيه والقسطرة البالونية بصورة منفصلة عن قناة عمل منظار المثانة لوضعها جنبًا إلى جنب.
4. استخدم منظار المثانة لتوجيه موضع DCB. بدلاً من ذلك، ضع DCB مع التنظير الفلوري باستخدام علامات معتمة الأشعة موجودة تحت انتقال جسم البالون/المخروط.

تنبيه: *لا تقدم سلك التوجيه أو قسطرة التوسيع بالبالون عند مواجهة مقاومة دون تحديد سبب المقاومة أولاً واتخاذ إجراءات علاجية.*

13.6 نفخ OPTILUME DCB

تنبيه: *أجهزة النفخ قادرة على تحقيق ضغوط عالية جدًا بأقل جهد. يوصى بشدة باستخدام جهاز نفخ بمقياس ضغط عالٍ لتحسين قوة التوسُّع لإخراج تضيق الإحليل والسماح باختراق الدواء في الظهارة البولية.*

1. تأكد من دفق المحلول الملحي في الإحليل.
2. ضع DCB عبر التضيق مع منظار المثانة بعيدًا عن البالون (بعيدًا عن المثانة) لتصور الموضع الصحيح للبالون عبر التضيق. اترك البالون في وضع غير منفوخ لمدة دقيقة واحدة على الأقل قبل النفخ. تحقق من أن العلامات معتمة الأشعة في الوضع الصحيح باستخدام التنظير الفلوري.
3. انفخ البالون إلى ضغط الانفجار المقنن باستخدام جهاز النفخ. لا تتجاوز ضغط الانفجار المقنن (RBP) للبالون. حافظ على الضغط لمدة لا تقل عن 5 دقائق، أو حتى يتم تحقيق التوسيع المطلوب.
4. قم بتفريغ البالون عن طريق تطبيق فراغ على البالون باستخدام جهاز النفخ. عندما يتم تفريغ البالون تمامًا، اسحب سلك التوجيه وDCB ببطء. إذا شعرت بمقاومة طفيفة عند إزالة البالون، فقم بتدوير القسطرة برفق لمساعدة البالون على الانحناء حول عمود القسطرة وتسهيل السحب.

تنبيه: *إذا واجهت مقاومة عند إزالة سلك توجيهي من خلال قسطرة من خلال منظار المثانة، فتوقف وقم بإزالتهما معًا في نفس الوقت كوحدة كاملة لمنع تلف سلك التوجيه أو القسطرة أو تشريح المريض.*

12.0 العناصر الموصى بها

تحضير العناصر التالية باستخدام تقنية معقمة:

- سلك توجيه بحجم مناسب مع رأس مرن (راجع ملصقات المنتج)
- منظار المثانة (مرونة مفضلة)
- محلول ملحي معقم
- محقنة 10 سم 3
- محبس ثنائي الاتجاه
- جهاز نفخ مع مقياس ضغط
- وسائط التباين - ملاحظة: اختياري للاستخدام مع العمليات الموجهة بالكاشف الفلوري

13.0 تعليمات الاستخدام

13.1 قبل الاستخدام

أدوية الإجراءات المحيطة

من المستحسن أن يتبع الأطباء المبادئ التوجيهية للأدوية السابقة للإجراء والتحضير لإجراء بالمنظار، بما في ذلك إعطاء مضاد حيوي قبل الإجراء حسب الاقتضاء. يوصى أيضًا بإعطاء مضادات الالتهاب اللاستيرويدية الفموية قبل الإجراء.

في حالة وجود التهاب في المسالك البولية (UTI) في وقت العلاج، يجب علاج المريض حتى يتم الشفاء من العدوى قبل أن يتم إجراء العلاج.

13.2 تحضير تضيق الهدف

يوصى بالتوسيع المسبق للإحليل لتضيق الهدف، باستخدام طريقة التحضير المناسبة كما يحددها الطبيب المعالج (بالون التوسيع غير المغلف أو DVIU)، للتضيق الشديد وصعوبة عبور التضيقات قبل استخدام Optilume DCB. قم بإجراء توسيع مسبق "لإعطاء" التضيق. يتم تعريف هذا بأنه قطر تجويف التضيق المتوسع > F20 أو > 50% أكبر من تجويف التضيق غير المتوسع.

13.3 تحديد حجم الجهاز

تحقق من أن قطر بالون DCB المحدد عند الضغط الاسمي هو نفسه أو أكبر قليلاً من قطر الإحليل الصحي المجاور للحافة البعيدة للتضيق. يُعرَّف قطر البالون مقسومًا على الإحليل المجاور الصحي البعيد باسم نسبة التمدد.

حجم الإحليل البصلي

بالنسبة للتضيقات البصلية، لا تتجاوز نسبة التمدد 1.3 من قطر البالون إلى الإحليل الصحي البعيد. إذا كان حجم الإحليل يقع بين أحجام الأجهزة المتاحة، فاستخدم الحجم الأكبر شريطة أن تكون نسبة التمدد أقل من أو تساوي 1.3. إذا كان الحجم الأكبر التالي ينتج نسبة تمدد أكبر من 1.3 ، فاستخدم الجهاز الأصغر.

حجم إحليل القضيب

بالنسبة لتضيقات إحليل القضيب، حدد قطر البالون الذي يتطابق بشكل أفضل مع الإحليل الصحي البعيد. يجب ألا تتجاوز نسبة تمدد إحليل القضيب 1:1. إذا كان حجم الإحليل يقع بين أحجام البالون المتاحة، فحدد حجم البالون الأصغر. لا تتجاوز نسبة التمدد 1:1.

بالنسبة لإحليل القضيب والإحليل البصلي، يجب أن يكون طول بالون DCB أطول من طول التضيق المراد معالجته. يجب أن يمتد طول البالون تقريبًا 0.5-1 سم بعد التضيق على كلا الجانبين. على سبيل المثال، إذا كان طول التضييق 2 سم، فاختر بالون DCB بطول 3 سم.

Fr30 (10 مم) x 50 مم

بالون (مم)		كيلوباسكال	الضغط (ATM)
(Fr30) 9.98	اسمي	600	6.0
10.23		800	8.0
10.44	RBP	1000	10.0

تنبيه: *ينبغي عدم تجاوز ضغط الانفجار المقنن. راجع ملصق المنتج للتعرف على ضغوط الانفجار المقننة. قد يتسبب النفخ الذي يتجاوز ضغط الانفجار المقنن في تمزق البالون. في حالة حدوث فقدان للضغط داخل البالون أثناء النفخ أو إذا تمزق البالون أثناء التوسيع، توقف فورًا عن الإجراء. قم بتفريغ البالون بعناية وإزالته من الإحليل. لا تعد تعقيمه.*

14.0 الضمان

تضمن Urotronic أنه تم اتباع العناية المعقولة في تصميم هذا المنتج وتصنيعه. يحل هذا الضمان محل جميع الضمانات الأخرى غير المنصوص عليها صراحةً في هذه الوثيقة، سواء كانت صريحة أو ضمنية، ويستبعدها من خلال تطبيق القانون أو غير ذلك، بما في ذلك، على سبيل المثال لا الحصر، أي ضمانات ضمنية لغرض معين. إن معالجة هذا الجهاز وتخزينه وتنظيفه وتعقيمه بالإضافة إلى العوامل الأخرى المتعلقة بالمريض والتشخيص والعلاج والإجراءات الجراحية وغيرها من الأمور الخارجة عن سيطرة Urotronic تؤثر بشكل مباشر على الجهاز والنتائج التي يتم الحصول عليها من استخدامه.
يقتصر التزام Urotronic بموجب هذا الضمان على إصلاح هذا الجهاز أو استبداله ولن تكون Urotronic مسؤولة عن أي خسارة عرضية أو تبعية أو تلف أو نفقة تنشأ بشكل مباشر أو غير مباشر عن استخدام هذا الجهاز. لا تتحمل Urotronic أي مسؤولية فيما يتعلق بالأجهزة التي تم إعادة استخدامها أو إعادة معالجتها أو إعادة تعقيمها ولا تقدم أي ضمانات، صريحة أو ضمنية، بما في ذلك على سبيل المثال لا الحصر لغرض معين، فيما يتعلق بهذه الأجهزة.

عربي

5. إذا كان المنتج يعاني من فشل قبل النفخ أو في أثنائه، فاستبدل بالون DCB وانفخه وفقًا للعملية. إذا كان الفشل بعد النفخ إلى RBP، فلا تكرر عملية DCB.
6. أدخل قسطرة فولي مشحمة 12-14 Fr واتركها في مكانها لمدة يومين على الأقل أو وفقًا لمستوى الرعاية القياسي، أيهما أكبر.

13.7 مخطط التوافق

Fr18 (6 مم) x 30 مم

بالون (مم)		كيلوباسكال	الضغط (ATM)
(Fr18) 6.11	اسمي	600	6.0
6.23		800	8.0
6.34		1000	10.0
6.45	RBP	1200	12.0

Fr18 (6 مم) x 50 مم

بالون (مم)		كيلوباسكال	الضغط (ATM)
(Fr18) 5.87	اسمي	600	6.0
6.03		800	8.0
6.16		1000	10.0
6.25	RBP	1200	12.0

Fr24 (8 مم) x 30 مم

(مم) بالون		كيلوباسكال	الضغط (ATM)
(Fr24) 7.98	اسمي	600	6.0
8.16		800	8.0
8.32		1000	10.0
8.46	RBP	1200	12.0

Fr24 (8 مم) x 50 مم

بالون (مم)		كيلوباسكال	الضغط (ATM)
(Fr24) 8.00	اسمي	600	6.0
8.20		800	8.0
8.37		1000	10.0
8.54	RBP	1200	12.0

Fr30 (10 مم) x 30 مم

(مم) بالون		كيلوباسكال	الضغط (ATM)
(Fr30) 9.83	اسمي	600	6.0
10.09		800	8.0
10.29	RBP	1000	10.0

15.0 الرموز المستخدمة في ملصقات الجهاز

	كمية 1 لكل عبوة
	تنبيه: تحظر القوانين الفيدرالية بيع هذا المُنتج إلا لطبيب أو بموجب طلب طبيب.
	يشير إلى تاريخ تصنيع الجهاز الطبي.
	لا تعد تعقيمه
	لا تعد استخدامه
	لا تستخدمه في حالة تلف العبوة
	قابل للكسر
	يُستخدم قبل تاريخ
	يحفظ بعيدًا عن أشعة الشمس
	يحفظ جافًا
	الشركة المصنعة
	لا يحتوي على لاتكس
	حد درجة الحرارة 15 درجة مئوية - 30 درجة مئوية
	تنبيه: راجع تعليمات الاستخدام
	معقم بأكسيد الإيثيلين
	رقم الكتالوج
	رقم المجموعة
	منتج مميز بعلامة السلامة الأوروبية (CE) وفقًا لتوجيه الأجهزة الطبية EEC/42/93 للاتحاد الأوروبي (هيئة التصديق رقم 1434)
	ممثل الاتحاد الأوروبي المعتمد

1434

Urotronic, Inc.
2495 Xenium Lane North
Minneapolis, MN 55441
USA

EC REP
MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany

Rev	Date	Change Description	Author Initials
A	26 Feb 2018	Initial Release	LM
B	10 Apr 2018	Updates to address IDE approval conditions requested by the FDA in G180041: - Addition to paclitaxel exclusion critiera - Clarification regarding sexual contact following treatment - Change to definition of de novo stress urinary incontinence - Spelling and formatting for consistency throughout document	LM
C	16 Apr 2018	Update to Principal Investigators (PI) Revision to Exclusion Criteria #29	LM
D	Jun 2018	Exclusion #2 updated using language recommended by FDA	LM
E	15 Aug 2018	Changes to exclusion criteria #8, #9, and #30 for clarification Addition of A1C test at baseline as applicable Addition of CBC with CMP at the Foley Removal and 30-day visit recommended by FDA Additions to section 9.5.1 (Drug Risk) recommended by FDA Updates to section 12.1 (Clinical Events Committee) to align with section 9.1 (Reporting of all Adverse Events)	LM
F	09OCT2018	Changes to inclusion/exclusion criteria for clarification Adding additional sites	LM
G	16APR2019	Changes to inclusion/exclusion criteria Inclusion Criteria • Decrease IPSS from 13 to 11 • Clarify lumen diameter to be less or equal to 12F Exclusion Criteria • Delete redundant bacterial urethritis criteria • Change “Prior diagnosis of UTI to “Untreated UTI” • Remove exclusion of radical prostatectomy • Remove History of pelvic radiation • Include presence of sling in exclusion #16	LM

		• Increase the HB A1c limit from 7 to 8 Updates to Randomization and Stratification (Figure 5-1)	
H	20Dec2019	Changes per FDA Feedback: 1. Removal of retreatment arm for subjects enrolled in the treatment arm 2. Include the 3-5 year follow-up visits as required 3. Change window for pre-treatment urine analysis and urine culture from 7 days to 14 days 4. Update to definition of Serious Adverse Event 5. Urotronic Address Change	IS

UROTRONIC

ROBUST III Clinical Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease – A Randomized Control Trial

PROTOCOL No. PR1076-001 Rev H

SPONSOR
Urotronic Inc
2495 Xenium Lane N
Minneapolis, MN 55441

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

UROTRONIC

ROBUST III Clinical Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease – A Randomized Control Trial

PROTOCOL No. PR1076-001 Rev H

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Ethics Committee/Research Ethics Board (EC/REB). I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to this protocol, ICH Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki, 21 CFR 50, 56 and 812, and hospital EC/REB requirements.

I agree to and understand the material presented in this protocol, and must not publicly disclose in any manner the design, results, or conclusions of this investigation without prior written consent from Urotronic.

_____
Clinical Site Name

_____ _____
Site Investigator Signature Date

_____
Site Investigator
Printed Name

Protocol Summary

Title:	ROBUST III Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease- A Randomized Control Trial
Objective:	The study described below is designed to establish the safety and effectiveness for the Optilume™ Stricture Drug-Coated Balloon (DCB).
Study Design:	This is a prospective, multi-center, randomized controlled adaptive sample size clinical trial with one planned interim analysis for sample size re-estimation.
Interventions:	Study Device: Urotronic Optilume Stricture DCB Control: Standard of care dilation method as determined by the treating physician
Enrollment:	Approximately 140 Subjects A subject will be considered enrolled when they have signed informed consent and have been randomized. Individual site enrollment may not exceed 30% of the total study enrollment.
Inclusion Criteria:	1. Male subjects ≥ 18 years' old 2. Visual confirmation of stricture via cystoscopy or urethrogram 3. Single, tandem or diffuse anterior urethral stricture(s), less than or equal to 3.0 cm total length measured by retrograde urethrogram. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture). 4. Two or more prior dilation treatments of the same stricture, including DVIU (Direct Vision Internal Urethrotomy), but no prior urethroplasty. *Note: Catheterization is not considered a dilation treatment*. 5. Significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent urinary tract infections (UTI's). 6. International Prostrate Symptoms Score (IPSS) score of 11 or higher (assumed to be "35" if suprapubic catheter is present) 7. Lumen diameter ≤12F by urethrogram 8. Qmax <15 ml/sec (assumed to be "0" if suprapubic catheter is present) 9. Guidewire must be able to cross the lesion

Exclusion Criteria:	1. Subjects with diffuse stricture length, greater than 3.0 cm in total length. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture). 2. Subjects with a history of hypersensitivity reactions to TAXOL, on medication that may have negative interaction with paclitaxel, with solid tumors who have a baseline neutrophil counts of <1500 cells/mm^3 or subjects with AIDS-related Kaposi's sarcoma with baseline neutrophile counts of <1000 cells/mm^3. 3. Subjects who had an indwelling suprapubic catheter longer than three (3) months total prior to enrollment. 4. Previous urethroplasty within the anterior urethra. 5. Stricture dilated or incised within the last six (6) weeks (urethral catheterization is not considered dilation) 6. Presence of local adverse factors, including abnormal prostate making catheterization difficult, urethral false passage or fistula. 7. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture at the discretion of the physician 8. Diagnosis of untreated and unresolved BPH or BNC 9. Untreated stress urinary incontinence (SUI). 10. History of diagnosed radiation cystitis 11. Diagnosis of carcinoma of the urethra, bladder or prostate within the last two (2) years 12. Active kidney, bladder, urethral or ureteral stone passage in the last six (6) weeks or concern of stone passage in the next 6 weeks at the discretion of the investigator. 13. Diagnosis of chronic renal failure and treatment with hemodialysis 14. New diagnosis of OAB (overactive bladder) within the last six (6) months 15. Use of alpha blockers, OAB (Overactive Bladder) medication, anticonvulsants (drugs that prevent or reduce the severity and frequency of seizures), and antispasmodics where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last six months.) 16. Dependence on Botox (onabotulinumtoxinA) in urinary system 17. Presence of an artificial urinary sphincter, slings or stent(s) in the urethra or prostate 18. Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function 19. Diagnosed with Lichen Sclerosus, or stricture due to balanitis xerotica obliterans (BXO) 20. Previous hypospadias repair 21. History of cancer in non-genitourinary system which is not considered in complete remission (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered in complete remission if there has been no evidence of cancer within two (2) years of enrollment 22. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires 23. Unwilling to use protected sex for thirty (30) days' post treatment

	24. Unwilling to abstain or use protected sex for ninety (90) days post treatment if sexual partner is of child bearing potential. 25. Inability to provide Informed Consent Form (ICF) and/or comply with all the required follow-up requirements 26. Participation in other pre-market studies or treatment with an investigational drug or device. Long term follow up or post market study of an approved device is allowed. 27. Current active infection in the urinary system 28. Current uncontrolled diabetes (hemoglobin A1c > 8.0%) or evidence of poor wound healing due to diabetes 29. Diagnosed or suspected primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function, sphincter function or poor detrusor muscle function. 30. Visible hematuria in subject's urine sample without known contributing factor 31. Invisible hematuria (or significant microscopic hematuria, i.e. hematuria of ≥ 3 RBC's/HPF) that may be caused by a clinically significant disease unless it is attributed to the urethral stricture disease or other causes which are benign and not requiring treatment.
Follow-up:	Follow-up visits required post-procedure: Foley Removal (2–5 days), 30 days, 3 months, 6 months, 12 months, and annually thereafter for 5 years post-procedure.
Clinical Sites:	Up to thirty (30) clinical sites in the US and Canada willing to participate in the study
Primary Efficacy Endpoint	Stricture Free Rate at six (6) months • Measured by passing a 16F flexible cystoscope at 6 months' post-treatment • If a 16F flexible cystoscope cannot pass, a 14F rubber catheter will be used A stricture is defined to be resolved when a 16F flexible cystoscope or a 14F rubber catheter can be passed through the stricture.
Primary Safety Endpoint	This safety endpoint is defined as a composite device related serious complications at three (3) months. Device related is defined to include both device and procedure related. • Device related formation of fistula • Device related unresolved de novo stress urinary incontinence (requiring ≥1 pad/day) at ninety (90) days • Urethra rupture or burst
Secondary Endpoint 1 - Efficacy	Change in Qmax (Peak Flow Rate) at six (6) months
Secondary Endpoint 2- Efficacy	Percent responder at tweleve (12) months (IPSS) • A responder is defined as a subject with a 50% improvement of IPSS score or an IPSS of eleven (11) or lower.
Secondary Endpoint -3- Efficacy	Time to treatment failure • Defined as any stricture treatment at the target treatment site.

Statistical Considerations	The study is designed as a prospective, multi-center, randomized, controlled adaptive sample size clincial trial. Subjects will be randomized in a 2:1 ratio to Test:Control and randomization will be stratifed by site. Sample size for the study is based on power considerations for the primary efficacy endpoint. Sample size for the study is based on the primary effectiveness endpoint using the following assumptions: • 2:1 randomization allocation • Type 1 error of 0.025, one sided • Statistical power of approximately 90% • Assumed population success rate of 40% for the Control arm and 72% for Treatment arm, corresponding to a difference of 32%. • 10% loss of follow-up rate Based on these assumptions, an initial sample size of 126 evaluable subjects (Test: 84; Control: 42) provides approximately 90% power. Assuming a 10% lost to follow up, the initial randomized sample size is one hundred forty (140) subjects. The primary safety endpoint will be analyzed with descriptive statistics and nominal 95% confidence intervals; there will be no formal statistical hypotheisis test. Due to uncertainty with respect to the design assumptions, an adaptive sample size methodology is planned[i,ii]. An interim analysis of the primary effectiveness endpoint is planned when primary effectiveness endpoint data is available on the first 60 randomized subjects (approximately 48% of the planned original total evaluable sample size). At the interim analysis, the primary effectiveness endpoint will be evaluated; if warranted, the sample size of the trial may be increased up to a maximum of two hundred (200) total subjects to maintain the study power. Additional statistical details, including plans for subgroup analyses, poolability, handling of missing data, control of the type I error rate for secondary endpoints, as well as details on the interim analysis and sample size re-estimation will be provided in a separate standalone Statistical Analysis Plan.
Primary Efficacy Hypothesis	For the trial to be successful, the statistical evaluation for the resolution of the stricture at six (6) months of the Optilume arm will be statistically compared to the control arm. Ho: $P_t \leq P_c$ Ha: $P_t > P_c$ Where P_t is the stricture free rate at 6 months in the Treatment arm and P_C is the stricture free rate at six (6) months in the Control arm.
Primary Safety Hypothesis	The primary safety endpoint will be analyzed with descriptive statistics and nominal 95% confidence intervals; there will be no formal statistical hypotheisis test.

Principal Investigators	Sean Elliott, MD University of Minnesota Department of Urology 420 Delaware St. SE, MMC 394 Minneapolis, MN 55455 Ramon Virasoro, MD Urology of Virginia 225 Clearfield Ave Virginia Beach, VA 23462
Independent Review Committees:	An independent Clinical Events Committee (CEC) will be utilized for this study. The CEC will be responsible for adjudicating the seriousness and relatedness of all potential device and/or procedure related adverse events occurring during the study period. A charter will be completed for the CEC outlining membership, duties and functions. An independent Data Monitoring Committee (DMC) will be utilized for this study. The DMC will be responsible for evaluating safety by reviewing overall study outcomes, adverse events and determining the implementation of the adaptive design protocol. The DMC will review the first interim analysis and provide feedback to the sponsor and study sites regarding the adaptation of the study design if required. A charter will be completed for the DMC outlining membership, duties and functions.
Study and Data Management:	Overall study management will be conducted by Clinlogix. Clinlogix 8 Spring House Innovation Park 727 Norristown Rd, Suite 100 Lower Gwynedd, PA 19002 Data Management will be conduted by Libra Medical Libra Medical 8401 73rd Ave N Suite 63 Brooklyn Park, MN 55428
Study Monitors:	Clinlogix 8 Spring House Innovation Park 727 Norristown Rd, Suite 100 Lower Gwynedd, PA 19002
Sponsor:	Urotronic Inc 2495 Xenium Lane N Minneapolis, MN 55441

1 INTRODUCTION

1.1 Disease State Overview and Epidemiology

A urethral stricture is scarring in the urethra or surrounding tissue that narrows or blocks the passageway through which urine flows from the bladder. The stricture can result from inflammation, infection or injury, and is much more common in men than in women. The scarring can occur anywhere between the bladder and the tip or opening of the urethra. In addition to uncomfortable urinary symptoms such as reduced flow rate and frequent urination, a urethral stricture can lead to complications that include urinary tract infections, prostatitis, urinary retention and kidney damage. There were 1.5 million office visits from 1992 to 2000 in US for the treatment of urethral strictures, and resulted in $191 million in health care expenditures[iii].

1.2 Stricture Diagnosis

Patients with lower urinary tract symptoms will have their urinary flow rate measured as part of the initial investigation of lower urinary tract symptom. In those who have a urethral stricture, the peak flow rate is typically low but with a flat flow pattern as shown in Figure 1-1.

This flow pattern is pathognomonic of a urethral stricture. The presence of the stricture must be diagnosed by urethrogram to determine the exact site and length of the stricture and its potential complications. Ultrasound may show a thickening of the bladder wall associated with longstanding outflow obstruction, and a presence of residual urine.

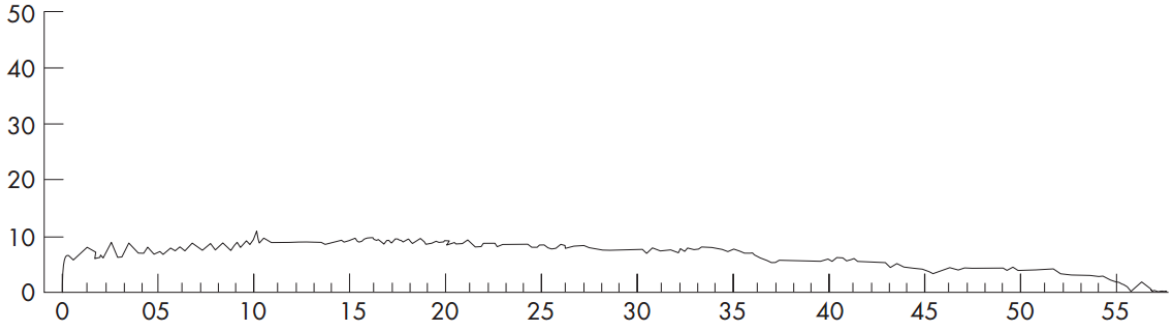


Figure 1-1: Characteristic Pattern for Urine Flow in the Presence of Stricture

1.3 Current Standard of Care

Urethral strictures are still a common and challenging problem in urology. In the United States, the most common minimally invasive treatment for strictures is dilation (92.8%), or opening of the urethral stricture to allow normal voiding.[iv] Balloon dilation allows less discomfort and reduced risks because of less shearing force and reduced trauma, compared to the traditional rigid dilators.[v] More severe strictures can require surgical intervention for recurrent or long complicated lesions.

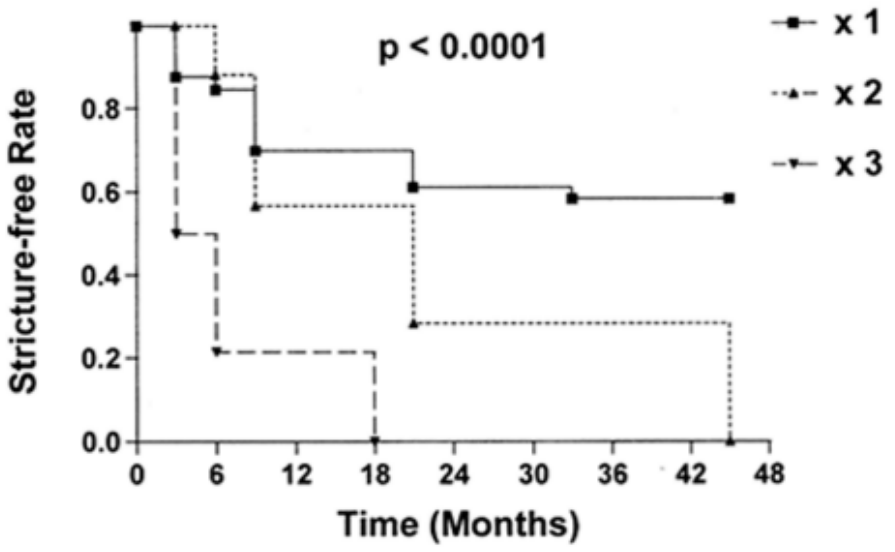
The most common complication after dilation is stricture recurrence, with average time to recurrence for a previously treated stricture being 3 months.[v] Hazard function analysis showed that the risk of stricture recurrence was greatest at 6 months, whereas the risk of failure after 12 months was slight.[vi]

Due to the high recurrence rate of strictures following dilation, treatment often progresses to more invasive treatments such as internal urethrotomy or urethroplasty. Open urethroplasty remains the gold standard of care, but it requires good expertise and is invasive.[iv] However, balloon dilation has also been shown to be a safe, and well-tolerated procedure and previously compared to rigid dilation.[vii]

The principle of urethral dilation is to stretch the urethral stricture up or to disrupt it to restore the urethral caliber to normal or thereabout. The normal urethral caliber is 24-26F at the external urinary meatus, a little wider in the penile urethra, and about 36F at the bulbar urethra.[viii] Urethrotomy and dilation are equally effective with expected cure rate of about 50% for short bulbar urethral strictures when first used. The success rate of repeated procedure is lower.[viii]

When strictures recur, they usually do so within weeks to months and almost always within two years. The expected recurrence rate reported are schematically summarized in Figure 1-2.

The following graph demonstrates the likelihood of success from a urethral dilation.



from The Journal of Urology: Volume 160(2) August 1998 pp 356-358

Figure 1-2: Stricture Recurrence Rate

1.4 History of Use of Paclitaxel

Paclitaxel has been used extensively and successfully in drug-coated devices to reduce the rate of stenosis in vascular tissue, due to its anti-proliferative properties. It is dosed systemically to treat multiple types of cancers including prostate cancer, as well as delivered locally to the cardiovascular system via drug eluting stents (coronary and peripheral vasculature) as well as drug coated balloons. Examples of the devices coated with this drug and the dates of approval in the US are shown in Table 1-1. The improvement in restenosis rates, along with the minimally invasive nature of dilation for urethral strictures, led Urotronic to design a similar system to treat urinary strictures.

Table 1-1: US Approved Paclitaxel Coated Devices

Drug Coated Balloon	US Approval Date
Boston Taxus DES	2004
Cook Zilver PTX DES	2012
Lutonix DCB	2014
Medtronic DCB	2015

1.5 Rationale for Study

Balloon dilation is the least invasive treatment for strictures. However, because of the nature of strictures, recurrence of the stricture (50% - 75%) following balloon dilation is common especially for strictures that were treated more than two times.[v] When strictures recur after balloon dilation, treatment often progresses to more invasive treatments:

- Direct Visual Internal Urethrotomy (DIVU) is a slightly more invasive approach that involves an endoscopic incision of the stricture, but is not more effective than dilation.[ix, x, xi]
- Urethroplasty is an open surgery for stricture disease that is more effective but far more invasive than dilation or DVIU and is the treatment of last resort for strictures.

Urethroplasty is performed by a minority (~2%) of urologists and the vast majority of subjects are managed by less invasive therapies. Any improvement in technique or means of changing the natural history and progression of the disease would make a significant clinical contribution. The study described below is designed to assess the safety and effectiveness for the Urotronic Optilume™ Stricture Drug-Coated Balloon (DCB) for the treatment of anterior urethral stricture.

2 PRIOR CLINICAL EXPERIENCE OF DCB USE IN STRICTURE

Urotronic has sponsored two clinical trials utilizing the Optilume DCB. A summary of each is provided below.

2.1 ROBUST I

ROBUST I is a pilot study conducted at four Latin American investigational sites, two in the Dominican Republic and two in Panama. ROBUST I enrolled and treated 53 subjects with urethral strictures with the Optilume DCB. Subject follow-up is currently ongoing. As of February 2, 2018, 25 subjects have returned for the 6-month follow-up while 51 subjects had their 3 month follow up.

2.1.1 Outcome Results

Table 2-1 is a summary of the outcomes in ROBUST I.

Table 2-1: Robust I Efficacy Results

Efficacy Measurements	Baseline	3 months	6 months
Stricture Free (Passing of 16Fr scope or 14Fr Rubber Cath)	0	Not evaluated	76% (19/25)
IPSS	25.2 ± 4.5 (N=53)	6.1 ± 7.63 (N=51)	6.9 ± 8.32 (N=24*)
% Responder (IPSS<11)	0	84.3% (43/51)	83.3% (20/24*)
QOL (0 – delighted; 6 – terrible)	4.9 ± 0.86 (N=53)	0.8 ± 1.32 (N=51)	1.0 ± 1.25 (N=24*)
Qmax	5.0 ± 2.56 (N=46*)	20.9 ± 12.73 (N=56)	18.5 ± 10.60 (N=24*)
PVR	141.4 ± 105.05 (N=43*)	38.1 ± 37.05 (N=56)	37.7 ± 55.86 (N=23*)
Repeat Treatment @ 6 Mo			20% (5/25)

* indicates some subject data was missing at this time point

2.1.2 Adverse Event Results

A total of thirty-one (31) adverse events (AE) were reported as of February 2, 2018. Thirteen of these AEs were classified as possibly or probably related to the procedure or device.

The reported AEs are summarized as follows:

- Total of 31 AEs reported
  - 13 graded as Class 1 (mild)
  - 14 graded as Class 2 (moderate)
  - 1 graded as Class 4 (life threatening) – Myocardial infarction
- No serious device related complications
- One SAE – Myocardial infarction, non-device related
- One definite procedure-related AE was reported

2.1.3 Pharmacokinetic Results

Pharmacokinetic (pK) testing was studied for PTX in a subset of the ROBUST I subjects on the plasma, urine and semen samples collected. Test results confirmed that the amount of drug found in the plasma or semen following treatment is very small and does not present a health hazard. Drug concentration in the urine dropped significantly between the procedure day and day 5. The pharmacokinetics of the drug in the blood, semen, and urine is shown in Figure 2-1. As shown, the drug is meaningfully available only in the urine samples immediately post treatment.

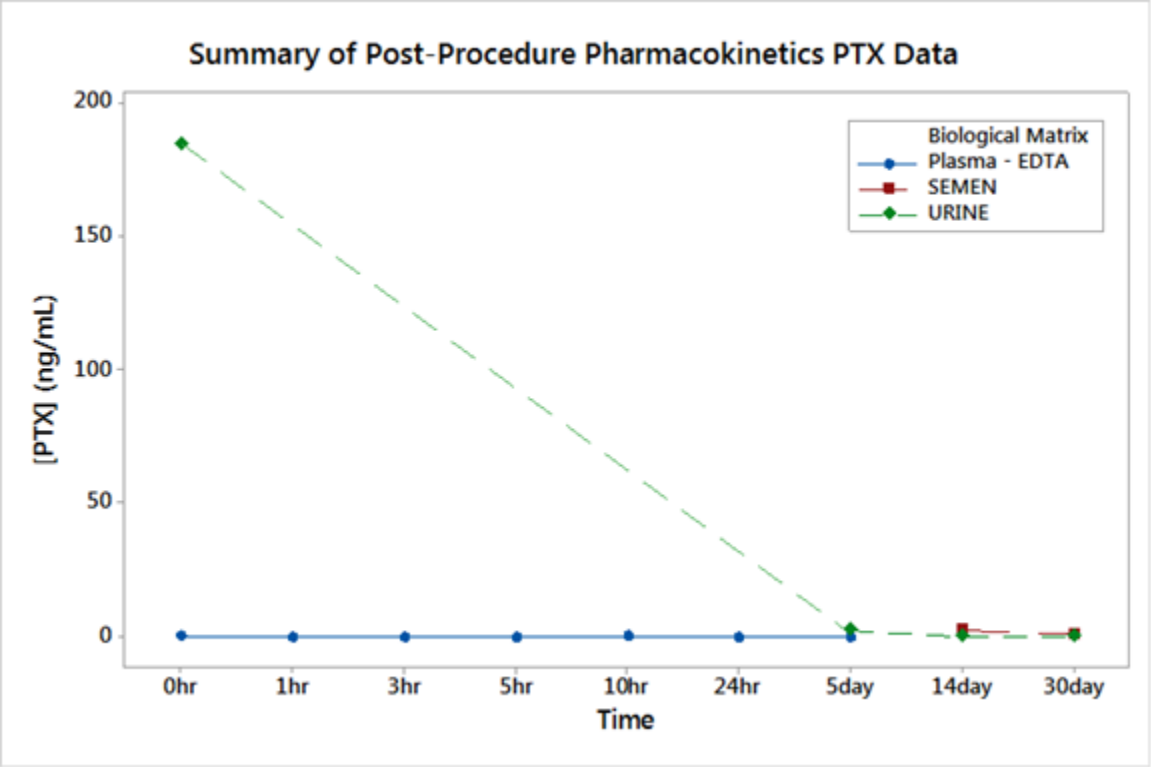


Figure 2-1: Summary PK Data

Data collected from the ROBUST I study indicated the Optilume DCB treatment appeared to be safe and the device performed as intended with promising efficacy report.

2.2 ROBUST II

ROBUST II is a feasibility study started at five (5) investigational sites in the United states. ROBUST II is expected to enroll and treat fifteen (15) subjects with urethral stricture with the Optilume DCB. As of January 31, 2018, one (1) subject has been treated in the study. Subject follow-up is currently ongoing. This study will be running concurrently with Robust III for publication and reimbursement reasons.

3 DEVICE DESCRIPTION

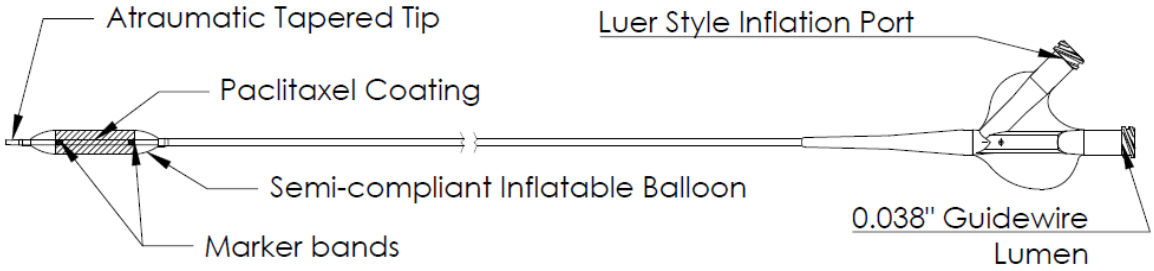


Figure 3-1: Urotronic Optilume™ Drug Coated Balloon Catheter

The Urotronic Optilume™ Drug Coated Balloon (DCB) is a 0.038" guidewire compatible over-the-wire catheter with a tapered atraumatic tip. The distal end of the catheter has a semi-compliant inflatable balloon coated with a proprietary coating containing the drug paclitaxel and carriers that facilitates the drug's transfer to the urethral wall upon inflation. Paclitaxel is an anti-inflammatory and anti-proliferative drug commonly used to prevent arterial restenosis. The drug coating evenly coats the working length of the balloon body only. The device has two radiopaque marker bands that indicate the drug coated working length of the balloon under fluoroscopy (Figure 3-1). The device is provided sterile, and is intended for single use only.

The device is available in multiple diameters and balloon body lengths. The full matrix of device availability is described in the Instruction for Use (IFU). Table 3-1 shows the current device sizes available. However, during the study, other sizes will be introduced when available. The IFU will be updated with the additional sizes as they become available. Please refer to the IFU for the full list of device sizes available. All devices will be full tested and submitted to FDA for IDE approval prior to introduction into the study.

Table 3-1: Optilume Device Sizes

	Length (mm)	
Diameter (Fr/mm)	**30**	**50**
18.0 / 6.0	X	X
24.0 / 8.0	X	X
30.0 / 10.0	X	X

3.1 Intended Use

The Optilume DCB is intended to dilate stricture(s) in the anterior urethra.

3.2 Proposed Indication for Use

Optilume Drug Coated Balloon Catheter is used to treat patients with bothersome urinary symptoms associated with anterior urethral stricture. It is designed to be used in men as a

standalone dilation balloon for urethral stricture or used as an adjunctive therapy with other medical dilation devices and/or procedure

4 RISK-BENEFIT ANALYSIS

4.1 Risk Analysis

Balloon dilation to treat urethral stricture is an established treatment and the risk associated with the procedure is well understood. The biggest risk of traditional dilation is recurrence of the stricture. The investigational device is a drug coated balloon that is supposed to suppress cellular proliferation and hence potentially mitigate the risk of recurrence of the stricture at the treatment site.

4.1.1 Risk Assessment

In conducting the risk analysis, the concepts of risk estimation, risk acceptability, risk control and overall risk evaluation were applied in accordance with ISO 14971. The intended use and treatment procedure was taken into consideration along with the materials and mechanical features of the Optilume DCB. Based on an evaluation of residual risk acceptability, it was determined that no individual residual risks values are considered unacceptable and that all individual risks are balanced against the benefit of the device.

4.1.2 Risk Mitigation

A potential health risk of study participation is due to the paclitaxel drug coating. Paclitaxel is a lipophilic, anti-mitotic agent that has been reported to prevent proliferation of smooth muscle cells, inflammatory cells and fibroblast. The purpose of using paclitaxel in the coating of the device is to prevent or reduce stricture recurrence by inhibiting smooth muscle cell proliferation and neourothelial hyperplasia. The potential risks of Paclitaxel in the coating can cause include:

- Chromosomal abnormalities and the risk of cancer,
- Fetal harm when a pregnant woman is exposed,
- Anaphylaxis and hypersensitivity with paclitaxel intravenous infusion have been reported
- It may inhibit the healing of the urethra post procedure
- Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered is much lower than a single dose of chemotherapy provided to cancer patients and the drug appears essentially localized to the urethra (**Fehler! Verweisquelle konnte nicht gefunden werden.**Figure 2-1).

Therefore, the risk of drug toxicity is anticipated to be very low as the concentration of the drug in the body fluid is very low. The complete list of potential anticipated adverse events is provided in Section 9.5 of this protocol.

4.2 Potential Benefit

The subjects participating in this study potentially could benefit from the reduction in the rate of recurrence of stricture. Data from Robust I showed that majority of the subjects treated received a benefit from the treatment. The data obtained from this study will be used to establish the safety and efficacy of the device and this data may benefit others in the future.

4.3 Study Participation Associated Risks

In addition to the risk to health, there is a risk of violation of subject's privacy during the data collection and monitoring of the subject's health data. All precaution will be taken to prevent the accidental disclosure of subject's medical records. All subjects will be listed by the study ID and no personal data will be collected.

The risks associated with study participation (Table 4-1) are those associated with standard clinical diagnostic and evaluative practice procedures. All subjects will provide informed consent prior to participating in the study.

The procedures required per study protocol are consistent with standard of care procedures given the indication for the associated treatment.

Table 4-1: Study Participation Associated Risks

Study Procedure	Risk(s)
Medical History, Physical Exam, Quality of Life Questionnaires	None, minimal
Urinalysis	None, minimal
Uroflowmetry and Post-Void Residual	Written informed consent consistent with clinic policy
Cystoscopy	Written informed consent consistent with clinic policy
Retrograde Urethrogram	Written informed consent consistent with clinic policy
Laboratory Testing	Usual risks associated with phlebotomy

5 STUDY DESIGN

5.1 Study Objective

The objective of this pivotal trial is to establish the safety and effectiveness of the Optilume DCB in the treatment of anterior urethral strictures. The data gathered in this study will be used to support US market approval and for reimbursement purposes of the Optilume DCB.

5.2 Study Design

This is a prospective, multi-center, single blind randomized controlled clinical trial in a 2:1 allocation of treatment versus control device.

This study is an adaptive design with an interim analysis for sample size re-estimation performed after sixty (60) subjects have been enrolled. The interim analysis will be undertaken following completion of the 6-month follow-up data from these subjects. Based on the results of the interim analysis, the final total sample size required for the study will be re-estimated. A minimum of one hundred forty (140) subjects, and a maximum of 200 subjects (pending the re-estimation) will be enrolled in the study. The Data Monitoring Committee (DMC) will review the interim analysis results, including the sample size re-estimation and make recommendations related to trial continuation to the Sponsor.

Subjects will be stratified by prior radiation treatment, followed by the number of prior stricture treatments (less than 5 prior dilations versus ≥ 5prior dilations) before randomization to ensure a balanced distribution of the subjects between the two arms. Individual site enrollment may not exceed 30% of the total study enrollment.

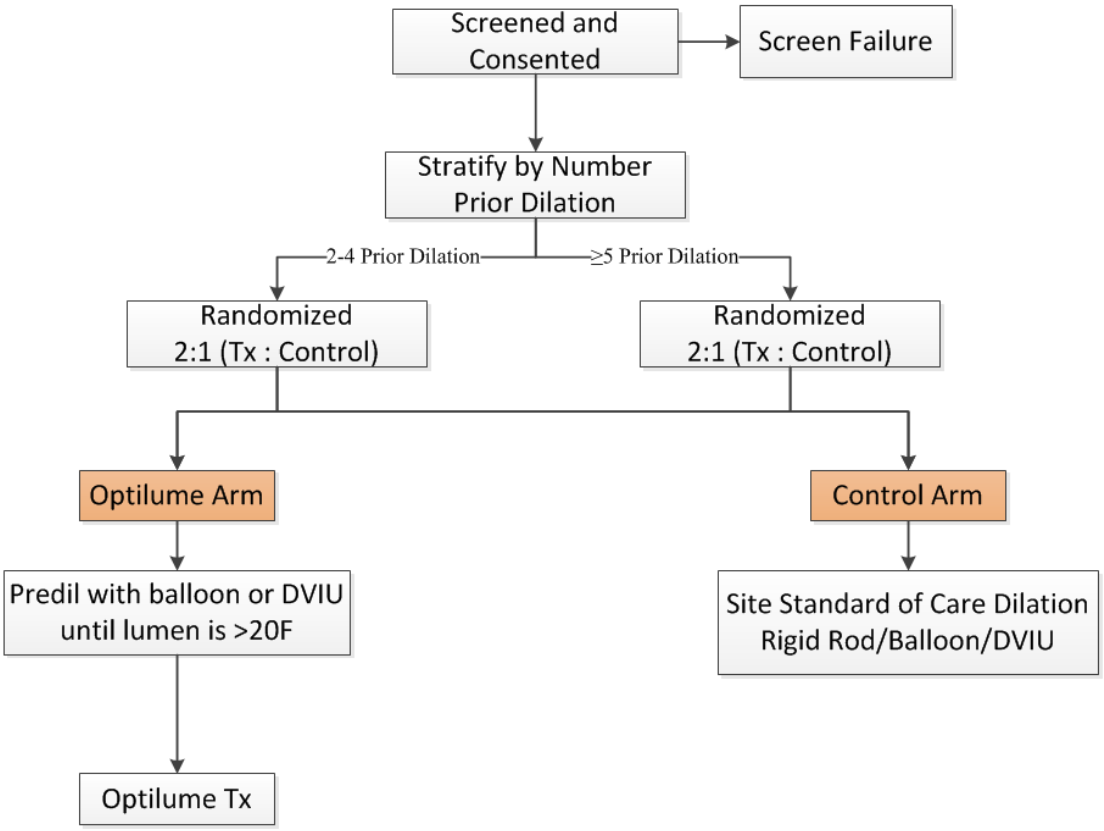


Figure 5-1: Randomization and Enrollment Schematic

5.2.1 Definition of Dilation Methods

Dilation methods are defined as:

- Rigid rod dilation
- DVIU
- Balloon dilation

All three methods of dilation have been shown to be equivalent in terms of outcome and safety profile[v] and therefore are considered interchangeable and equivalent in this study.

Physicians may use one or more of these methods to dilate the stricture as is his/her best practice to dilate the lesion.

5.2.2 Control Arm Treatment Description

Subjects randomized to the control arm will be treated by the dilation method that is the best standard of care for the site and the subject during the index procedure. Therefore, a control subject may be dilated with either a rod, uncoated balloon or DVIU until the desired result is reached. All index dilation methods must be done during the same procedure. Results from all subjects in the control arm will be considered equivalent and pooled for analysis.

5.2.3 Optilume Arm Treatment Description

The treatment arm will be the Urotronic Optilume Stricture DCB. The stricture must show evidence of yielding (defined as a stricture lumen greater or equal to 20F) to the dilation prior to treatment with the Optilume. The physician may choose to predilate the lesion with balloon or DVIU. The size of the predilation balloons and the Optilume balloon selected will be based on the urethral lumen and the stricture length.

A subject will be considered enrolled when they have meet all selection criteria, signed informed consent and have been randomized. Follow-up visits post-procedure will occur at 2-5 days' post-treatment, 30 days, 3 months, 6 months, 12 months and 2-5 years' post-procedure (Fehler! Verweisquelle konnte nicht gefunden werden.).

5.2.4 Crossover

The subjects in the control group that have been unblinded after the 6 months follow up evaluations or unblinded earlier for medical reasons will be given the option to receive the Optilume treatment and continued to be followed according to the Optilume arm follow up schedule. Crossover to the Optilume arm is allowed only before the 12 months follow up period from randomization.

Alternatively, subjects may opt to receive another dilation, or other alternative treatment at which point they will exit the study unless there is an unresolved device or procedure related adverse event at which point, they may be followed for another 30 days or until the AE is resolved, whichever comes first. If the subject chooses not to receive either the Optilume treatment or received an alternative therapy, he will be followed up to 12 months and exited from the study. The schematic of this treatment, retreatments and cross overs are shown schematically in Figure 5-2**.**

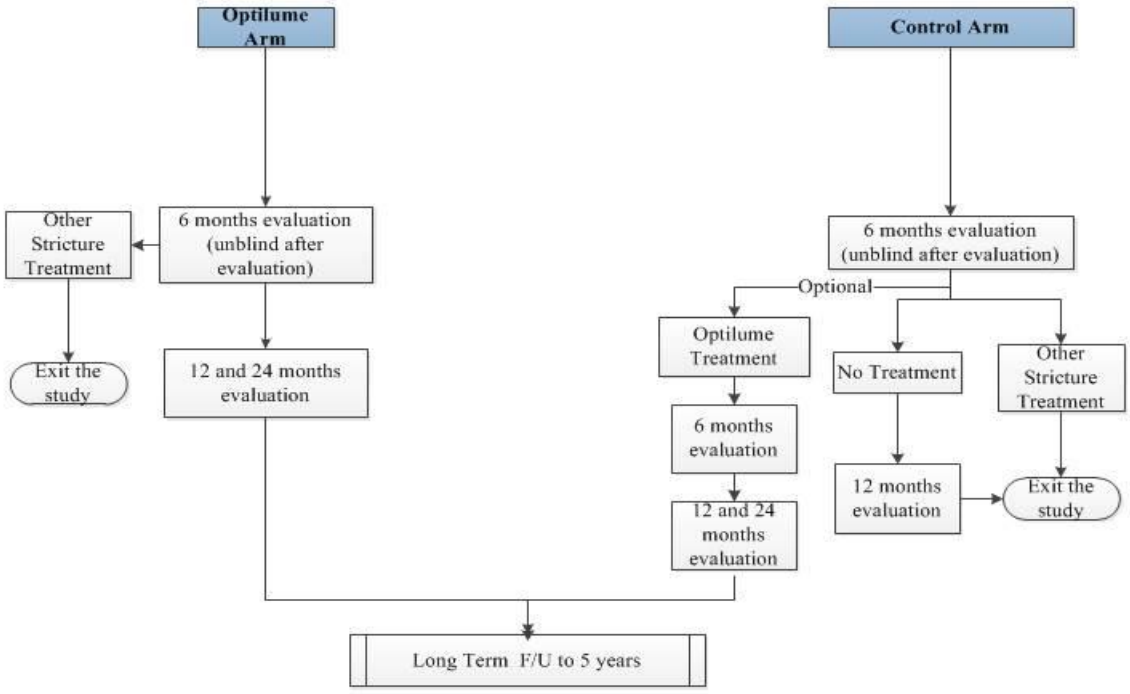


Figure 5-2: Schematic of the ROBUST III Follow-up Algorithm

5.3 Study Duration and Site Number

Up to 30 sites will be recruited for the study. The study duration is anticipated to be up to 8 years.

5.4 Subject Selection Criteria

5.4.1 Inclusion Criteria

1. Male subjects ≥ 18 years old
2. Visual confirmation of stricture via cystoscopy or urethrogram
3. Single, tandem or diffuse anterior urethral stricture(s), less than or equal to 3.0 cm total length measured by retrograde urethrogram. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture).
4. Two or more prior dilation treatments of the same stricture, including DVIU (Direct Vision Internal Urethrotomy).

   Note: Catheterization is not considered a dilation treatment.

5. Significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent UTI's.
6. IPSS score of 11 or higher (assumed to be “35” if suprapubic catheter is present)
7. Lumen diameter ≤12F by urethrogram

8. Qmax <15 ml/sec (assumed to be "0" if suprapubic catheter is present)
9. Guidewire must be able to cross the lesion

5.4.2 Exclusion Criteria

1. Subjects with diffuse stricture length, greater than 3.0 cm in total length. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture).
2. Subjects with a history of hypersensitivity reactions to TAXOL, on medication that may have negative interaction with paclitaxel, with solid tumors who have a baseline neutrophil counts of <1500 cells/mm^3 or subjects with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm^3.
3. Subjects who had an indwelling suprapubic catheter longer than 3 months total prior to enrollment.
4. Previous urethroplasty within the anterior urethra
5. Stricture dilated or incised within the last six (6) weeks (urethral catheterization is not considered dilation)
6. Presence of local adverse factors, including abnormal prostate making catheterization difficult, urethral false passage or fistula.
7. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture at the discretion of the physician
8. Diagnosis of untreated and unresolved BPH or BNC
9. Untreated stress urinary incontinence (SUI).
10. History of diagnosed radiation cystitis.
11. Diagnosis of carcinoma of the urethra, bladder or prostate within the last 2 years
12. Active kindey, bladder, urethral or ureteral stone passage in the last six (6) weeks or concern of stone passage in the next 6 weeks at the discretion of the investigator.
13. Diagnosis of chronic renal failure and treatment with hemodialysis
14. New diagnosis of OAB (overactive bladder) within the last 6 months
15. Use of alpha blockers, OAB (Overactive Bladder) medication, anticonvulsants (drugs that prevent or reduce the severity and frequency of seizures), and antispasmodics where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last six months.)
16. Dependence on Botox (onabotulinumtoxinA) in urinary system
17. Presence of an artificial urinary sphincter, slings or stent(s) in the urethra or prostate
18. Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function
19. Diagnosed with Lichen Sclerosus, or stricture due to balanitis xerotica obliterans (BXO)
20. Previous hypospadias repair
21. History of cancer in non-genitourinary system which is not considered in complete remission (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered in complete remission if there has been no evidence of cancer within two years of enrollment

22. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires
23. Unwilling to use protected sex for 30 days' post treatment
24. Unwilling to abstain or use protected sex for 90 days' post treatment if sexual partner is of child bearing potential.
25. Inability to provide Informed Consent Form (ICF) and/or comply with all the required follow-up requirements
26. Participation in other pre-market studies or treatment with an investigational drug or device. Long term follow up or post market study of an approved device is allowed.
27. Current active infection in the urinary system
28. Current uncontrolled diabetes (hemoglobin A1c > 8.0%) or evidence of poor wound healing due to diabetes
29. Diagnosed or suspected primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function, sphincter function or poor detrusor muscle function.
30. Visible hematuria in subject's urine sample without known contributing factor
31. Invisible hematuria (or significant microscopic hematuria, i.e. hematuria of ≥ 3 RBC's/HPF) that may be caused by a clinically significant disease unless it is attributed to the urethral stricture disease or other causes which are benign and not requiring treatment.

6 STUDY ENDPOINTS

Data from all subjects will be analyzed as Intent to Treat (ITT), per protocol, and as treated regardless of final treatment disposition, device success or procedural success.

6.1 Primary Endpoint- Efficacy: Stricture Free Rate at 6 Months

This endpoint will be evaluated by the ability to pass a 16F flexible cystoscope or a 14F rubber catheter at 6 months' post-treatment. If a 16F cystoscope cannot be passed, a 14F red rubber catheter will be used.

A stricture is defined to be resolved when a 16F flexible cystoscope or a 14F rubber catheter can be passed through the stricture.

The stricture free rate at 6 months will be compared between the two treatment groups.

6.2 Primary Endpoint- Safety: Rate of Major Device or Procedure related complications through 90 days

This safety endpoint is defined as a composite device related serious complications at 3 months. Device related is defined to include both device and procedure related.

- Device related formation of rectal fistula

- Device related unresolved de novo stress urinary incontinence (requiring ≥1 pad/day)
- Urethra rupture or burst

The primary safety endpoint will be analyzed with descriptive statistics and nominal 95% confidence interval.

6.3 Secondary Endpoints

The following secondary endpoints will be statistically assessed to provide additional characterization of the Optilume DCB device in the treatment of stricture and to support potential labeling claims

6.3.1 Secondary Endpoint 1: Efficacy- Change in Qmax (Peak Flow Rate)

Results from the treatment arm will be compared to the control arm at 6 months' post treatment. After 6 months, Qmax changes will be compared to the changes from the baseline values.

6.3.2 Secondary Endpoint 2: Efficacy- Percent Responder at 12 months (IPSS)

A responder is defined as a subject with a 50% improvement of IPSS score

6.3.3 Secondary Endpoint 3: Efficacy- Time to Treatment Failure

Defined as any stricture recurrence at the target treatment site. Stricture is assumed to recur under these criteria:

- A 16F flexible cystoscope or 14F rubber catheter cannot pass through the target treatment site
- Subject had an alternative treatment of the target treatment site
- Subject had to be placed on extended catheterization (>14 days) because of narrowing of the target treatment site

Note: Cystoscope or catheter should not be passed through the treatment area for at least 6 months following dilation treatment, unless medically indicated, required by the protocol or physician suspects the subject's health is in jeopardy or treatment failure is suspected based on one or both of the criteria above. Treatment of obstructive symptoms due to reasons (e.g. BPH) other than stricture is not considered a treatment failure.

6.3.4 Ancillary Endpoints

The following ancillary endpoints are to provide additional characterizations of the safety and effectiveness of the Optilume DCB stricture device in the treatment of anterior stricture.

6.3.4.1 Ancillary Endpoint 1– A1: Efficacy- Long Term Re-treatment Rate at 12 months or longer

Defined as any stricture re-treatment (including but not limited to urethroplasty, DVIU, other dilation) at the target treatment site.

6.3.4.2 Ancillary Endpoint 2 – A2: Long Term Treatment Success, Qmax

6.3.4.3 Ancillary Endpoint 3 – A3: Long Term Treatment Success, IPSS

6.3.4.4 Ancillary Endpoint 4 – A3: Rate of acute urinary retention requiring catheterization or retreatment at 6 months

6.3.4.5 Ancillary Endpoint 5 – A4: Changes in QOL

6.3.4.6 Ancillary Endpoint 6 – A5: Procedural Parameters

- Procedure time
- Treatment time
- Healing time (Length of time the post treatment catheterization was left in during the healing period)

7 PHYSICIAN SELECTION

Physicians selected must have experience in performing cystoscopies, treating strictures endoscopically and/or other male urological therapies. Selected physicians will be trained in the use of the Urotronic Optilume DCB prior to enrolling subjects. The primary investigator will ensure that only trained sub-investigators who satisfy the physician selection criteria can perform any part of the study procedure.

Healthcare professionals or site staff that assist or perform the follow-up evaluations do not need to be trained on the use of the device, but must be delegated and trained to perform the follow-up visit procedures.

7.1 Training

The Sponsor, or designee, will be responsible for training of appropriate clinical site personnel. Prior to the start of study enrollment at a study site, The Sponsor or designee will perform formal device and study training for study site personnel to ensure proper procedural technique, uniform data collection and protocol compliance. At this training session material will include, but may not be limited to:

- Investigational Plan
- Techniques for the identification of eligible subjects
- Device Training
- Instructions on data collection including adverse events
- Schedules for subject follow-up

- Regulatory requirements

After a site completes all required approvals and training, a site initiation visit will be conducted as a final check of the site readiness. If a site is not able to enroll its first subject 3 months after "Ready to Enroll" status, the Sponsor may elect to terminate the investigational site and allocate the slot to another candidate site.

8 STUDY PROCEDURES

8.1 Pre-Screening, Screening, and Baseline

All subjects seen for the treatment of urethral stricture should be screened for study eligibility. The site may pre-screen potential subjects by reviewing medical records to identify the study population. If inclusion criteria are met and no exclusion criteria are present, the subject should be entered into a screening log. Once identified, these subjects are approached to discuss the study, asked to participate and sign the IRB approved informed consent form. The site may not initiate any study specific (non-standard of care) procedures without first obtaining informed consent.

All baseline testing and evaluations must be done as close to the time of treatment as possible and repeated if needed. If an evaluation is repeated, the latest evaluation data will be used as baseline.

A baseline urethrogram must be performed prior to enrollment. Any required procedures performed before obtaining informed consent as part of the standard of care may be used in lieu of the study tests as described in Table 8-1.

The following evaluations will be completed for all study candidates. Evaluations performed within the screening window may be acceptable. The required baseline evaluations prior to enrollment are shown below:

Table 8-1: Screening Evaluations

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Medical history	Within 30 days	Evaluation is complete and adequately documented in source documents
Physical exam evaluation	Within 30 days	Evaluation is complete and adequately documented in source documents
Current or prior (up to 6 months) medication use	Prior to enrollment	A list of current and prior medication is required to determine if the dose is stable.
Urethral Stricture Score (USS)	Within 30 days	None
Blood analysis	Within 30 days	CBC includes: hemoglobin, hematocrit, platelets, RBC and

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Complete blood cell count (CBC) with differential Comprehensive Metabolic Panel (CMP)		WBC. Differential includes absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils. CMP includes: glucose, A1c (as appropriate) calcium, protein (albumin, total protein), electrolytes (bicarbonate, chloride, sodium, potassium), kidney (creatinine, blood urea nitrogen [BUN]), liver (alkaline phosphatase [ALP], alanine amino transferase [ALT], aspartate amino transferase [AST], bilirubin)
Dipstick Urine analysis • Sugar • Protein • WBC/RBC • Bacteria	Within 14 days	Must be negative for infection before treatment procedure Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotics.
Urine culture for infection	Within 14 days	Must be negative for infection before enrolling. Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotics.
Uroflowmetry Voided volume (must be ≥ 125 mL or test must be repeated for all the uroflow tests) Voiding time Peak flow rate (Qmax) Average flow rate	The uroflow reading must be within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy. There must be no evidence of UTI prior to conducting test
Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)	Within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy. There must be no evidence of UTI. The PVR method used during screening must be the same as that used in the follow-up tests.
Cystoscopy[1]	Within 30 days prior to treatment up to the day of the procedure.	Prior cystoscopy before enrollment is acceptable only if images were collected in the last 3 months and images are

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
		available for source documentation.
Screening urethrogram (recorded)	Within 30 days prior to treatment.	Prior urethrogram before enrollment is acceptable only if images were collected in the last 3 months and images are available for source documentation.
Subject questionnaires International Prostate Symptoms Score (IPSS) - Standard International Index of Erectile Function (IIEF) VAS Pain Scale	Within 30 days	Must have documented negative for urinary infection before enrolling and before taking the IPSS at baseline
1 – The baseline cystoscopy may be conducted during the treatment procedure. Only one pre-treatment cystoscopy is required per subject.		

8.2 Subject Enrollment

Only subjects who meet all inclusion criteria and no exclusion criteria, agree to comply with the follow-up visit schedule and provide informed consent will be eligible to be enrolled and participate in the study. If a subject moves away during the study, every effort should be made to maintain the follow-up schedule including having an appropriate physician follow the subject.

A subject is considered enrolled if they:

- Meet all the inclusion criteria
- Do not meet ANY exclusion criteria
- Provide informed consent
- Are randomized to a treatment group

8.3 Concomitant Therapy

Therapy (medication and non-medication therapies) not restricted by a protocol requirement may be used during the study for the treatment or prevention of disease or to maintain good health. However, the subjects should not take concomitant medications that affect the urinary symptoms which might confound the study results.

8.4 Randomization

Subjects will be stratified based on prior radiation treatment, then by dilation history, then randomized in a 2:1 allocation of treatment (Optilume DCB) to control (best dilation practice). Randomization will also be stratified using permuted blocks within each site using an Electronic Data Capture (EDC) system. Each subject will be randomized prior to

initiation of the treatment/control procedure. Only randomized subjects will be considered enrolled and evaluable. Those subjects who do not meet inclusion/exclusion criteria after baseline evaluation will be counted as screening failures and will be withdrawn from the study.

8.5 Blinding

In order to execute this study design, the treating physicians will not be blinded. Subjects will be blinded to the treatment received through their 6-month follow-up visit, at which point the subjects will be unblinded. All test and control procedures will take place in the same setting at each investigational site (in-office, hospital OR ambulatory surgical center). The treatment procedure location must be identified upfront and used for all study treatments, test or control. Switching between study treatment locations at a site will not be allowed.

During the treatment procedure, a sheet should be placed to block the subject's view of the treatment area.

Subjects will be unblinded after the 6-month follow-up examination, or to protect the subject's health prior to the 6-months follow-up. If a subject requires a re-treatment due to a medical necessity, prior to the 6 months follow up, they will be unblinded in order to consent for the re-treatment or crossover procedure. These subjects will be considered treatment failures, and effectiveness data collected post-retreatment will be summarized separately. If a non-urgent clinical need requires the subject be unblinded prior to the 6-month follow-up and if time allows, the physician will notify the Sponsor prior to unblinding the subject.

Blinding procedures will be reviewed at the time of each Site Initiation Visit (SIV) by a Sponsor representative. Blinding procedures and instructions are summarized in **Table 8-2.**

Table 8-2: Blinding Procedures

Time Point	Blinding Procedure
Informed Consent	During the informed consent process, the study procedures, treatments and blinding procedure should be discussed with the subject and family/caretakers as appropriate.
Randomization	The randomization assignment should be communicated to the Investigator in a way to prevent the subject from overhearing which group they have been assigned to if applicable. Ideally, discussions on the assignment should be done outside of the procedure room. Each site should develop a process that works best with their treatment location and processes.

Time Point	Blinding Procedure
Treatment	All treatment procedures will take place in the same setting at each investigational site (in-office, hospital OR or ambulatory surgical center). The treatment procedure location must be the same for all study treatment arms. Switching treatment locations based on treatment arms will not be allowed. During the treatment procedure, a sheet should be placed to block the subject's view of the treatment area for all subjects. For all subjects, the Optilume device will be visible in the treatment room when subject is being prepped for the procedure irrespective of treatment assignment. The number of medical personnel exposed to the randomization assignment should be limited as far as possible on a need to know basis.
Post-Procedure	All subjects will be provided the same instructions on post-procedure recovery precautions including: • ABSTAIN from ALL sexual activities including masturbation for a minimum of fourteen (14) days post procedure • All subjects will be asked to use a condom or abstain from sex for a minimum of thirty (30) days immediately after treatment. The time of protected sex may be extended by the physician. • All subjects who have a female sexual partner of child bearing potential should use a condom or abstain from sex for at least ninety (90) days to prevent potential transfer of the study drug to their partner and/or off-spring Any recovery and hospital/clinic staff should be educated to the protocol blinding procedures and instructed to not inadvertently unblind the subject and/or family/caretakers during the recovery period. In addition, the subject's medical record should clearly identify the subject as a study participant and not list the treatment assignment.

Time Point	Blinding Procedure
Follow-up	The site study staff should maintain blinding procedures through the 6-month follow-up at a minimum. Clinic staff will be educated to the protocol blinding procedures and instructed not to inadvertently unblind the subject and/or family/caretakers during the follow-up period.
Unblinding	A subject should not be unblinded to the treatment assignment prior to the 6-month follow-up unless it is determined to be medically necessary by the Investigator.
Crossover	In the event a subject in the control arm requires a re-treatment due to recurrent stricture prior to the 6-month follow-up, the subject may be unblinded to discuss treatment options, including a crossover into the treatment (Optilume DCB) arm and to consent for treatment with the Optilume DCB if appropriate. Subject may choose to opt for non-study treatments at which point, the subject will exit the study.

8.6 Treatment Procedures

The treatments for the study may be performed in a hospital, ambulatory surgical center, or office setting. The treatment procedure location must be identified and used for all study treatments.

8.6.1 Pre-Treatment

8.6.1.1 Peri Procedural Medication

It is required that physicians follow the American Urological Association (AUA) guidelines for pre-procedure medications and preparation for an endoscopic procedure, including the administration of a pre-procedure antibiotic as appropriate. Oral NSAIDs are also recommended to be given prior to the procedure. All pre-procedure medications and anesthetics will be recorded on the case report form.

If a urinary tract infection (UTI) is present at the time of enrollment, the subject must be treated until the infection is cured before the treatment procedure can take place.

8.6.2 Test (Optilume DCB) Treatment Procedure

The DCB should be prepared per the Instructions for Use (IFU). A summary is provided below. If the summary is different from the IFU, follow the instruction in the IFU. The treatment algorithm is schematically shown in Figure 8-1.

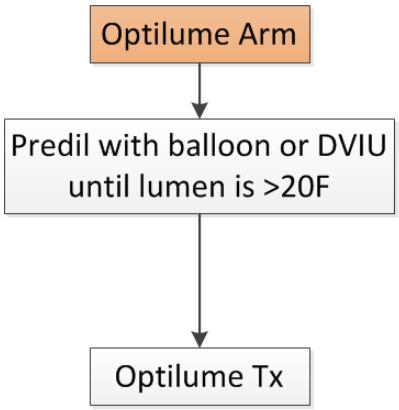


Figure 8-1: Test Arm Treatment Algorithm

8.6.2.1 Device Sizing

1. Verify the selected predilation and DCB balloon diameter at nominal pressure is the same or slightly greater than the diameter as the healthy urethra adjacent to the distal edge of the stricture. Do not use a DCB that is smaller in diameter that the predilation balloon to ensure urethra wall opposition for drug delivery.

   For Bulbar strictures do not exceed a 1.3 stretch ratio of balloon diameter to distal heathy urethra

   For Penile urethral strictures select the balloon diameter that best match the distal healthy urethra (balloon diameter must not be smaller than the diameter of the healthy urethra). A stretch ratio of 1:1 is recommended
   Note: In the event the penile healthy urethra measurement falls between device sizes, we recommend using the next smaller balloon diameter.

2. Select a predilation balloon length that is slightly longer than the stricture length to be treated. Refer to IFU for direction in selecting the DCB sizes.

8.6.2.2 Predilation

3. Perform a pre-treatment urethrogram. Record the urethrogram.
4. Predilate the stricture with a standard uncoated balloon (POBU, plain old balloon urethroplasty) or DVIU and ensure that the predilation yielded the stricture. Stricture is considered to yield to predilation if the predilated lumen is greater or equal to 20F.
5. Record the predilated lumen size.
6. A minimum of 5 subjects will be selected to be predilated directly with DVIU only.

8.6.2.3 Optilume DCB Treatment

1. Refer to the IFU for detailed instructions on using the Optilume. If the summary below is different from the Instructions for Use (IFU), follow the IFU.
2. Select a DCB, place across the predilated stricture.
3. Inflate the DCB.
4. RECORD the fluoroscopic image with the balloon inflated. Record the inflation pressure.
5. Deflate the balloon and remove the device(s)
6. If the product has a failure prior to, or during inflation (but less than rated burst pressure (RBP)) replace DCB and inflate per procedure. If failure is after inflation to RBP do not repeat DCB procedure.
7. Insert a 12-14 F lubricious Foley catheter and leave in place for a minimum of 2 days or per standard of care, whichever is greater. Record the Foley catheter size and time of catheter removal.

Caution: The rated burst pressure (RBP) should not be exceeded. Refer to the IFU for the complete device information.

8.6.2.4 Treatment Rules

- An increase of urethral caliber lumen to 20F or greater must be achieved by predilation to proceed to DCB treatment. At the physician discretion, the subjects may be enrolled directly into the DVIU group.
- After DCB dilation no instrumentation can be passed through the stricture acutely and until the 6 months' evaluation period with the exception of a Foley catheter (≤ 14F size) when medically needed.

8.7 Control Treatment

For subjects randomized to the control arm, treatment following the physician's best practice for dilation will be performed. Rigid rods, balloons, DVIU or combination thereof may be used for dilation at physician's discretion. A target of a minimum of 5 subjects within the study will be dilated with DVIU only.

8.8 In-Hospital to Discharge

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are recommended together with the use of antibiotic post procedure according to treatment guidelines.

8.9 Sexual Activities

All subjects must be counseled about sexual activities post treatment as follows:

- All subjects will be asked to ABSTAIN from ALL sexual activities including masturbation for a minimum of fourteen (14) days post procedure

- All subjects will be asked to use a condom or abstain from sex for a minimum of thirty (30) days immediately after treatment. The time of protected sex may be extended by the physician.
- All subjects who have a female sexual partner of child bearing potential should use a condom or abstain from sex for at least ninety (90) days to prevent potential transfer of the study drug to their partner and/or off-spring.

8.10 Crossover

The cross-over algorithm is schematically shown in Figure 8-2Fehler! Verweisquelle konnte nicht gefunden werden..

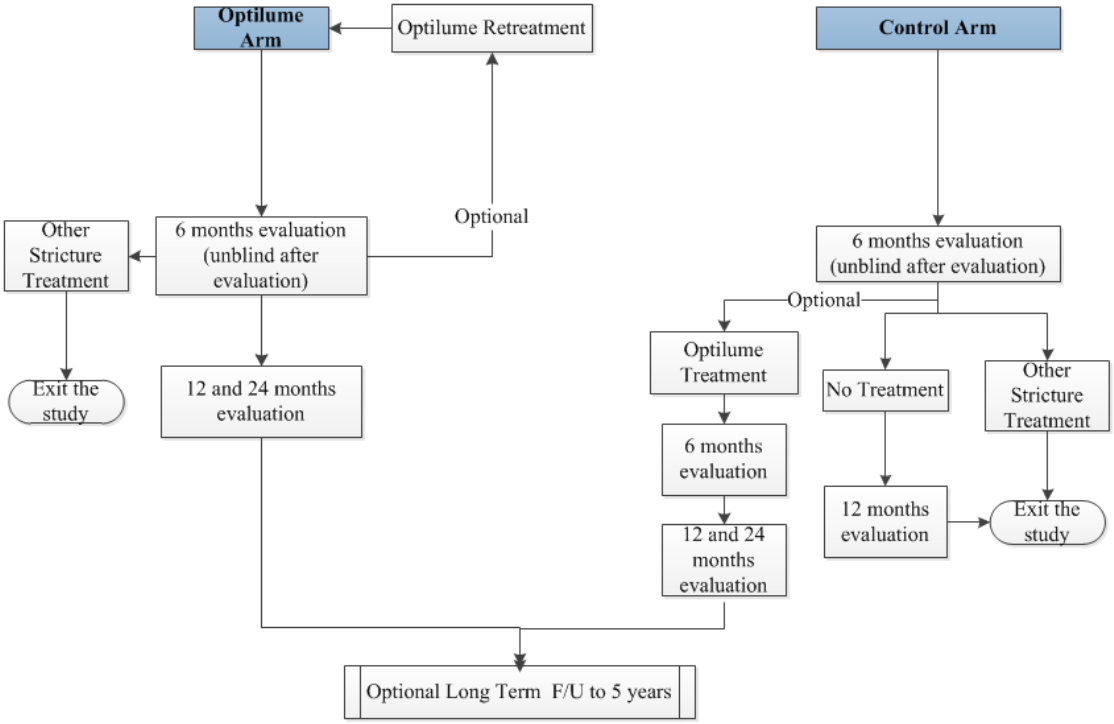


Figure 8-2: Schematic of Retreatment and Cross-Over Algorithm

8.10.1 Crossover Rules For Control Subjects

If a subject's urinary condition did not improve after the first assigned (index) treatment, and the subject and physician are considering alternative treatments, the subject's treatment assignment may be unblinded before the 6 months follow up. Under this condition, the subjects in the control arm may be allowed to consider crossing-over to the treatment arm. Any subjects who cross over or seek alternative treatments before the 6 months follow up will automatically be considered "treatment failure".

If a subject's urinary condition did not improve and he and the physician are considering alternative treatments after the subject has been unblinded (after the 6-month follow-up) but before the 12-month follow-up, the subject may be allowed to consider crossing-over to the treatment arm.

Subjects must meet all re-treatment inclusion criteria and no re-treatment exclusion criteria. (Section 8.10.2.1 and 8.10.2.2). The safety and effectiveness data collected in the crossover cohort will be summarized separately. Crossover subjects will be followed out to at the 5-year time point, starting from the crossover procedure, under the same subject ID.

A crossover of a control subject into the treatment arm or a retreatment with an alternative therapy will be considered a control treatment failure. The safety and effectiveness data collected post-crossover will be summarized separately. If a subject requires an additional intervention for a recurrent stricture after a crossover, the subject will be considered a re-treatment failure and should be exited from the study prior to seeking further treatment.

8.10.2 **Cross-Over Selection criteria**

Subject must meet all the inclusion and none exclusion criteria for retreatment listed below.

8.10.2.1 Cross Over Inclusion Criteria

1. Must have been previously enrolled and treatment attempted in this study, but stricture did not resolve
2. Single, tandem or diffuse anterior urethral stricture, less than or equal to 3.0 cm total length. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture).
3. Significant symptoms of stricture such as frequency of urination, dysuria, urgency, hematuria, slow flow, feeling of incomplete emptying, recurrent UTI's.
4. Lumen diameter ≤12F by urethrogram
5. Qmax <15 ml/sec
6. Guidewire must be able to cross the lesion

8.10.2.2 Crossover Exclusion Criteria

1. Strictures greater than 3.0 cm long.
2. Subjects with diffuse stricture, greater than 3.0 cm in total length. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture).
3. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture at the discretion of the clinical investigator
4. Diagnosis of untreated and unresolved BPH or BNC
5. New diagnosis of over active bladder (OAB) within the last 6 months
6. Diagnosed with chronic renal failure and treatment with hemodialysis
7. Unwilling to use protected sex for ≥thirty (30) days post treatment

8. Unwilling to abstain or use protected sex for ninety (90) days' post treatment if intending to father children Active infection in the urinary system or other system
9. Visible hematuria with subject urine sample without known contributing factor
10. Invisible hematuria (or significant microscopic hematuria, i.e. hematuria of ≥ 3 RBC's/HPF) that may be caused by a clinically significant disease unless it is attributed to the urethral stricture disease or other causes which are benign and not requiring treatment.

8.11 Baseline Evaluations for Crossover Subjects

The following evaluations will be completed for all retreatment subjects. Evaluations performed within the screening window may be acceptable. The required baseline evaluations prior to retreatment are shown below:

Table 8-3: Baseline Evaluations for Crossover

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Physical exam evaluation	Within 30 days	Evaluation is complete and adequately documented in source documents
Current or prior (up to 6 months) medication use	Prior to enrollment	A list of current and prior medication is required to determine if the dose is stable.
Urethral Stricture Score (USS)	Within 30 days	None
Blood analysis Complete blood cell count (CBC) with differential Comprehensive Metabolic Panel (CMP)	Within 30 days	CBC includes: hemoglobin, hematocrit, platelets, RBC and WBC. Differential includes absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils. CMP includes: glucose, A1c (as appropriate) calcium, protein (albumin, total protein), electrolytes (bicarbonate, chloride, sodium, potassium), kidney (creatinine, blood urea nitrogen [BUN]), liver (alkaline phosphatase [ALP], alanine amino transferase [ALT], aspartate amino transferase [AST], bilirubin)
Dipstick Urine analysis • Sugar • Protein	Within 14 days	Must be negative for infection before treatment procedure

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
• WBC/RBC • Bacteria		Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotic.
Urine culture for infection	Within 14 days	Must be negative for infection before treatment procedure. Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotic.
Uroflowmetry Voided volume (must be ≥ 125 mL or test must be repeated for all the uroflow tests) Voiding time Peak flow rate (Qmax) Average flow rate	The uroflow reading must be within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy. There must be no evidence of UTI prior to conducting test
Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)	Within 30 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy. There must be no evidence of UTI. The PVR method used during screening must be the same as that used in the follow-up tests.
Cystoscopy[1]	Within 30 days prior to treatment.	Prior cystoscopy before re-treatment is acceptable only if images were collected in the last 3 months and images are available for source documentation.
Subject questionnaires International Prostate Symptoms Score (IPSS) - Standard International Index of Erectile Function (IIEF) VAS Pain Scale	Within 30 days	Must have documented negative for urinary infection before enrolling and before taking the IPSS at baseline
1 – The baseline cystoscopy may be conducted during the treatment procedure. Only one pre-treatment cystoscopy is required per subject.		

8.12 Scheduled Follow-up Evaluations

The following evaluations will be completed at each visit as indicated in **Table 8-4**. Subjects will be evaluated at baseline, immediately post-procedure, Foley Removal (2–5 days), 30 days, 3 months, 6 months and 12 months post-procedure.

Annual evaluation of the stricture treatment will be followed for up to 5 years' post treatment. Details of each requirement can be found in the sections below.

Table 8-4: Scheduled Evaluations and Follow Up

	Baseline	Procedure	Pre-Discharge	Foley Removal	30 days	3 Months	6 and 12 Months	24 months	3 to 5 years	Unscheduled
Compliance Window	-30 days	N/A	N/A	2-5 days	± 5 days	± 14 days	± 30 days	± 60 days	± 60 days	
Medical History	√									
Physical Examination	√		√		√	√	√	√	√	√
Medication Usage Review	√	√	√	√	√	√	√	√	√	√
USS	√									
Blood Analysis	√			√	√					√ **If indicated**
Dipstick Urine Analysis	√				√	√	√			√
Urine Culture	√				√ **If Indicated**	√ **If indicated**	√ **If indicated**			√ **If indicated**
Review Protected Sexual Activities			√	√	√	√				
Uroflowmetry (including Qmax)	√			√ **If Indicated**	√	√	√	√	√	√
PVR	√			√ **If Indicated**	√	√	√	√	√	√
Retrograde Urethrogram	√ Record	√					√ (Optional)	√ (Optional)		√ **If indicated**
Cystoscopy	√ Record	√					√ Record if scope can pass (6 months only)	√ (Optional)		√ **If indicated**

							(16F scope)			
14F Rubber Catheter Urethral Lumen Evaluation							√ (6 months only) (If 16F scope failed to pass)			
IPSS, IIEF	√				√	√	√	√	√	√ **If indicated**
VAS Pain score	√		√	√	√					√ **If indicated**
Subject Satisfaction Questionnaire						√	√			
AE Review	√	√	√	√	√	√	√	√	√	√

8.13 \Subject Evaluations

8.13.1 Medical History and Physical Exam

All baseline testing and evaluations must be done as close to the time of scheduled treatment as possible and repeated if necessary. Any required procedures performed before obtaining informed consent as part of the standard of care may be used in lieu of the study tests. Baseline testing will include:

1. Physical exam with demographics, height, weight and vital signs
2. Complete general medical and genitourinary history (including any previous treatments for stricture) and duration of subject's symptoms
3. Urethral Stricture Score (USS)

   The USS is a numerical score based on five components of anterior urethral stricture disease that help dictate operative decision-making: (1) urethral stricture etiology; (2) total number of strictures; (3) retention (luminal obliteration); (4) anatomic location; and (5) length. The USS describes the essential factors in determining surgical treatment selection for urethral stricture disease. The USS is a concise, easily applicable instrument that delineates the clinically significant features of urethral strictures.
4. Medication Use Review, including current and prior medications begun within the last 6 months is required to determine if the dose is stable.

8.13.2 **Blood Analysis**

Complete Blood Count (CBC) with differential:

- CBC includes hemoglobin, hematocrit, platelets, RBC and WBC
- Differential includes absolute neutrophils, lymphocytes, monocytes, eosinophils and basophils.

Comprehensive Metabolic Panel (CMP):

- Glucose, A1c (as appropriate) calcium, protein (albumin, total protein), electrolytes (bicarbonate, chloride, sodium, potassium), kidney (creatinine, blood urea nitrogen [BUN]), liver (alkaline phosphatase [ALP], alanine amino transferase [ALT], aspartate amino transferase [AST], bilirubin)

8.13.3 **Dipstick Urine Analysis**

This test needs to be performed within fourteen (14) days prior to treatment. Samples taken for this test must be taken at least seven (7) days following discontinuation of all antibiotics. Subjects need to have a negative urine analysis prior to being enrolled. Data collected should include:

- Sugar
- Protein
- WBC/RBC
- Bacteria

8.13.4 **Urine culture**

A urine culture needs to be performed within fourteen (14) days prior to treatment. Samples taken for this test must be taken at least seven (7) days following discontinuation of all antibiotics. Subjects need to have a negative urine culture prior to being enrolled.

8.13.5 **Uroflowmetry**

The uroflow test must be performed before cystoscopy or greater than or equal to fourteen (14) days after cystoscopy and no evidence of UTI. Data collected should include:

- Voided volume (must be ≥ 125mL or test must be repeated)
- Total time of voiding
- Peak flow rate (Qmax, or PFR)
- Average flow rate

If multiple Qmax/PVR are conducted at visit window, the last value of measurements will be used unless there are valid scientific reasons to exclude one or more of the readings (e.g., if the voided volume is too low or subject voided within two (2) hours when taking the test).

8.13.6 Post-void residual volume (PVR)

PVR may be measured either by ultrasound or catheterization but the same method must be used for all subsequent tests.

8.13.7 Retrograde Urethrogram (RUG)

A retrograde urethrogram (RUG) is taken to diagnose the stricture. A prior urethrogram before a subject signs the informed consent is acceptable only if images were collected in the last 3 months and are available for source documentation. Ideal image frames used for analysis demonstrate the entire length of the urethra with contrast beginning to fill the bladder.

8.13.8 Cystoscopy

A flexible cystoscopy may be performed to confirm the presence of stricture and to estimate the stricture conditions (length and size) prior to enrollment in the study. The size and length is to be estimated without crossing the stricture at screening. A prior cystoscopy before a subject signs the informed consent is acceptable only if images were collected in the last 3 months and are available for source documentation. A post treatment flexible cystoscopy will be performed at the 6 month follow-ups as well as unscheduled visits if indicated. At the 6 follow-ups, a standard 16F flexible scope is required to aid in evaluating the urethral lumen diameter.

8.13.9 Urethral Lumen Evaluation

At the 6-month follow-up a urethral lumen evaluation will be performed. A standard 16F flexible cystoscope will be used to estimate the urethral lumen diameter at the site of the stricture dilation. If a 16 F flexible cystoscope cannot pass through the previously dilated area, a 14F Foley catheter will be used to assess the urethral lumen dimeter at the site of stricture dilation.

8.13.10 Subject Questionnaires

All questionnaires are self-administered and will be completed at baseline and at required follow-up visits. Questionnaires completed at baseline will be compared to those completed at follow-ups to assess the effect of treatment. The major instruments and assessments administered are described in this section.

If multiple responses to the same questionnaires are available for each visit window, the last set of scores will be used unless there are valid scientific reasons to exclude one of the readings.

IPSS (Standard)
The International Prostate Symptom Score (IPSS) contains the well-validated, highly reliable and responsive American Urological Association symptom score (AUASS) assessment to identify the severity of BPH symptoms. However, the

symptoms of BPH and urinary stricture are very similar and has been used with strictures.

The first seven questions in the IPSS address frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency, and scored on a 6-point scale (0 to 5). Although there are no standard recommendations for grading subjects with mild, moderate, or severe symptoms, subjects can be tentatively classified as follows: 0-7 mildly symptomatic, 8-19 moderately symptomatic, and 20-35 severely symptomatic.

The IPSS also includes the following eighth question that is designed to assess the degree of "bother" associated with the subject's urinary symptoms: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" Answers range from "delighted" to "terrible" (0-6). This question correlates well with the overall BPH symptom score and summarizes the impact of urologic symptoms on quality of life.

The standard IPSS will be administered at baseline and at each follow-up visit.

International Index of Erectile Function
The International Index of Erectile Function (IIEF) is a standardized, validated, self-administrated questionnaire that is used to assess the subject's erectile function. The Sexual Health Inventory for Men (SHIM) is part of the IIEF and consist of 5 questions. This is sometimes called IIEF-5 and is used as a diagnostic test for erectile dysfunction and impotence.

Visual Analog Pain Score (VAS)
Pre- and post-procedure pain will be evaluated using a standardized visual-analog pain score (1 to 10 scale).

Subject Satisfaction Questionnaire
This questionnaire is specific to the Urotronic Optilume Urethral DCB procedure and will measure overall satisfaction with the procedure, recommendation of the treatment to family/friends and if the subject would undergo the treatment again if symptoms to recur within 1 year.

8.14 Unscheduled Follow-up Visits

If a subject returns for a visit outside of the regular study visit schedule due to an Adverse Event (AE), an AE CRF should be completed if applicable. In addition, the following examinations or tests should be completed and captured on the corresponding CRF:

- Physical exam
- Medication use review
- Dipstick urine analysis
- Uroflow and PVR

If any additional tests or procedures listed within this protocol are performed during an unscheduled visit the results should be provided on the corresponding CRF.

8.15 Subject Withdrawal from Study

8.15.1 Alternate Treatments

Subjects that opt for alternate treatments for stricture outside the study within 6 months of treatment will be considered a treatment failure and will be exited from the study if the alternate treatment procedure was received. Crossovers within the study should follow the procedures listed in **Section 8.10.** Any treatment due to BPH symptoms will not be considered a treatment failure.

8.15.2 Lost to Follow-up

If a subject fails to comply with the follow-up evaluations, the investigational site must make at least three repeated attempts to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records.

If a subject does not return within 30 days after the visit window closes, the visit will be considered missed. If a subject misses one of the follow-up evaluations, but is present at the subsequent follow-up, the subject can be readmitted into the study and queried retrospectively for basic information (e.g., AEs); however, the missed evaluation must be documented on a Protocol Deviation CRF. All subject questionnaires will be collected prospectively only.

8.15.3 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject had an ongoing AE at the time of withdrawal, the subject should be followed until the resolution of the AE, if possible. Data from these subjects will be included in the analysis up to the point of each subject's withdrawal.

8.15.4 Data Withdrawal Due to Exclusion Criteria

A subject's data will be excluded from the analysis if the subject is later found not to meet one or more major exclusion criteria in the per protocol analysis. However, their data will be included in the ITT analysis unless required to be excluded by the IRB/EC.

These subjects will continue to be followed per the requirements of their particular arm unless instructed otherwise by the IRB/EC. The major exclusion criteria that would cause the withdrawal of the subjects' data are:

- Failure to obtain an informed consent prior to treatment;
- Subject has severe BPH;
- Subject had bladder or sphincter dysfunctions or anything else that will confound the results;
- Subject had a neuromuscular disorder that will confound the results.

The decision to exclude the subject's data from analysis will be documented on the study exit CRF.

8.15.5 Involuntary Withdrawal

A subject also may be withdrawn by the investigator if the subject's participation in the study will have a negative effect on the safety of the subject. Data obtained up to the date of the subject's withdrawal will be included in the study, if applicable.

8.16 End of Study

Subjects receiving treatment should be followed until they complete the 5-year follow-up, or at the end of the study (i.e. the study is discontinued by the Sponsor), whichever comes first, unless the subject opted to find an alternative treatment. An End of Study CRF will be completed for each subject.

8.17 Protocol Deviations

A protocol deviation/violation is generally an unplanned digression from the protocol that is not implemented or intended as a systematic change. An investigator failing to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. These types of deviations are reported to the sponsor and in accordance with the EC/IRB policy.

A Protocol Deviation CRF must be completed by the site for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion / exclusion criteria, not performing required testing, missed follow-up window, etc.). An Investigator must notify the Sponsor and the reviewing EC/IRB of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five (5) working days after the emergency occurred.

Protocol Deviation Notification/Approval to EC/IRB/Sponsor before Implementation
A protocol deviation may be a limited prospective exception to the protocol (e.g., agreement between sponsor and investigator to enroll a single subject who does not meet all inclusion/exclusion criteria due to out of window historical data).

These types of deviations initiated by the clinical investigator must be reviewed and approved by the EC/IRB and the sponsor prior to implementation. These types of

deviations are only approved if they do not impact data integrity or put subjects at unreasonable risk.

Site Noncompliance and Nonperformance
Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

9 ADVERSE EVENT(S)

For purposes of this study, an adverse event (AE) is defined as any untoward medical occurrence in a subject during the course of the study. This definition does not imply that there is a relationship between the adverse event and the device used for treatment. For the purpose of AE reporting, the start of the course of the study is defined as any time after treatment assignment or randomization.

9.1 Reporting of all Adverse Events

All AEs will be recorded in the CRF whether considered device-related or not, and will be classified as described in Section 9.2. All adverse events will be reviewed and adjudicated by the Clinical Events Committee to determine whether they are related to the device (treatment or control) or procedure.

Pre-existing conditions will not be reported as an AE unless there is an adverse change in that condition. Any AE which resolved and then recurred will be reported as a separate AE.

Additional information, such as procedural notes, treatment notes, or a signed clinical summary, may be required as supporting documentation for the reported AE.

During the study, all deaths must be reported to the Sponsor within the period outlined in **Table 12-1**. All deaths also should also be reported on the End of Study CRF. A copy of the subject's death records, medical records for the events that led to the subject's death, and a death certificate (if available) should be provided.

9.2 Coding or Classification of AEs

Adverse events should be reported according to their primary diagnosis or underlying cause, if known (e.g., fever resulting from infection should be reported as "infection"). Symptoms related to a diagnosis should not be reported as separate AEs. In the example above, fever is a symptom caused by infection and should be reported as infection only.

Concomitant AEs that are unrelated (in the clinician's judgment) should be reported as separate events.

AE determination is based on three levels of evidence:

Level 1 – final diagnosis
Level 2 – signs
Level 3 – symptoms

Every effort should be made to collect Level 1 evidence of any AE. If an AE has all three levels of evidence, the AE should be reported only once at the highest level of severity, which is the final diagnosis (Level 1). A single AE should not be reported as multiple AEs based on separate symptoms and signs.

In cases where a diagnosis is not possible, AE determination should be based on the next highest level of evidence (i.e., Level 2: signs), followed by symptoms (Level 3), if symptoms are all that are available to the investigator.

A corrective action or treatment (e.g., catheterization) itself is not an AE but the reason of the catheterization may be an AE. The AE determination always should be based on the reason that a corrective action was taken. Note: there may be multiple signs or symptoms representing only one AE. Figure 9-1 below is an AE determination and outcome flowchart.

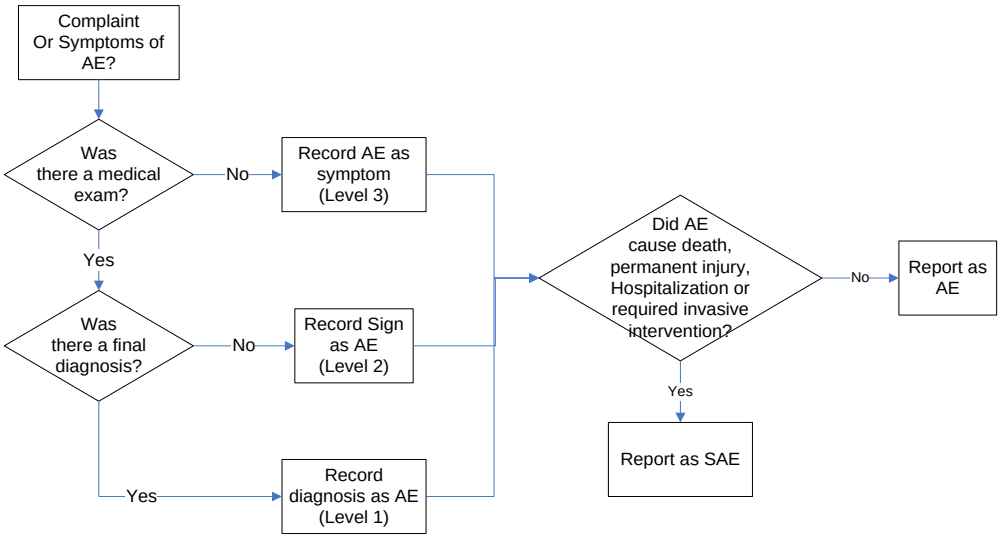


Figure 9-1: AE Determination and Outcome Flowchart

The CEC will also classify all adverse events by the Common Terminology Criteria for Adverse Events (CTCAE) classification system for the purpose of regulatory reporting or publication.

9.3 Treatment Related Symptoms

The Urotronic DCB procedure is designed to treat strictures. Subjects to be treated have moderate to severe lower urinary tract symptoms (LUTS) prior to treatment. These

symptoms are expected to continue and may even worsen slightly prior to improvement as part of the healing process. All reported LUTS will be documented on follow-up visit CRFs. Other expected acute but transient worsening of symptoms from the treatment are dysuria, frequency of urination, urgency of urination, urge incontinence, hematuria, slowing of the urinary stream and acute retention as the tissue heals.

Worsening or new onset LUTS, dysuria or non-obstructive hematuria that occur and resolve within fourteen (14) days of treatment that do not require intervention (other than catheterization, prophylactic antibiotic, anti-inflammatory medication, and pain medication) will not be considered an AE as these are expected and part of the healing process. However, all potential treatment related events or symptoms will be recorded on the AE CRF.

Intervention as it relates to hematuria includes but is not limited: hospitalization, the need to irrigate the bladder and urethra, or the need for transfusion therapy.
Common urinary symptoms will be considered an AE if any of the following occur:

a. Worsening or new onset LUTS requiring intervention or persisting beyond fourteen (14) days' post treatment;
b. Worsening or new onset LUTS requiring hospitalization or intervention other than the use of catheterization, one standard course of antibiotic, anti-inflammatory and/or pain medication;
c. Hematuria that requires irrigation or is obstructive;
d. Urinary tract infection defined as $>10^5$ CFU of a single organism plus symptoms localized to bladder;
e. If new onset LUTS recurs after the same symptom is resolved and is considered clinically significant.

9.4 Urinary Retention and Catheterization

Urinary retention after the healing period will be considered an adverse event. The healing period is defined as the time immediately post procedure until the time the subject can void without the aid of a catheter for at least twenty-four (24) hours. Irrespective of the above, if the healing period is greater than seven (7) days, the subject will be considered to have "reduced healing ability" and an AE will be recorded.

Acute urinary retention that requires medical intervention will be considered an SAE. All catheterizations and cystoscopies will be recorded in the CRF. Resolution is defined as a removal of the catheter without the need to either reinsert it or use intermittent self-catheterization for a contiguous 24-hour period. A re-catheterization that occurs within 24 hours of a prior catheterization will be considered as the same event.

While catheterization in and of itself is not an AE, the ***reason*** for catheterization must be evaluated for purposes of determining an AE. All catheterization periods will be recorded in the CRF.

9.5 Potential Anticipated Adverse Events

Potential anticipated adverse events are those that may occur in association with a stricture treatment or procedure, include those AEs listed below or reported in the literature associated with surgical or minimally invasive stricture procedures:

9.5.1 Drug Risk

Adverse reaction to the paclitaxel and symptoms observed derived primarily from IV infusion studies of the drug in treating cancer subjects include

- Chromosomal abnormalities and the risk of cancer
- Fetal harm when a pregnant woman is exposed
- Anaphylaxis and hypersensitivity with paclitaxel
- Inhibition of the healing of the urethra post procedure
- Myelosuppression including: neutropenia, leukopenia, thrombocytopenia, anemia
- Arrhythmia
- Peripheral nueorpathy
- Myalgia or Arthralgia
- Alopecia
- Hypotension
- Nausea, vomiting or diarrhea
- Elevated bilirubin, ALP and AST
- Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered locally during the Optilume DCB procedure is much lower than a single dose of systemic chemotherapy provided to cancer patients and the drug appears to be essentially remain localized in the urethra.

9.5.2 Surgical and Procedural Risks

- Sepsis and infection
- Fever
- Perforation or damage to the urethra
- Perforation of adjacent organs including the rectum, bladder and GI tract
- Urinary symptoms including:
  - Dysuria
  - Frequency
  - Urgency
  - Nocturia
  - Acute urinary retention
  - Incontinence
  - Sensation of not emptying bladder completely
  - Urethritis
  - Irritative urinary symptom
  - Urethral injury causing false passage or adhesion
  - Urinary clot retention

  - Chronic pain in the pelvic area
  - Bladder spasm
  - Urethrorrhagia or Hematuria with or without clot in urethra
  - Discharge or cloudy urine
  - Discharge of tissue material during urination
  - Scarring of the urethral system
  - Urinary tract infection
- Abscess (prostatic, bladder, scrotal)
- Bladder problems or damage (reduced bladder sensation, spasms, bladder neck contracture, bladder neck stenosis)
- Bladder perforation or rupture
- Damage to the urethral system
- Worsening of stricture or new onset stricture
- Seroma
- Kidney compromise or failure
- Reproductive system disturbances such as infertility and miscarriages
- Prostate abnormalities and damage
- Damage of urinary sphincter leading to incontinence

Other Pelvic Health Risks

- Unmasking of incontinence – underlying stress or urge incontinence may be unmasked and symptoms of incontinence controlled previously by the stricture may be evident
- Rectal incontinence
- Rectal damage
- Rectal stenosis
- Rectal, perineal findings
- Anal irritation
- Elevated PSA
- Nerve damage
- Weakness or numbness
- Abdominal or low back pain
- Flu-like symptoms
- Hematospermia
- Epididymitis
- Bowel irritation
- Erectile dysfunction
- Retrograde ejaculation or ejaculatory dysfunction
- Pressure sensation
- Prostatitis

Other potential non-pelvic anticipated adverse events that may occur in this subject population are:

- Blood pressure change during therapy

- Arrhythmia
- Flank pain
- Blood loss (> 500 ml)
- Adverse reaction to medication and anesthesia as listed in the labeling
- Low blood pressure (hypotension)
- High blood pressure (hypertension)
- Fainting, dizziness, or blurred vision (vasovagal reaction, syncope)
- Allergic reaction
- Fatigue
- Dyspnea
- Confusion
- Memory loss
- Swelling or bruising (edema, hematoma)
- Aneurysm – thoracic and cranial
- Low back pain
- Pneumonia
- Collapsed lung
- Pulmonary embolism
- Pneumothorax
- Upper respiratory disease
- Cough
- Sore throat
- Apnea
- Coughing up blood (hemoptysis)
- Choking (aspiration)
- Venous thrombosis
- Myocardial infarction, angina, ischemia
- Cardiac arrhythmia
- Stroke or transient ischemic attack
- Brain damage
- Headache
- Depression
- Perforation of, or damage to, the gastrointestinal tract
- Abdominal pain
- Constipation
- Nausea or vomiting
- Adverse reaction to medication

9.6 Definition of Serious Adverse Event(s)

A serious adverse event (SAE) is an AE that led to any of the following:

- Death

- Serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function including chronic diseases, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or is considered an important medical event
- Led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event.

9.7 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects" (21 CFR 812.3(s)).

If a USADE associated with the investigational device occurs, the investigator shall notify the Sponsor and the IRB/EC as soon as possible. The sponsor will investigate the event and notify the authorities, IRB/EC, FDA and all other participating IRBs/EC and investigators within 10 working days from the time the Sponsor first learns of the event in writing. Should the Sponsor determine that an unanticipated adverse effect presents an unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/EC, and FDA.

Note: Extravasation due to overdilation in the penile urethral will be reported as a USADE.

9.8 Relationship of AEs to the Treatment and Procedure

A description of how an AE relates to the treatment (test or control) and procedure will be determined by the Investigator and reported on the Adverse Event CRF using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index

procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.

- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Reported SAEs that are possibly related to the device, the procedure, or the disease state being treated will also be reviewed and adjudicated by the CEC.

9.9 Device Failures, Malfunctions and Near Incidents

A device malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended. Device failures or malfunctions will be reported to the sponsor by the clinical sites. If the failure or malfunction results in an AE, the event shall be reported to the Sponsor within two (2) working days after the Investigator becomes aware of the device-related adverse event and reported to the IRB/EC (if required) within the IRB/EC required timeframe. The malfunctioning investigational device involved in the incident should be returned to the Sponsor for evaluation.

10 DATA MANAGEMENT

10.1 Central Database and Electronic Case Report Forms (eCRF)

All required clinical data will be collected and compiled on web-based standardized eCRFs. Site numbers, subject numbers and initials will be used to track subject information throughout the study.

The eCRFs are designed to accommodate the specific features of the study design. Modification of the eCRF will only be made if deemed necessary by the Sponsor and/or appropriate regulatory body. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the study database.

10.2 Subject Identification

Subjects that successfully pass the screening tests and wish to participate in the study will be assigned a unique identification code (ID) using the format “XXX-YYY” where:

XXX = Institution Number, assigned by the Sponsor to each study site
YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study

In addition to the ID, each subject's initials will be used as an identifier included on documentation submitted to the Sponsor.

11 REGUALTORY RESPONSIBLITIES

11.1 Regulatory Approval

The Sponsor will be responsible for submitting an IDE application to the FDA. IDE approval must be received prior to the inclusion of the first subject.

11.2 Ethics Committee (EC) / Institutional Review Board (IRB)

Investigators must submit the study protocol to their respective Ethics Committee (EC) and or Institutional Review Board (IRB) and obtain the EC's/IRB's written approval before being allowed to conduct and participate in the study. Each Investigator is responsible for fulfilling any conditions of approval imposed by their respective EC/IRB, such as regular reporting, study timing, etc. Investigators will provide the Sponsor or its designee with copies of such approvals and reports.

11.3 Amending the Investigational Protocol

Neither any Investigator nor the Sponsor will modify the Investigational Protocol without first obtaining concurrence of the other in writing. All changes to the Investigational Protocol must be submitted to the FDA and EC/IRB as applicable for review and approval unless the changes do not affect the subject's safety or the integrity of the data (e.g. administrative changes). Any change that would require alteration to the ICF must receive approval from the applicable EC/IRB prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

11.4 Informed Consent Form (ICF)

The Sponsor will provide a template informed consent form (ICF) to each study site for EC/IRB submission. The template may be modified to suit the requirements of the individual study site but the Sponsor must pre-approve all changes to the ICF prior to initial submission to the EC/IRB.

Each Investigator or assigned designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature, or a legally-approved designee's signature if applicable, along with the date of consent prior to enrollment in the study. The ICF must be obtained in accordance with the applicable guidelines of the Declaration of Helsinki, or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and must also be informed that withdrawal from the study will not jeopardize their future medical care. A copy of their signed ICF must be

given to each subject enrolled in the study. The institutional standard subject consent form does not replace the study ICF.

12 STUDY RESPONSIBILITIES AND MANAGEMENT

12.1 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be utilized for this study. The CEC will be responsible for adjudicating the seriousness and relatedness of all potential device and/or procedure related adverse events occurring during the study period. A charter will be completed for the CEC outlining membership, duties and functions.

All members of the CEC will be blinded to the primary results of the trial. The CEC will meet regularly to review and adjudicate all adverse events. The committee will also review and rule on all deaths that occur throughout the trial.

12.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized for this study. The DMC will be responsible for evaluating safety by reviewing overall study outcomes, adverse events and determining the implementation of the adaptive design protocol. The DMC will review the first interim analysis and provide feedback to the sponsor and study sites regarding the adaptation of the study design if required. A charter will be completed for the DMC outlining membership, duties and functions.

The DMC will be comprised of leading experts in urology and biostatistics who are not participating in the trial and have no affiliation with the Sponsor. The DMC will meet at regular intervals.

12.3 Investigator Responsibilities

Each investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, EC/IRB requirements, and applicable laws and regulations. Also, Investigators may not begin enrollment until Sponsor or its designee receives and approves (when necessary) the following documents at a minimum:

- Signed Investigator Agreement
- Financial disclosure forms for all participating investigators
- EC/IRB roster (or Registration number from the Office of Human Research Protection)
- EC/IRB protocol and ICF approvals
- Investigators' current curricula vitae (CV)
- Signed Site Delegation Log

It is acceptable for Investigators to delegate one or more of the above functions to an associate or Co- or Sub-Investigator, or a trained Study Coordinator; however, the Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each study site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations. Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate EC/IRB and the Sponsor.

12.3.1 **Study Coordinator**

To ensure proper execution of the Study Protocol, each Investigator must identify a Study Coordinator for the site. The Study Coordinator should help ensure that all study requirements are fulfilled and is the contact person at the site for all aspects of study administration. The Investigator has the ultimate responsibility of all study requirements.

12.3.2 **Records**

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but not limited to:

- All signed agreements;
- IRB/EC approval letter(s);
- Signed ICF;
- Records of AEs, including supporting documents;
- Records of protocol deviations, including supporting documents;
- Records showing receipt, use and disposition of all investigational devices, including:
  - Date, quantity, model and serial numbers of devices received,
  - Name of person(s) who received, used or disposed of each device,
  - The number of devices returned to the Sponsor and the reason(s) for return;
- All correspondence related to the study;
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;
- Signature authorization and delegation log; and,
- Any other records that applicable regulation requires to be maintained.

12.3.3 **Reports**

Table 12-1 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the EC/IRB reporting requirements for their respective site. If applicable regulations or EC/IRB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 12-1: Reports Required from Investigators to Sponsor

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, EC/IRB	Within 10 working days of knowledge
Death	Sponsor, EC/IRB	Written reports (e.g., via e-mail) within 48 hours
SAE	Sponsor EC/IRB, if required	Within 10 working days of knowledge Per EC/IRB requirement
Device malfunction with clinical sequelae	Sponsor EC/IRB, if required	Within 48 hours via written communication. Return the device to Sponsor within 48 hours.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor EC/IRB, if required	Within 5 working days of knowledge Per EC/IRB requirement
Withdrawal of EC/IRB approval	Sponsor	Within 5 working days of knowledge
Progress report	Sponsor, EC/IRB	As required by EC/IRB
Final report	Sponsor, EC/IRB	Within 3 months of study completion or termination
Note: Each IRB/EC may require more stringent reporting requirements than those listed in this table.		

12.4 Sponsor Responsibilities

Urotronic, Inc. is the Sponsor of this study. The Sponsor's responsibilities in the study include:

- Selecting the Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Providing study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Following/promoting all regulatory standards per appropriate regulations for study sites, core laboratories, and other participants, and ensure compliance by periodically monitoring sites.
- Ensuring completion of site monitoring of clinical data at each clinical study site.

- Retaining ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.
- Reviewing and approving publication of study results in the literature.

12.4.1 Sponsor Reporting Responsibilities

Table 12-2 lists those reports that are the sponsor's responsibility and timelines to report to the IRB and FDA. If applicable regulations or EC/IRB and FDA requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 12-2: Sponsor Reporting Responsibilities

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	**Reporting Time Frame**
Unanticipated Adverse Device Events	Investigators, IRB/ECs and FDA	**Written** - Within 10 working days from the time the Sponsor first learns of the effect.
Withdrawal of IRB/EC Approval or other action on part of the IRB/EC that affects the study	Investigators, IRB/ECs and FDA	**Written** – Within 5 working days.
Withdrawal of FDA approval	Investigators and IRB/ECs	**Written** – Within 5 working days.
Current investigator list	FDA	**Written** – At 6-month intervals. Submit the first list 6 months after FDA approval.
Device Recall	Investigators, IRB/ECs and FDA	**Written** – Within 30 working days.
Progress Reports	Investigators, IRB/ECs and FDA	At regular intervals, but in no event less than yearly.
Inappropriate Informed Consent	IRB/EC and FDA	Investigator's report submitted within 5 working days of notification
Study Closure	Investigators, IRB/ECs and FDA	Within 10 days

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	**Reporting Time Frame**
Final Report	Investigators, IRB/ECs and FDA	Significant risk device – Notify FDA within 30 working days of the completion the investigation Final report - within 6 months of study closure.

12.4.2 **Confidentiality**

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential according to the country's patient confidentiality regulations. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. Investigators will consent to visits by Sponsor's staff and its authorized representatives, as well as by the FDA or local governmental body, to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., urethrogram).

13 DEVICE ACCOUNTABILITY

The Optilume DCB allocated for investigational site use will be stored in a secured area until use. Each site will be responsible for tracking the receipt and disposition of all Investigational Devices.

The Investigator must ensure the device is used only in accordance with the protocol and current IFU. The Investigator must maintain records that document device delivery to the study site, inventory at the site and administration to subjects. This record should include dates, quantities, model/lot numbers and the unique subject ID assigned to trial subjects. The Investigator should maintain records that document which device the subject received according to the protocol and assigned randomization. In the case where a device has failed, the Investigator must make every possible effort to return the device to the Sponsor. All unused Investigational Devices must be returned to the Sponsor at the end of the study.

14 STUDY ADMINISTRATION

14.1 Monitoring Procedures

It is the responsibility of the study sponsor to ensure that proper monitoring of this investigation is conducted. A formal written Monitoring Plan will be developed in accordance with appropriate guidelines and regulations by the CRO appointed for this study and will be approved by the Sponsor. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement

- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing EC/IRB and/or other regulatory agencies

The clinical study will be monitored according to the guidelines summarized below. The Sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures.

A study specific Monitoring Plan will be created and implemented to standardize monitoring activities across centers and ensure human subject protection and verify data integrity. The monitors shall receive study and device specific training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications and experience to monitor the progress of an investigation. Study monitoring will include a site qualification, study initiation, interim, and close out visits. Prior to protocol submission at a site, a formal qualification visit will be conducted by a Sponsor employee or designee at sites who have not been previously involved in a Urotronic sponsored trial. Qualification visits are done to confirm the appropriate staff, experience, resources, equipment and subject population are present for this protocol.

Each site will have an initiation visit conducted by the Sponsor and/or designee. This visit will ensure that the Investigator understand their responsibility for conducting the study at their center. This visit will include training on, but is not limited to: protocol compliance, device accountability, informed consent process, and IRB/EC submissions.

Monitors will require direct access to subjects' medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents, and Subject Informed Consent documents, as well as other potential applicable records not listed here.

Monitors may ensure the clinical investigators have and continue to have staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current EC/IRB-approved informed consent was signed and dated by each subject prior to participating in the study required procedures.
- Verification of documentation in the subject's record that informed consent was signed prior to initiation of the study procedures and that a copy of the signed and dated consent was provided to the subject.
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information.
- Verification that the device is being used according to the Clinical Investigation Plan, Instructions for Use and all malfunctions/ IFU deficiencies are reported. as required.

- Verification that subjects met study enrollment criteria.
- Confirmation that the study is being conducted according to the Clinical Investigation Plan and applicable regulations.
- Verification that study deviations are documented and reported.
- Verification that the procedures for recording and reporting adverse events to the sponsor are followed.
- Ensuring proper error correction.
- Verification of training documentation of all study personnel participating in study related activities.
- Reviewing all correspondence and regulatory documents, including confirmation of IRB-approved Clinical Investigation Plan or amendments.
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

Each monitoring visit will be documented via a monitoring report and follow-up letter. The follow-up visit letter shall be sent to the Investigator to document issues identified, corrective actions and if applicable preventative actions. At subsequent visits the issues resolved shall be documented in this letter to demonstrate resolution.

Any evident pattern of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to stop enrollment and complete outstanding follow-up visits for subjects enrolled at their site.

At the close of the study at an investigational site, the Sponsor and/or designee will make a final study closure visits at all enrolling clinical sites in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.) The visit will ensure all outstanding documentation is collected, files are accurate and complete, make a final account of all investigational product shipped to the Investigator, and ensure all regulatory requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or EC/IRB.

15 PUBLICATIONS

The study will be registered on the ClinicalTrials.gov website upon approval by an EC/IRB in order to meet the criteria of the International Committee of Medical Journal Editors.

At the conclusion and final analysis of the trial results, a formal abstract may be submitted at a major urologic conference and the study results will be submitted to a reputable scientific journal.

Following publication of the main manuscript, secondary analyses proposals will be considered for publication from individual Investigators. Before publishing or presenting data from the study, the Investigator(s) agree to submit copies of any and all proposed

manuscripts or abstracts to the Sponsor at least 30 days in advance of submitting for publication. No submissions may be made without the written approval of the Sponsor.

16 STATISTICAL CONSIDERATIONS

This section summarizes the main statistical considerations for data analysis. A detailed description can be found in the Statistical Analysis Plan (SAP).

16.1 Primary Endpoints Analysis

The study is designed as a prospective, multi-center, randomized, controlled adaptive sample size clinical trial. Subjects will be randomized in a 2:1 ratio to Test:Control and randomization will be stratified by site. Individual site enrollment may not exceed 30% of the total study enrollment.

The statistical hypothesis test for the primary efficacy endpoint will be based on a two-sample continuity corrected Chi-square test at the two-sided 0.05 alpha level (equivalent to a one-sided 0.025 alpha level). Based on the assumed stricture rates, a total sample size of 126 subjects will provide approximately 90% power.

For the trial to be successful, the statistical evaluation for the resolution of the stricture at 6 months of the Optilume arm will be statistically compared to the control arm.

$$\text{Ho: } P_t \leq P_c$$

$$\text{Ha: } P_t > P_c$$

Where P_t is the stricture free rate at 6 months in the Treatment arm and P_C is the stricture free rate at 6 months in the Control arm.

16.1.1 Primary Efficacy Endpoint Treatment Failures Definition

Any subjects who have a second dilation procedure after the index procedure, or seek alternative treatments outside of the study before unblinding at the 6 months follow up are considered treatment failures for the primary analysis. At the 6 months follow up, if a 16F flexible cystoscope or a 14F rubber catheter cannot cross the treated stricture, the subject will be considered a treatment failure.

Note: Treatment of obstructive symptoms due to other reasons (e.g. BPH) is not considered a treatment failure.

16.2 Primary Safety Endpoint

The primary safety endpoint will be analyzed with descriptive statistics and nominal 95% confidence intervals; there will be no formal statistical hypothesis test.

16.3 Sample Size Justification

Sample size for the study is based on the primary effectiveness endpoint using the following assumptions:

- 2:1 randomization allocation
- Type 1 error of 0.025, one sided
- Statistical power of approximately 90%
- Assumed population success rate of 40% for the Control arm and 72% for Treatment arm, corresponding to a difference of 32%.
- 10% loss of follow-up rate

Based on these assumptions, an initial sample size of 126 evaluable subjects (Test: 84; Control: 42) provides approximately 90% power. Assuming a 10% lost to follow up, the initial randomized sample size is 140 subjects.

16.4 Sample Size Re-estimation

Due to uncertainty with respect to the design assumptions, an adaptive sample size methodology is planned[i,ii]. An interim analysis of the primary effectiveness endpoint is planned when primary effectiveness endpoint data is available on the first 60 randomized subjects (approximately 48% of the planned original total evaluable sample size). At the interim analysis, the primary effectiveness endpoint will be evaluated; if warranted, the sample size of the trial may be increased up to a maximum of 200 total subjects to maintain the study power.

The study will not stop because of effectiveness or futility at the interim analysis. The planned final sample size (randomized subjects) will not be adjusted downward from the originally planned 140 subjects, and the maximum sample size that may be randomized in this study following the sample size re-estimation is 200 subjects.

The interim analysis will be performed by an independent statistician blinded to the treatment group success rate. For the interim analysis, conditional power calculations for sample sizes up to the maximum of 200 will be performed using the observed success rate among the first 60 randomized subjects with available primary effectiveness endpoint data.

The final recommendation regarding the final sample size will be based on a combination of factors, both statistical and logistic (i.e. the past and expected future enrollment rate, attrition rate, etc.). As a guiding base, results from the following formula for the evaluable sample size will be provided to the DMC:

$$M = \max\left(N, \min\left(200, N\left(\frac{\delta}{\Delta}\right)^2\right)\right)$$

where N is the original planned evaluable sample size (126), δ is the original assumed treatment effect defined (32%), Δ is the observed treatment effect at the interim, and M is the planned evaluable final sample size. M is constrained to be no less than 126 subjects, and no more than 200 total subjects. Accounting for possible attrition, the enrollment will be no less than 140 and no more than 200 subjects. If 140 subjects are randomized prior to having primary effectiveness endpoint data on the first 60 randomized subjects, enrollment

will halt until the interim analysis takes place. If dictated by the results of the interim analysis, enrollment may then continue up to the maximum of 200 subjects.

Only the recommendation from the DMC will be shared with Urotronic and the clinical team to avoid the potential for bias. Details of the formula used in the sample size re-estimation may be found in the Statistical Analysis Plan (SAP).

16.5 Analysis Population Set

The primary endpoints analyses and the S1, S2, and S3 secondary endpoints will be performed on the intent-to-treat (ITT) population, under which all randomized subjects will be included for the analysis, regardless of whether or not the subjects received the treatment to which they were randomized.

In addition to the ITT analysis, these endpoints analyses also may be performed on the as treated population and per-protocol (PP) population, (*i.e.*, subjects treated and followed per the protocol) where appropriate.

16.6 Secondary Endpoints

The following secondary endpoints employ formal statistical hypothesis tests for the purposes of supporting labeling claims with inferential quantities. Endpoints will be tested in the sequential order listed, following a gatekeeping strategy to control the type I error rate.

16.6.1 Secondary Endpoint 1: Changes in Qmax at 6 months

The following hypothesis will be tested in a one-sided, two sample t-test for means:

$$\text{Ho: } \mu_{Test3} \leq \mu_{Control3}$$

$$\text{Ha: } \mu_{Test3} > \mu_{Control3}$$

Where μ_{Test3} is the change in Qmax at 6 months for subjects randomized to Optilume and $\mu_{Control3}$ is the change in Qmax at 6 months for subjects randomized to the Control. The test will be performed at the one-sided 0.05 alpha level. Successful rejection of the null hypothesis will indicate the change in Qmax for the device is statistically superior to the control. Non-parametric statistics will be used as a supportive analysis to protect against violations of the normality assumption.

16.6.2 Secondary Endpoint 2: Percent Responder at 12 Months (IPSS)

A responder is defined as a 50% improvement in IPSS score or an IPSS of 11 or lower

The following hypothesis will be tested in a one-sided, one-sample exact test for a binomial proportion.

$$H_o: P_{Test12} \leq 50\%$$

$$H_1: P_{Test12} > 50\%$$

Where P_{Test12} is the success rate at 12 months in all subjects treated with the Optilume, 50% is a performance goal). The test will be performed at the one-sided 0.05 alpha level. Successful rejection of the null hypothesis will indicate the success rate for the device is statistically greater than 50%.

16.6.3 **Secondary Endpoint 3: Time to treatment failure**

The following hypothesis will be tested in a one-sided, two sample log-rank test:

$$Ho: S_{Test} \leq S_{Control}$$

$$Ha: S_{Test} > S_{Control}$$

Where S_{Test} and $S_{Control}$ are the survival distributions for the time to treatment failure (i.e. they represent the freedom from treatment failure). The test will be performed at the one-sided 0.05 alpha level. Successful rejection of the null hypothesis will indicate the freedom from treatment failure for the treatment group is superior (i.e. longer time free from treatment failure) than for the control. Results will be described via Kaplan-Meier analysis.

16.6.4 **Ancillary Endpoints and Other Analyses**

The ancillary endpoints are to provide additional characterization of the safety and effectiveness of the Optilume in the treatment of stricture. No formal hypotheses tests for the purposes of supporting labeling claims are planned for ancillary endpoints. Quality of Life (QoL) changes will be measured using the QoL question in the IPSS and also the average time before subjects was able to resume pre-treatment activity.

Time to treatment failure will also be analyzed once all randomized patients are through 12, 24, 36, 48, and 60 months of follow-up.

In supportive analyses, data on the primary endpoints for control subjects who crossover to receive the active treatment will be summarized, based on treating their time of crossover as baseline. These results may be pooled with randomized treatment group subjects to better inform the performance of the device.

Generally, descriptive statistics will be used in reporting outcomes for other effectiveness secondary endpoints. Continuous variables will be summarized with means or medians, standard deviations. Adverse events, protocol deviations and device malfunction will be summarized with descriptive statistics.

16.7 Poolability

16.7.1 **Sites**

This study is designed and conducted as a multicenter randomized-control clinical trial. Data from all the sites will be pooled. All subjects will be treated and evaluated following the same protocol to ensure generalizability of the study results.

Heterogeneity in the treatment effect for the primary effectiveness endpoint will be assessed via logistic regression models with covariates for site, treatment group, and the

interaction of site and treatment group. A p-value for the interaction term <0.15 will suggest evidence of variation in the treatment effect and will trigger additional exploratory analyses to attempt to further quantify and explain the variation. Firth's penalized likelihood may be used if needed due to sparse data. Sites with fewer than 4 subjects will be combined into a single super-site for these analyses.

16.7.2 **Subgroup Analysis**

Subgroup analyses will be performed for the 6-month primary effectiveness endpoint to understand potential variation in the treatment effect. Statistical methods will follow the same as those outlined for poolability of site (Section 16.7.1). Subgroups will be defined based on the following baseline factors:

- Baseline number of prior treatments
- Baseline lesion length (≤ the median length vs. > the median length)
- Subject age at the time of randomization (≤ 50 years vs. > 50 year)
- Subject race
- IPSS Score (≤19 vs. ≥20, i.e. moderate vs. severe)
- Use of supra-pubic catheter at baseline (yes vs. no)

16.8 Handling of Missing Data

Every effort will be made to reduce the incidence of missing data. All available data on subjects who drop out during the study will be included.

16.8.1 **For the Primary Effectiveness Endpoint**

1) Subjects will be considered a treatment failure for the primary effectiveness endpoint if the subject opts to break blinding and seek alternative treatment or retreatment before the 6-month follow-up visit.
2) For subjects who either drop out or are lost to follow-up prior to the 6-month evaluation, baseline carried forward data will be used in the analysis (that is, no improvement). These subjects will be considered failed treatment
3) For subjects, whose stricture assessment was done after the 6 months' compliance window, the assessment will be accepted for this endpoint. However, assessment done before the 6 months' compliance window will not be accepted for this primary endpoint. [*Note: The later assessment is the worst case for this endpoint*]

16.8.2 **For the Primary Safety Endpoint**

Unless there is evidence of occurrence of a primary safety endpoint, subjects with missing data for the primary safety endpoint are presumed to not have experienced a primary safety endpoint.

16.8.3 For the Secondary Endpoint

For subjects who dropped out or are lost to follow-up, the last data carried forward will be used. The continuous variable data will be imputed by a linear interpolation if the subject returns at a later date.

16.8.4 Sensitivity Analyses for Missing Data

For the primary effectiveness endpoint, sensitivity analysis, *e.g.*, tipping point analysis, will be performed to evaluate the impact of missing data on study conclusion. Multiple imputation will be used as additional sensitivity analysis.

16.9 Multiple Responses

If a subject has multiple evaluations at baseline, the last baseline value prior to the procedure will be used in the analysis. If subject had multiple evaluations during the study follow up window, the last data set within the follow up window will be used in the analysis unless. This is based on the assumption that the test (e.g. IPSS or Qmax) was repeated because the physician felt that the previous data was compromised in some way.

16.10 Study Success

The study will be declared a success when the primary endpoint is met.

17 STUDY CONTACT

17.1 Study Principal Investigator

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17.2 Sponsor

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17.3 Monitor

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18 POTENTIAL DEVICE CHANGE

Future product line extensions or design changes may be introduced into the study based on feedback from investigators. In addition, manufacturing changes may be introduced. All design and manufacturing process changes will be performed under the Sponsor's design control process and fully tested to ensure that it meets specifications. Potential changes are not anticipated to affect the poolability of the study data.

The device design or process changes will be evaluated to ensure that it continue to meet the product specifications.

19 GLOSSARY OF ABBREVIATION

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AUA	American Urological Association
AUASS	American Urological Association symptom score
BPH	Benign Prostatic Hyperplasia
BUN	Blood urea nitrogen
CBC	Complete blood cell count
CFU	Colony Forming Unit
CIP	Clinical Investigation Plan
CRF	Case Report Form
DCB	Drug Coated Balloon
DES	Drug-eluting stent
DVIU	Direct Vision Internal Urethrotomy
EC/IRB	Ethics Committee / Institutional Review Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ID	Identification code
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptoms Score
LUTS	Lower urinary tract symptoms
NSAID	Nonsteroidal anti-inflammatory drug
OAB	Overactive Bladder
POBU	Plain old balloon urethroplasty
PROM	Patient-reported outcome measure
PSA	Prostate Specific Antigen
PVR	Post Void Residual Urine Volume
Qmax	Peak Flow Rate Measurement
RBP	Rated burst pressure
RUG	Retrograde Urethrogram
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device EFFECT(s)
USS	Urethral Stricture Score
UTI	Urinary Tract Infection

20 DEFINITIONS

20.1 Adverse Event

Any untoward medical occurrence in a subject during the course of the study. This definition does not imply that there is a relationship between the adverse event and the device used for treatment. For the purpose of AE reporting, the start of the course of the study is defined as any time after treatment has been initiated.

20.2 Adverse Device Effect

An adverse device effect is any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in instructions for use for preparation or deployment of the device.

20.3 Anticipated Adverse Event

Any adverse event occurring to a subject whether or not considered related to the stricture treatment prescribed as part of the protocol, predefined in the protocol, Instructions for Use (IFU), Sponsor quality documents or published literature that is identified or worsens during a clinical study.

20.4 Serious Adverse Event

A serious adverse event (SAE) is an AE that:

- Leads to death
- Leads to serious deterioration in the health of the subject, that either resulted in:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or a body function, or
    - In-patient or prolonged hospitalization, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function or is considered an important medical event
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event.

20.5 Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences of a serious adverse event.

20.6 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect (UADE) is “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of

incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects" (21 CFR 812.3(s)).

20.7 Relationship to the Treatment and Procedure

A description of how an AE relates to the treatment (test or control) and procedure will be determined by the Investigator and reported on the Adverse Event CRF using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.
- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

20.8 Device Malfunction

A device malfunction is a failure of a device to meet its performance specifications or otherwise perform as intended.

20.9 Discharge

The time point at which the subject was released from the treatment location (in-office, hospital OR or ambulatory surgical center).

20.10 Enrollment

The point at which a subject:

- Meets all the inclusion criteria
- Does not meet ANY exclusion criteria
- Provides informed consent
- Is randomized to a treatment group

20.11 Intent-To-Treat (ITT)

The principle of including outcomes of all subjects in the analysis who are randomized into the study, analyzed according to their originally randomized treatment, regardless of the treatment actually received.

20.12 Obstructive LUTS

Obstructive LUTS have some symptoms similar to Urinary Retention. Obstructive LUTS is usually a chronic condition and is sometimes referred to as chronic urinary retention. Symptoms of obstructive LUTS are:

- Poor stream
- Hesitancy
- Terminal dribbling
- Incomplete voiding
- Overflow incontinence (occurs in chronic retention)

20.13 Per-Protocol (PP)

A PP analysis is based on all subjects characterized by appropriate exposure to the pre-specified treatment, availability of measurements and absence of major protocol violations (including violations of inclusion/exclusion criteria).

20.14 As Treated (AT)

An AT analysis is based on all subjects that actually received the assigned treatment.

20.15 Screen Failures

Subjects who do not meet inclusion/exclusion criteria after baseline evaluations. Screen fail subjects will be withdrawn from the study.

20.16 Treatment Success

Treatment success of the procedure is defined as the ability to pass a 16F flexible cystoscope at 6 months' post-treatment. If a 16F cystoscope cannot be passed, a 14F red rubber catheter will be used.

A stricture is defined to be resolved when a 16F flexible cystoscope or a 14F rubber catheter is able to be passed through the stricture.

20.17 Urinary Retention

Urinary retention, also known as ischuria, is a total lack of ability to urinate. It is sometimes referred to as acute urinary retention and typically has to be treated with a catheter or stent to avoid serious complications of the bladder and/or kidney.

Acute urinary retention is expected immediately following treatment as the tissue undergoes the healing process and will not be considered an AE. However, any catheterizations or cystoscopies will be recorded in the CRF. Resolution is defined as a

removal of the catheter without the need to reinsert it or use of intermittent self-catheterization.

While catheterization in and of itself is not an AE, the ***reason*** for catheterization must be evaluated for purposes of determining an AE.

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EAU Guidelines on Urethral Strictures

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European
Association
of Urology

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urethral Strictures Guidelines aim to provide a comprehensive overview of urethral strictures in male, female and transgender patients. The Panel is aware of the geographical variations in healthcare provision.

It must be emphasised that guidelines present the best evidence available to the experts; however, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urethral Strictures Guidelines panel consists of an international multidisciplinary group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/urethral-strictures/.

1.3 Available publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/urethral-strictures/. A list of supplementary tables supporting this text can also be found online, along with an appendix of abbreviations specific to this text: https://uroweb.org/guideline/urethral-strictures/?type=appendices-publications.

1.4 Publication history

This document is a new Guideline first published in 2021. Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2. METHODOLOGY

2.1 Methods

For the 2021 Urethral Strictures Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2008 and 2019 and restricted to English language publications. The panel defined by consensus inclusion and exclusion criteria for each topic before the scope search. Detailed search strategies are available online: https://uroweb.org/guideline/urethral-strictures/.

Relevant literature prior to the 2008 scope search cut-off was allowed if it was estimated to be of exceptional value by the panel. Relevant literature after the 2019 scope search cut-off was searched for by the panel member dedicated to a specific topic.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternatives.

The Panel wants to highlight that "success" in urethral stricture treatment is poorly defined and subjective. "Success" is usually defined as urethral patency, either subjective by the absence of voiding symptoms or objective by imaging or urethral calibration. Despite urethral patency, the patient themselves might not consider the treatment as successful because of functional consequences (e.g., post-void dribbling, erectile/ejaculatory dysfunction, altered genital appearance). In this Guideline, the Panel agreed to avoid the term "success". Instead, the term "patency rate" or "stricture recurrence rate" will be used to clarify that only stricture recurrence was taken into consideration (as assessed by the authors).

The Panel would like to stress that patency after urethral surgery is dependent on the general principles of wound healing. These principles have stood the test of time and need to be respected at any time [5]. Some examples:

- An anastomosis should be made between healthy urethral ends and without any tension.
- A graft requires a well-vascularised graft bed with a close contact between the graft and graft bed to promote imbibition and inosculation.
- If the full circumference of the urethral mucosa is destroyed, spontaneous regeneration will not take place.
- Contraction and fibrosis in a wound stops only after it is covered by its epithelium.

The Panel conducted two systematic reviews to support guideline recommendations:

- What is the role of one-stage oral mucosa urethroplasty in the management of strictures due to male Lichen Sclerosus (LS)?
- A systematic review of various free graft urethroplasty (FGU) techniques for the management of bulbar urethral strictures.
- The results of these reviews are included in the 2021 Urethral stricture guidelines.

2.2 Review

The Urethral Strictures Guidelines were peer reviewed prior to initial publication in 2021.

2.3 Future goals

The results of the two systematic reviews will be submitted for publication in European Urology (Focus). Summary papers of the guidelines will be drafted and submitted for publication to European Urology (Focus). These papers will include the following topics:

- Diagnosis, peri-operative care and follow-up of urethral strictures
- Treatment of strictures in females and transgender patients
- Treatment of male strictures

An update of the strictures guideline will be conducted when deemed necessary, but at latest after five years. Further systematic reviews will be conducted after approval of the Guidelines Office.

3. DEFINITION, EPIDEMIOLOGY, AETIOLOGY AND PREVENTION

3.1 Definitions

In males, a urethral stricture refers to a narrowed segment of the anterior urethra due to a process of fibrosis and cicatrisation of the urethral mucosa and surrounding spongiosus tissue ("spongiofibrosis") [6, 7]. In the male posterior urethra, there is no spongiosus tissue and at this location the terms stenosis is preferred [6, 7]. The definition of meatal stenosis is generally accepted as a short distal narrowing at the meatus, without involvement of the fossa navicularis [7].

There is no universal definition for what constitutes a female urethral stricture (FUS). Female urethral stricture is defined by most authors as a 'fixed anatomical narrowing' causing reduced urethral calibre [8, 9]. This reduced

urethral calibre is variously defined as between < 10 Fr to < 20 Fr [10, 11] with the majority of series defining < 14 Fr as diagnostic, compared with a 'normal' urethral calibre of 18-30 Fr.

In transgender patients, the term stricture is also used to define a narrowing of the reconstructed urethra despite the absence of surrounding spongious tissue.

3.2 Epidemiology

In males, a sharp increase in incidence is observed after the age of 55 years, with a mean age of 45.1 [12, 13]. Overall, the incidence is estimated to be 229-627 per 100,000 males [12]. The anterior urethra is most frequently affected (92.2%), in particular the bulbar urethra (46.9%) [13].

In females, 2-29% of patients presenting with refractory lower urinary tract symptoms (LUTS) have bladder outflow obstruction (BOO) [14-17] of whom 4-20% will have a urethral stricture [16-18]. True FUS therefore occurs in 0.08-5.4% of women with refractory LUTS. There is a markedly increased incidence in women over 64 years old [19].

In children, most strictures are traumatic: related to iatrogenic causes in 27.8-48% and external trauma in 34-72% [20]. Less frequent congenital (13%), inflammatory (4%), or post-infectious strictures (1%) are seen. The bulbar urethra is the most frequently affected part of the urethra [20].

After hypospadias repair, meatal stenosis and urethral strictures are reported in 1.3-20% of cases, depending on the severity of the hypospadias and the technique used [21]. There is a significantly higher incidence of this type of strictures in well-resourced countries due to a higher surgical repair rate [22].

Up to 18% of all urethral strictures have been reported to involve the meatus or fossa navicularis usually due to failed hypospadias repair (FHR), lichen sclerosus (LS), trauma/instrumentation or idiopathic causes [23-26].

Meatal stenosis post-circumcision has been reported in less than 0.2% of children undergoing circumcision as neonates [12].

In female-to-male (FtM) transgender patients ("trans men"), approximately 51% will suffer a urethral stricture [27]. Strictures almost exclusively arise at the neomeatus in male-to-female (MtF) transgender patients ("trans women") and occur in 14.4% of cases [28].

3.3 Aetiology and prevention

Stricture aetiology differs significantly throughout different regions in the world, due to differences in healthcare quality and environmental and practice patterns [22]. Regardless of geography, urethral stricture disease adversely impacts physical health and quality of life (QoL) [29, 30], notwithstanding costs associated with the treatment of primary and recurrent disease [31, 32]. The rationale for preventing urethral strictures is to avoid morbidity to the individual and costs to society. Prevention of urethral strictures encompasses reducing the causes of stricture (e.g., infection, trauma, iatrogenic injury) and where this is not possible mitigating the risk.

3.3.1 Aetiology and prevention in males

a. Sexually transmitted infection

Urethritis due to sexually transmitted infection (STI), in particular gonorrhoea, was previously a major cause of urethral strictures in well-resourced countries accounting for 40% of all cases [33]. The wide-scale promotion of safe sexual practices and easier access to sexual health services, resulting in timely treatment with antimicrobials, is thought to have led to the considerable reduction in the problem [33]. Infective urethritis now accounts for 0.9% to 3.7% of cases in contemporary series from well-resourced countries [33, 34] but continues to be the major cause of strictures in low-resourced countries comprising 41.6% of all strictures [35].

Summary of evidence	LE
Access to investigation and treatment of STI is associated with a temporal decline in the incidence of infective urethritis related strictures.	3

Recommendation	Strength rating
Advise safe sexual practices, recognise symptoms of sexually transmitted infection and provide access to prompt investigation and treatment for men with urethritis.	Strong

b. Inflammation

Lichen sclerosus involves the urethra in 20% of cases [36] and is the most common cause of panurethral stricture disease (48.6%) [13]. The aetiology of LS has not been fully elucidated but is thought to be have an autoimmune origin [37]. Lichen sclerosus may be associated with environmental factors and non-autoimmune comorbidities. Uncircumcised men are far more likely to suffer LS than circumcised men [age-adjusted odds ratio (OR) of 53.55; (95% confidence interval (CI): 7.24-395.88] [38]. Lichen sclerosus is also associated with higher mean body mass index (BMI), diabetes mellitus, coronary artery disease, tobacco usage, hyperlipidaemia, and hypertension [39-41].

c. External urethral trauma

External trauma to the urethra is the second most common cause of stricture formation in adults [33]. The urethra is vulnerable to trauma during certain activities including sport, driving a vehicle, sexual intercourse and during combat. The bulbar urethra is the site most frequently affected by blunt trauma [7], usually as a result of straddle injuries or kicks to the perineum. Penile fracture is associated with a urethral injury in 15% of cases [42]. Motor vehicle accidents are the main cause of blunt injuries to the posterior urethra associated with pelvic fractures [43]. Penetrating injuries of the urethra are uncommon during non-combat situations [44].

d. Iatrogenic urethral injury

Iatrogenic injury to the urethra is one of the most common causes of strictures in well-resourced countries [13, 33] accounting for 32% to 79% of all strictures [33, 45]. In children, specifically iatrogenic causes were identified in 6.7-25% of cases [46]. Preventing iatrogenic urethral injury represents the main way in which urologists can prevent urethral strictures. Iatrogenic urethral injury most commonly results from urethral instrumentation (e.g., catheterisation, cystoscopy), surgery for benign prostatic obstruction (BPO), surgery for prostate cancer, or radiotherapy [34].

d.1 Urethral catheterisation

Urethral strictures are a recognised complication of urethral catheterisation accounting for 11.2-16.3% of all strictures [13, 33]. In a meta-analysis by Hollingsworth and colleagues the pooled percentage of patients who developed urethral stricture or erosion after short-term catheterisation (< 3 weeks) in higher quality studies was 3.4% (CI: 1.0% to 7.0%) [47]. In studies comprised mainly of men with spinal cord injury with indwelling urethral catheters, the pooled estimate of urethral stricture or erosion was 8.7% (CI: 0.0%-18.7%) [47].

Urethral strictures following catheterisation may arise as a consequence of injury during attempts at insertion or during the period a catheter remains *in situ*. During insertion the urethra may be injured by formation of a false passage by the catheter tip (29.7%) or inflation of the balloon within its lumen (70.3%) [48]. The rate of urethral injuries due to catheterisation was found to be 3.2 per 1,000 inpatients [49]. A six-month prospective multicentre study found that of 37 patients with catheter-related urethral trauma referred to urologists, 24% continued to perform intermittent self-dilatation (ISD) once weekly and 11% required at least one urethral dilation for urethral stricture [50]. In another follow-up study of 37 patients with catheter-related urethral trauma, 78% of patients developed urethral stricture [48]. The most common locations of trauma are the bulbar and posterior urethra [51].

Catheter-related trauma can be prevented through several measures [52]. Studies have indicated around 25% of all indwelling catheterisations in hospitals were unnecessary and inappropriate [53, 54]. Implementation of guidelines [55, 56] and specific criteria [57] have been shown to reduce catheterisation rates. Several studies have identified deficits' in the knowledge of urethral catheterisation amongst resident doctors [58, 59]. This is postulated to be a factor in catheter-related trauma [59]. A targeted training program on urethral catheterisation for nursing staff was shown to be effective in reducing iatrogenic urethral injuries in a prospective single institution study [49].

In addition to guidance and education, another approach to safer catheterisation is modification of the standard Foley catheter. A novel catheter balloon pressure valve safety system was developed to prevent balloon inflation injury though this has not been assessed in comparative studies [60, 61]. Bugeja *et al*. studied the use of urethral catheterisation device (UCD) incorporating a guidewire, in prospective observational cohort study that included 174 patients. The incidence of adverse events was 7% with standard Foley catheterisation vs. 0% with the UCD (no statistical analysis was performed) [62]. A further prospective observational study found that Seldinger technique catheterisation could be used successfully by non-urology trained doctors [63]. These technologies need to be further assessed in prospective randomised studies incorporating cost-benefit analysis.

Catheter diameter is suggested as a possible contributing factor to urethral stricture due to a pressure effect on the urethral wall [64]. Decreasing the catheter size from 22 Fr to 18 Fr significantly decreased the risk of fossa navicularis strictures (6.9% vs. 0.9%, p=0.02) after radical prostatectomy (RP) [65]. Catheter material may also have an influence on the occurrence of stricture. In the 1970s/80s several comparative studies in patients undergoing cardiac surgery demonstrated that non-coated latex catheters were associated with a greater incidence of urethritis and more stricture formation than silicone catheters [66-68]. Other studies showed no difference [69-71]. Modern latex catheters have polymeric coatings [72] due to the concern with regards to stricture alongside the risk of hypersensitivity and the demonstrable *in vitro* toxicity of latex. Prolonged urethral catheterisation has also been implicated in the aetiology of stricture (e.g., poly-trauma, burns patients) [45].

Summary of evidence	**LE**
A significant proportion of catheter insertions in hospitalised patients were considered unnecessary.	2b
Education programs can reduce the incidence of catheter-related urethral injury.	2a
Larger catheter size was associated with a greater risk of navicular fossa strictures.	3
Non-coated latex catheters are associated with a greater degree of urethritis and possibly a greater risk of urethral strictures than non-latex catheters or coated latex catheters.	1a

Recommendations	**Strength rating**
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage only is the purpose.	Weak
Avoid using non-coated latex catheters.	Strong

d.2 Transurethral prostate surgery

Urethral stricture following transurethral prostate surgery occurs in between 4.5% to 13% of patients [73], whereas bladder neck stenosis (BNS) occurs in between 0.3% to 9.7% [74]. Transurethral surgery is the most common cause of iatrogenic urethral stricture accounting for 41% of all causes [45]. The most common location for urethral stricture is the bulbomembranous urethra, followed by the fossa navicularis and penile urethra [75, 76]. Postulated mechanisms include friction at the penoscrotal junction, lack of adequate lubrication, repetitive 'in and out' movement of the resectoscope, breach of mucosal integrity leading to urine extravasation and monopolar current leak due to inadequate resectoscope insulation [77]. Bladder neck stenosis may be related to excessive and/or circumferential resection and the use of relatively large resection loops which may generate excessive heat in small intraurethral adenomas leading to scarring [74, 78]. Stenoses of the posterior urethra may also be due to a prolonged period of post-operative inability to void [79].

d.2.1 Risk factors for development of urethral stricture and bladder neck stenosis

Several risk factors for the development of urethral stricture and BNS following transurethral prostate surgery have been identified. Both prostatic inflammation (OR: 4.31) and operative time > 60 min (OR: 4.27) were found to be independent predictors of stricture after monopolar transurethral resection of prostate (TURP) [80]. In terms of bipolar TURP, slower resection rate (OR: 0.003), intraoperative urethral mucosa rupture (OR: 2.44) and post-operative infection were shown to be independent predictors (OR: 1.49) [81, 82]. A larger-calibre endoscopic sheath (26 Fr vs. 24 Fr) was associated with a greater risk of bulbar urethral stricture following monopolar TURP (11.4% vs. 2.9%, p=0.018) [83]. Room temperature irrigation solution was associated with a greater risk of urethral stricture following combined transurethral resection and vaporisation of the prostate compared to body temperature irrigation (21.3% vs. 6.3%, p=0.002) [84].

Bladder neck stenosis is known to occur more frequently in smaller prostate glands after both monopolar and bipolar TURP [85, 86]. Lee *et al*. found that adenoma weight was an independent risk factor for BNS after monopolar TURP [86]. Meanwhile, Tao *et al*. found total prostate volume (< 46.2 g) (OR: 1.5), but not resected gland weight, to be an independent risk factor [81].

d.2.2 Incidence of urethral stricture and bladder neck stenosis with different energy modalities

A systematic review and meta-analysis by Cornu *et al*. showed no significant differences in urethral stricture and BNS rates by energy modality (monopolar, bipolar, holmium laser enucleation, photoselective vaporisation) [73]. In another meta-analysis assessing outcomes of thulium (Tm:Yag) laser and bipolar TURP, no difference in urethral stricture and BNS rates were found between the two modalities [87]. The presence of potentially confounding factors such as endoscopic sheath diameter, energy setting used, procedural length and length of follow-up make inter-study comparisons between energy modalities problematic. Overall, there is no strong

evidence that any single modality is associated with a clinically significant higher incidence of urethral stricture and BNS than others. Selection of modality should be based on a comprehensive evaluation of clinical safety and efficacy. A summary of incidences of urethral stricture and BNS with different modalities is presented in Table 3.1.

Table 3.1: Incidence of urethral stricture and bladder neck stenosis by transurethral modality (adapted from Chen *et al*. 2016 [74]**)**

Modality	Urethral stricture	Bladder neck stenosis
Transurethral resection of prostate (TURP) - monopolar and bipolar	1.7 to 11.7%	2.4 to 9.7%
Holmium enucleation of the prostate (HoLEP)	1.4 to 4.4%	0 to 5.4%
Photo-selective vaporisation (PVP)	0 to 4.4%	1.4 to 3.6%

d.2.3 Interventions to prevent urethral stricture and bladder neck stenosis

Sciarra and colleagues conducted a single-blind randomised control trial (RCT; n=96) to assess the use of rofecoxib for stricture prevention following TURP. At twelve months follow-up a urethral stricture was found in 17% and 0% of cases in the placebo and rofecoxib groups, respectively (p=0.0039) [88]. Chung *et al*. conducted a single blinded RCT (n=180) evaluating the effect of urethral instillation of hyaluronic acid (HA) and carboxymethylcellulose (CMC). Urethral stricture on urethrography was diagnosed in 1.25% and 8.64% of patients in the treatment and placebo group respectively (p=0.031). Further randomised studies are needed to confirm these findings and the safety of the pharmacological interventions.

Several earlier comparative studies assessed whether routine preliminary urethrotomy with an Otis urethrotome prevented the incidence of stricture following TURP [89-92]. Only one of these reported at least twelve month follow-up, finding no significant difference in stricture rate in patients undergoing TURP alone vs. Otis urethrotomy followed by TURP (21% vs. 14%) [93]. Others have suggested performing internal urethrotomy where there is pre-existent meatal or urethral strictures [94].

Adjunctive transurethral incision of the prostate (TUIP) at the end of TURP to reduce the rates of BNS was studied by Lee and colleagues [86]. A total of 1,135 patients of whom 667 underwent TURP and 468 underwent TURP plus TUIP were retrospectively studied. At median follow-up of 38 months, the incidence of BNS was 12.3% for the TURP group vs. 6.0% for the TURP plus TUIP group ($p < 0.001$). In glands < 30 g, the incidence of BNS in the TURP vs. the TURP plus TUIP group was 19.3% and 7.7%, respectively ($p < 0.05$). The clinical efficacy and safety of additional surgical interventions to prevent urethral stricture and BNS need to be confirmed in larger prospective RCTs before their use can be recommended.

Summary of evidence	LE
An RCT with more than twelve months follow-up failed to demonstrate a significant reduction in stricture rate using routine urethrotomy prior to TURP.	1b

Recommendation	Strength rating
Do not routinely perform urethrotomy when there is no pre-existent urethral stricture.	Strong

d.3 Radical prostatectomy

Radical prostatectomy has been associated with vesico-urethral anastomosis stricture (VUAS) in between 0.5% to 30% of patients [74], though most modern series report it in the range of 1% to 3% [95]. The risk of stricture formation after salvage RP is notably higher (22-40%) [96]. Most VUAS develop within the first two years [96, 97]. A 2012 meta-analysis by Tewari *et al*. showed no significant difference in VUAS between open-, laparoscopic and robotic RP [98]. In contrast, a more recent analysis of a national cohort in the UK found that VUAS rate after robotic RP was 3.3%, which is significantly lower than following laparoscopic (5.7%) or open RP (6.9%) [99]. These findings are consistent with an earlier similar study conducted in the USA [100]. The difference in VUAS rates may be explained by the level of experience and surgical volume of surgeons [101]. The cohort studies represent “real world” data, including all levels of surgical experience and surgical volumes whereas the meta-analysis is based on clinical studies. Thus the better outcomes for robotic RP in the population studies may be related to the shorter learning curve [102].

d.3.1 Risk factors for development of vesicourethral anastomosis strictures

These include higher grade cancer, more advanced stage, higher prostate volume, coronary artery disease, obesity, hypertension, diabetes mellitus, previous bladder outlet surgery and older age [95, 103, 104]. Surgical factors include use of non-nerve-sparing technique, anastomotic urine leak, increased operative time and increased estimated blood loss [95, 103, 104]. In addition, low-volume surgeons (< 40/year) were shown to have higher VUAS rates, 27.7%, compared to high-volume surgeons (> 40/year), 22% [105].

d.3.2 Interventions to prevent vesicourethral anastomosis strictures

Srougi *et al*. studied bladder neck mucosal eversion in a prospective RCT of 95 patients. No significant difference was found in rates of VUAS at twelve months follow-up [106]. A meta-analysis by Kowelewski *et al*. comparing interrupted vs. continuous vesico-urethral anastomosis suturing found no difference in VUAS rates [107]. Another systematic review by Bai *et al*. compared barbed sutures to conventional sutures, although heterogeneity across studies precluded meta-analysis, no patients developed VUAS with either approach [108].

d.4 Prostate radiation and ablative treatments

Urethral strictures occur in 1.5% of patients undergoing external beam radiation therapy (EBRT), 1.9% having brachytherapy (BT) and 4.9% who receive combination EBRT-BT at around four years follow-up [109]. These strictures typically occur in the bulbomembranous urethra [110]. As opposed to RP, stricture incidence after irradiation increases with time [96, 109]. For the ablative treatments, the stricture incidence after cryotherapy and high-internsity focused ultrasound (HIFU) is 1.1-3.3% and 1-31%, respectively [96]. The use of these treatment modalities in the salvage setting is associated with increased risk of stricture formation: 3-10% after salvage EBRT, 5-12% after salvage cryotherapy and 15-30% after salvage HIFU [96]. Due to the increasing utilisation of prostate irradiation (EBRT, BT) and ablative treatments (cryotherapy, HIFU), an increasing number of respectively radiation-induced and ablative treatment-induced strictures are expected [111].

d.4.1 Risk factors for the development of radiation strictures

Awad *et al*., performed a multivariate meta-regression analysis including 46 studies, finding combining ERBT + BT and length of follow-up to be significant predictors of urethral stricture following prostate radiation [109]. Factors not shown to predict urethral stricture included biochemical equivalent dose, age and androgen deprivation therapy [109]. Previous TURP was not included in the analysis, but has been found to be independent predictor of stricture (HR: 2.81) in a previous multivariate analysis from a single institution [112] as has PSA level < 10 ng/ml (HR: 0.47) [113].

d.4.2 Interventions to prevent radiation induced urethral strictures

Delaying adjuvant or salvage EBRT by nine months is associated with lower rates of urethral stricture (HR 0.6) [114]. This has to be balanced with risk of delaying treatment in terms of cancer control [74]. In BT, it has been reported that downward movement of needle applicators occurs between fractions [115]. This may explain why strictures occur below the prostatic apex [113] in the so called “hot spot” [116]. Several measures taken together are thought to have contributed to a reduction in urethral stricture formation with BT including reduction of dose to the “hot spot”, more careful needle placement, avoiding midline insertion and the introduction of plastic needles rather than steel [109].

e. Failed hypospadias repair.

Although urethral strictures after hypospadias repair are sometimes considered as iatrogenic [33], they are a very specific subtype and should be considered as a separate entity. The main reasons for this are the absence of spongiosus tissue at different levels within the penile urethral segment, and the lack of high-quality local tissues for urethral reconstruction [117].

f. Congenital

The diagnosis of a congenital urethral stricture can only be made in the absence of other possible aetiology, such as iatrogenic, inflammatory and traumatic causes [20]. Congenital strictures are thought to be consequent to incomplete or incorrect fusion of the urethra formed from the urogenital sinus with the urethra formed following closure of the urethral folds. They typically have a deep bulbar location and are usually short. In general, congenital strictures are diagnosed at a young age (Moorman’s ring or Cobb’s collar).

g. Idiopathic

Idiopathic strictures are seen in 34% of all penile strictures and in 63% of all bulbar strictures [118]. Unrecognised trauma is thought to be a possible aetiology of idiopathic urethral strictures [22].

*3.3.2 **Aetiology in females***

The cause of FUS was idiopathic in 48.5%, iatrogenic in 24.1%, resulting from prior urethral dilations, difficult/traumatic catheterisation with subsequent fibrosis, urethral surgeries (mainly diverticulum surgery, fistula repair and anti-incontinence procedures) and trauma (mainly following pelvic fracture) in 16.4% [119-131]. Radiation therapy and infections are rare causes of FUS [132]. The commonest segment of urethra affected is the mid- or mid-to-distal (58%). Panurethral strictures are rare (4%) [10, 119, 121, 122, 124-126, 131, 133].

For further information see online supplementary Tables S3.1 and S3.2.

4. CLASSIFICATIONS

4.1 According to stricture location

Classification according to stricture location is important as this will affect further management.

*4.1.1 **In males***

4.1.1.1 Anterior urethra

The anterior urethra runs from the meatus to the urogenital diaphragm and is surrounded in its entire length by the corpus spongiosum [6, 134]. Further subdivision is made in three different areas (from distal to proximal) [7]:

Meatal strictures: these strictures are located at the external urethral meatus and may extend into the fossa navicularis of the glans.

Penile strictures: these are located in the segment between the fossa navicularis and the bulbar urethra. Externally, the penile urethra begins approximately at the balanopreputial sulcus and continues to the penoscrotal junction. The whole penile urethral segment lies in the groove ventral to corpora cavernosa and is surrounded by a thin layer of corpus spongiosum.

Bulbar strictures: the bulbar urethra starts at the penoscrotal junction and is surrounded by the bulbospongious muscle. It ends in the membranous urethra proximally at the level of the urogenital diaphragm. The bulbar urethra can be subdivided into a proximal and distal part. The proximal bulbar urethra is defined as the segment within 5 cm of the membranous urethra; the urethra lies eccentrically in this part with abundant ventral spongious tissue. The distal bulbar urethra is defined as the adjoining segment extending to the penoscrotal junction [135]. Strictures extending towards the membranous urethra are termed bulbomembranous strictures (BMS).

Penobulbar strictures: these extend from the penile urethra into the bulbar segment, compromising long segments of urethra.

The difference between penobulbar strictures and multifocal strictures should be noted. The latter are defined by two or more narrowed segments, either in the same or different subdivision of the urethra but preserving healthy lengths of urethra between them (e.g., iatrogenic strictures related to TUR procedures which typically affect the fossa navicularis and the penoscrotal junction with healthy urethra in between).

4.1.1.2 Posterior urethra

The posterior urethra is approximately 5 cm long, with three different segments [7]:

- The membranous urethra is the area of the urethra traversing the urogenital diaphragm, between the proximal bulbar and the distal verumontanum.
- The prostatic urethra runs through the prostatic gland, starting at the proximal membranous urethra and extending to the bladder neck.
- The bladder neck is surrounded by the internal urinary sphincter and is the junction between the prostatic urethra and the bladder. Stenosis (or contracture) of the bladder neck implies a prostate *in situ* (i.e., after TURP or simple prostatectomies). If the narrowing or obliteration appears at this level but after a RP, the correct term is VUAS [7].

4.1.2 *In females*

The female urethra is approximately 4 cm long and arbitrarily divided in an upper, mid and lower part [10, 119, 121, 122, 124-126, 131, 133].

4.2 According to stricture tightness

The definition of low- vs. high-grade strictures remains debatable [136-138]. A urethral plate less than 3 mm is considered a high-grade or tight stricture [139]. It has been demonstrated with a normally functioning bladder that flow rate will not diminish until the urethral lumen has a diameter below 10 Fr [137].

Table 4.1, presents a suggested classification for male patients with a normal functioning bladder. This classification was developed by the EAU Urethral Stricture Panel based on a consensus process.

Table 4.1: EAU classification according to the degree of urethral narrowing

Category	Description	Urethral lumen (French [Fr])	Degree
0	Normal urethra on imaging	-	-
1	Subclinical strictures	Urethral narrowing but ≥ 16 Fr	Low
2	Low grade strictures	11-15 Fr	
3	High grade or flow significant strictures	4-10 Fr	High
4	Nearly obliterative strictures	1-3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

4.3 Strictures in transgender men and woman

4.3.1 *Trans women*

After male-to-female gender confirming surgery, the penile urethra has been resected. Meatal strictures are defined as strictures occurring at the neomeatus, which is formed between the junction of the distal bulbar urethra and the neovagina. The other segments (bulbar and posterior) are the same as in a biological man.

4.3.2 *Trans men*

Four different areas can be identified in the urethra after female-to-male gender confirming surgeries [140]:

- The native urethra is the female urethral segment which remains preserved during surgery. It goes from the bladder neck to the original external meatus.
- The fixed part (pars fixa) or perineal urethra follows the native urethra, starting at the original external meatus. This segment is reconstructed using local tissues, typically vestibular mucosa or anterior vaginal mucosa. Its course is similar to the bulbar urethral segment in males, but without being covered by spongiosal tissue.
- The anastomotic part is the area where the pars fixa joins the neophallus.
- The phallic urethra is the segment located within the neophallus or the metoidioplasty and is usually made of skin tube. Its course is similar to the penile urethra in males, but without being covered by spongiosal tissue.

5. DIAGNOSTIC EVALUATION

A comprehensive diagnostic evaluation of urethral stricture disease encompasses clinical history and examination, urinalysis (+/- culture), uroflowmetry and post-void residual (PVR) assessment, radiography and endoscopy.

5.1 Patient history

The purpose of history taking is to assess symptoms including severity and duration, possible aetiology, prior treatments, complications, associated problems, and patient factors that may impact upon surgical outcome.

The clinical presentation of urethral stricture disease is varied. In a retrospective analysis of 611 patients with an endoscopically confirmed diagnosis of urethral stricture, LUTS were the most common presentation (54.3%) followed by acute urinary retention (22.3%), urinary tract infection (UTI) (6.1%) and difficult catheterisation (4.8%) [141]. In a retrospective study of 214 patients who underwent anterior urethroplasty, weak stream was

reported as the most common individual LUTS (49%) followed by incomplete emptying (27%) and urinary frequency (20%) [142]. A further retrospective series of 614 patients undergoing anterior urethroplasty found post-void dribble to be present in 73% [143].

Genitourinary pain is a common feature, affecting 22.9-71% [29, 141]. Pain may be felt in the bladder and/or urethra, is associated with more severe LUTS, is more likely to be felt by younger men and resolves in most following reconstruction [29]. Other complaints include spraying (9%), visible haematuria (3.1-5%), urethral abscess/necrotising fasciitis (2.3%), urgency (14%) and incontinence (1-4%) [141, 142].

To establish aetiology, an enquiry about a history of pelvic, genital or perineal trauma, prior instrumentation, prior surgeries, irradiation or focal therapies and urethritis should be made. It is important to document prior surgical approaches and date of the most recent intervention (e.g., dilatation) as this may impact upon the timing of radiological evaluation or surgical treatment.

Problems of sexual function are common in patients with urethral stricture disease [144, 145] and sexual function may be impacted upon by surgical intervention [146, 147], hence the status of erectile and ejaculatory function should be established and documented using validated tools.

The performance status of the patient should be determined as it may influence the choice of treatment (curative or palliative). A past medical history should assess for factors that may impact upon tissue healing including diabetes, immunosuppression and smoking. Oral tobacco use or the chewing of betel leaves may increase the risk of morbidity at the harvest site or render oral mucosa too poor for use. Prior harvest of oral mucosa should be noted as alternative sources for tissue transfer may need to be considered [148] or alternative surgical approaches (e.g., perineal urethrostomy [PU]).

5.2 Physical examination

The abdomen should be examined for the presence of a palpable bladder. The location of any suprapubic tube should be noted to assess its potential utility for antegrade cystoscopy or the placement of a sound (to facilitate repair) [149]. Examination of the genitalia should note the presence of foreskin, the position and size of the meatus as well as any evidence of scarring suggestive of LS. Pre-operative biopsy to confirm LS may be performed if this alters management and is essential if malignancy is suspected [150].

The presence of penile or perineal fistulae should be noted. The urethra should be palpated to assess for induration suggestive of significant fibrosis. Rarely a mass may signify a urethral carcinoma. A rectal examination to assess for prostatic pathology, which may be the cause of urinary symptoms, should be undertaken. In patients with posterior urethral stenosis rectal adherence to the prostate and the mobility of the surrounding tissues should be assessed [151]. The oral cavity should be examined for the suitability of oral mucosa. Measurement of BMI will identify obese individuals who are at greater risk of leg compartment syndrome when placed in the lithotomy position for a prolonged time period [152]. Assessing hip mobility is important when considering an exaggerated lithotomy position as some patients may have limited hip flexion due to unresolved orthopaedic problems [149].

*5.2.1 **Further diagnostic evaluation***

5.2.1.1 Patient reported outcome measure (PROM)

The first validated urethral stricture surgery PROM (USS-PROM) was reported in 2011 [153]. It consists of six LUTS questions derived from the International Consultation on Incontinence Questionnaire Male LUTS (ICIQ-MLUTS) module, a LUTS-specific QoL question, the Peeling voiding chart and the EQ-5D to assess overall health-related QoL (HRQoL). The post-operative questionnaire contains an additional two questions to assess overall patient satisfaction. This PROM has been validated in several other languages (German, Spanish, Italian, Dutch, Turkish, Polish, Japanese) and is increasingly used in research studies as well as clinical practice. A further PROM is in development in North America but requires validation [154] (see section 11. Follow-up).

Summary of evidence	LE
A specific urethral stricture surgery patient reported outcome measure was found to have psychometric validity in the assessment of patient-derived benefit from surgical intervention for urethral stricture disease.	2a
Sexual dysfunction is prevalent in patients with urethral strictures and sexual function can be affected by surgical management of urethral stricture.	3

Recommendations	Strength rating
Use a validated patient reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong

5.2.1.2 Urinalysis and urine culture

Urinalysis is an essential component of the work up of patients with LUTS. If infection is suggested, urine culture should be performed to confirm the diagnosis and identify the causative organism and sensitivity to antibiotics. Bacteriuria should be treated prior to surgical intervention to prevent peri-operative sepsis [155] (see section 10. Peri-operative care).

5.2.1.3 Uroflowmetry and post-void residual estimation

A reduced maximum flow rate with a prolonged plateau is characteristic of the constrictive obstruction caused by urethral stricture. However, interpretation of flow patterns is subjective and is not considered a reliable screening tool for the detection of stricture [156]. To overcome this, a statistical model based on uroflowmetry parameters was developed and was found to predict urethral stricture with a sensitivity of 80–81% and a specificity of 77–78% [156]. Uroflowmetry is usually combined with ultrasound (US) estimation of PVR to identify patients with urinary retention who may require emergent bladder drainage. Uroflowmetry parameters can also be used for monitoring patients and in the assessment of treatment response (see section 11. Follow-up).

Urodynamic studies are not indicated in the vast majority of patients with urethral stricture disease. In patients with suspected bladder dysfunction (e.g., severe storage LUTS, history of irradiation or neurological disease), an assessment of bladder function may help surgical decision making and patient counselling. Similarly, when there is concern that flow impairment or increased PVR are due to detrusor underactivity or an acontractile detrusor, a urodynamic study may help predict the likelihood that the patient would need to perform intermittent self-catheterisation (ISC) post-operatively. The only urodynamic parameter found to distinguish a diagnosis of urethral stricture from BPO is urethral closure pressure which is lower in the former due to the constrictive nature of the obstruction (22.07 vs. 28.4 cm H_2O, p=0.0039, r=0.61, BPO vs. stricture) [157].

Summary of evidence	LE
Uroflowmetry pattern interpretation by use of a statistical model was found to be predictive of urethral stricture disease.	3

Recommendation	Strength rating
Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease.	Strong

5.2.1.4 Urethrography

Retrograde urethrography (RUG) has widely been used as the investigation of choice for evaluating the stricture presence, location, length and any associated anomalies (e.g., false passages, diverticula) [158].

The reported sensitivity and specificity of RUG in the diagnosis of strictures is 91% and 72%, respectively [159]. The positive predictive value (PPV) was 89% and the negative predictive value (NPV) was 76% [159]. Most reports suggest that RUG underestimates stricture length [160, 161]. Interpretation of RUG findings by urologists were found to be more accurate at predicting urethral stricture location and length as compared to evaluation by an independent physician [162].

Limitations of RUG include difficulty assessing very distal strictures and assessing the proximal extent of strictures which are too narrow to permit passage of adequate contrast. Combining a RUG with voiding cystourethrography (VCUG) can allow adequate visualisation of the urethra proximal to the stricture and a more accurate assessment of stricture length in (nearly) obliterative strictures, stenoses and gap in pelvic fracture urethral injury (PFUI) [163, 164]. In addition, urethrography provides only a two-dimensional assessment of stricture and the results may be affected by the amount of penile stretch [165], degree of pelvic rotation and patient body habitus [166]. Risks of the procedure include infection, discomfort [157], contrast reaction from intravasation of contrast [167] in addition to the risk of radiation exposure. Urethrographic clamp devices (Brodny, Knutson) are available and were found to be less painful than using the Foley catheter technique [172].

Summary of evidence	LE
Retrograde urethrography is a widely available and easy to perform method of diagnosing and assessing urethral stricture but may underestimate stricture length.	2a
Retrograde urethrography alone is not able to assess stricture length (or gap) in obliterative strictures or stenosis.	2a
Urethrographic clamp devices are less painful than using the Foley catheter technique.	2a

Recommendations	Strength rating
Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine retrograde urethrography with voiding cystourethrography to assess (nearly)-obliterative strictures, stenoses and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak

5.2.1.5 Cystourethroscopy

Cystourethroscopy allows for accurate visual detection of a suspected stricture or can rule out a stricture as cause of obstructive voiding [159]. It can detect narrowing of the urethral lumen before changes in uroflowmetry and symptoms [138]. Cystourethroscopy can also assess the presence of LS or other pathology but cannot usually assess stricture length as the calibre of most cystoscopes is greater than most symptomatic strictures [168]. To overcome this, use of smaller calibre ureteroscopes (6.5 Fr and 4.5 Fr) has been reported [168]. This also allows an assessment of the bladder prior to surgery and may identify other pathology such as bladder stones. Cystourethroscopy is particularly helpful for diagnosing proximal BMS which may be missed on RUG [169].

Retrograde urethroscopy combined with antegrade cystoscopy via the suprapubic tract may be used to evaluate PFUI and plan the surgical approach. It allows an assessment of the length of the defect, the competence of the bladder neck, the involvement of the bladder neck in scarring in addition to identifying the presence of bony spicules or other abnormalities (e.g., fistulae, stones) [170]. Combined retrograde and antegrade cystoscopy was found to provide similar estimates of length of urethral defect in patients with PFUI as combined retrograde and antegrade cystourethrography, but was more likely to detect fistulae, false passages and calculi [170].

Summary of evidence	LE
Cystourethroscopy will reliably detect the presence of a urethral stricture.	3
Combined retrograde urethroscopy and antegrade cystoscopy is more accurate than retrograde and voiding cystourethrography at identifying associated abnormalities such as fistulae, false passages and calculi in patients with PFUI.	3

Recommendations	Strength rating
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak

5.2.1.6 Ultrasound

Ultrasound of the urethra or sonourethrography (SUG) provides a non-invasive three-dimensional assessment of anterior urethral stricture disease; including stricture location, length and the degree of associated spongiofibrosis [171].

Several studies have compared SUG to RUG and cystoscopic or intraoperative findings. Sonourethrograpy was found to be more accurate at diagnosing stricture presence compared to RUG [172, 173]. Sonourethrography was also found to more accurately estimate stricture length (94% correlation with intraoperative findings) than RUG (59% correlation with intraoperative findings) ($p < 0.001$) [161]. A further study showed similar findings and found that the closest correlation for stricture length at operation was for strictures in the penile urethra [160]. Intraoperative sonourethrogram findings have also been found to change the planned reconstructive approach (based on pre-operative retrograde urethrogram) in 19% of men undergoing anterior urethral reconstruction [166]. Sonourethrography incorporating real-time elastography

can provide a qualitative and quantitative assessment of spongiofibrosis [174, 175]. The clinical relevance of assessing the degree of spongiofibrosis pre-operatively remains to be established. Three-dimensional reconstruction of sonographic images is investigational at present [176].

The advantages of SUG are that it can be performed in the outpatient setting, provides information on the degree of spongiofibrosis and its relatively low cost [171]. Limitations of the technique include lower sensitivity for detection of strictures in the bulbar urethra, operator dependency, and the need for urethral distension requiring intraurethral anaesthesia. Sonourethrography requires specialised training in the use of US and is currently not in widespread usage.

Table 5.1: Diagnostic accuracy of sonourethrography compared to other modalities and surgical findings

Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Berne-Mestre *et al*. 2018 [172]	113	Anterior and posterior	RUG, VCUG, surgical findings	SUG more accurate than RUG ($p < 0.05$)	-	-
Ravikumar *et al*. 2014 [173]	40	Anterior and posterior	RUG, VCUG, surgical findings	Anterior: SUG 100% sensitivity, 100% specificity Posterior: SUG 75% sensitivity, 50% specificity.	-	-
Kalabhavi *et al*. 2018 [161]	30	Anterior	RUG, surgical findings	-	-	SUG more accurate than RUG (r_s=0.946, $p < 0.001$ vs. r_s=0.597, p=0.001)
Krukowski *et al*. 2018 [160]	66	Anterior	RUG, surgical findings	-	-	SUG more accurate than RUG (r_s=0.73, $p < 0.001$ vs. r_s=0.55, $p < 0.001$)

N = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

5.2.1.7 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to image PFUIs, posterior urethral stenoses and anterior urethral strictures.

Several studies have compared MRI urethrogram to RUG and intraoperative findings. Magnetic resonance imaging urethrogram was found to be as accurate as RUG at detecting stricture site in anterior urethral strictures [177]. In terms of stricture length both MRI urethrogram and RUG reliably correlated with intra-operative findings [177]. On the other hand, a further study of patients with anterior urethral strictures found MRI urethrogram stricture length to correlate more closely with surgical findings than RUG [178].

In a mixed group of anterior urethral strictures and posterior urethral stenoses, MRI urethrogram was as accurate (sensitivity = 100%, specificity = 91.7%) as combined RUG and sonourethrography (sensitivity = 100%, specificity = 91.7%) at diagnosing strictures [179]. There was no significant difference in the measurement of stricture length [179]. In a further study of patients with posterior urethral stenosis, MRI estimation of stenosis length correlated more closely with operative findings compared to RUG [180]. In patients with PFUI, MRI measurement of pubo-urethral stump angle (angle between long axis of pubis and line between the distal end of the proximal urethral stump and lower border of inferior pubic ramus) was predictive of an elaborated approach on multivariate analysis [181].

Magnetic resonance imaging was also found to be more accurate at diagnosing associated pathologies e.g., diverticula, tumours, fistulae and stones [179]. In cases of fistulation between the urinary tract and pubic symphysis after irradiation for prostate cancer, the fistula tract can be clearly demonstrated on MRI [182]. Other imaging modalities, including computed tomography (CT), may fail to identify the tract and the problem may be misdiagnosed as isolated osteomyelitis of the pubic bone leading to medical management with antibiotics rather than surgical excision [182].

The main advantage of MRI is greater anatomical detail, which is countered by the expense of the procedure and the greater complexity in interpreting images. The technique is not commonly used for routine situations, but it may be helpful in diagnosing associated pathologies which may alter patient management.

Table 5.2: Diagnostic accuracy of MRI compared to other modalities and surgical findings

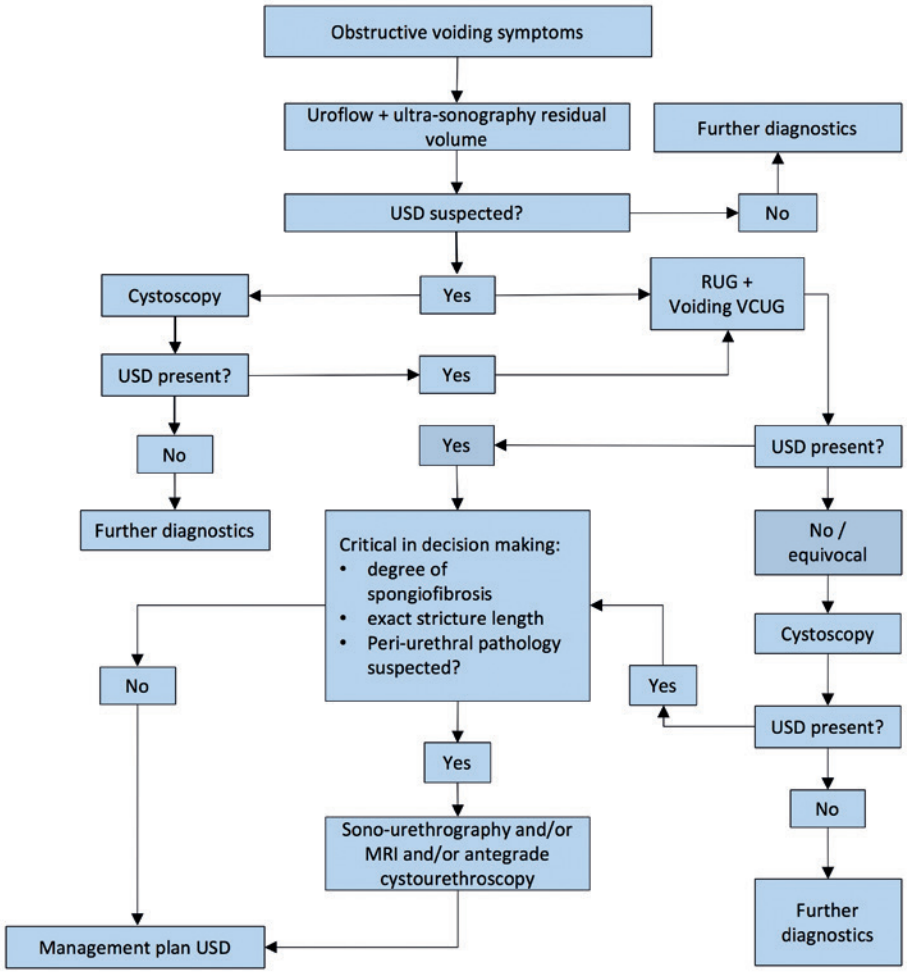
Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Murugesan *et al*. 2018 [177]	32	Anterior	RUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 100% specificity)	-	-
Fath El-Bab *et al*. 2015 [178]	20	Anterior	RUG, Surgical findings	-	-	MRI more accurate than RUG.
El-Ghar *et al*. 2010 [179]	30	Anterior and posterior	RUG + SUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 91.7% specificity)	-	MRI and RUG equivalent.
Oh *et al*. 2010 [180]	25	Posterior	RUG + VCUG, Surgical findings	-	-	MRI more accurate than RUG + VCUG.

MRI = magnetic resonance imaging; n = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

Summary of evidence	LE
Magnetic resonance imaging is more accurate than retrograde urethrography and voiding cystourethrography at determining length of posterior urethral stenoses and can detect alternative associated pathologies e.g., diverticula, fistulae.	2a

Recommendation	Strength rating
Consider MRI urethrography as an ancillary test in posterior urethral stenosis.	Strong

Figure 5.1: Diagnostic flowchart of patients with suspected urethral stricture disease



MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cystourethrogram.

6. DISEASE MANAGEMENT IN MALES

6.1 Conservative options

*6.1.1 **Observation***

A stricture will usually result in diminution in flow once the calibre of the urethral lumen is ≤ 10 Fr [137]. In other strictures (> 10 Fr), the diagnosis is often made by coincidence in asymptomatic patients because of a urologic examination for other reasons (e.g., cystoscopy, need for urethral catheterisation) [137]. Purohit *et al*. performed observation and repeated cystoscopic evaluation of 42 subclinical, incidentally encountered strictures (≥ 16 Fr). After a median follow-up of 23 months, only five (12%) strictures progressed to a low-grade stricture (11-15 Fr). No patient developed symptoms and none of them needed surgical intervention [137]. These patients are candidates for observation although no evidence exist on the long-term evolution of these strictures.

In a series of anatomic stricture recurrence (≤ 16 Fr) after urethroplasty, only 65% of patients were symptomatic [138]. Some asymptomatic patients refused further intervention because they had experienced substantial improvement after their primary urethroplasty. These patients were considered as functional “success” [138]. A multicentric study of the Trauma and Urologic Reconstructive Network of Surgeons observed an important discrepancy between cystoscopic recurrence and need for further intervention [136]. Patients with a large-calibre (> 16 Fr) recurrence had a one and two-year need for intervention rate of 4% and 12%, respectively. Of note, patients with small-calibre (≤ 16 Fr) recurrence had a one and two-year need for intervention rate of only 41% and 49%. Patients who needed intervention had poorer PROMs suggesting clinical symptoms and bother. There is no information on long-term complications in patients with recurrences who did not undergo

intervention. In cases of an asymptomatic stricture recurrence, it might be an option not to intervene but to perform regular follow-up.

Care must be taken about the term “asymptomatic” stricture (recurrence) as patients might conceal their bother and symptoms by different means (not drinking, social avoidance) and might only search for medical help once concealment is no longer tenable [183].

*6.1.2 **Suprapubic catheter***

Radiation-induced urethral strictures are a difficult to treat population as stricture-free rates for urethral reconstruction are lower compared to those in non-irradiated patients [184]. Fuchs et al. evaluated 75 patients who were initially treated by suprapubic diversion for radiation-induced isolated BMS [185]. Only 51% eventually decided to undergo urethroplasty after a mean follow-up period of 25 months. Although there was no significant difference in overall performance status between patients with a chronic suprapubic catheter versus those undergoing urethroplasty, all patients with a poor performance score remained with a suprapubic catheter. Patients with concomitant stress urinary incontinence (SUI) opted more often to keep their suprapubic catheter as the SUI improved in 61% of cases. On the other hand, patients who kept their suprapubic catheter suffered from catheter-related complications in 27% of cases. Urinary diversion by ileal conduit was performed in 30% of patients who remained with a suprapubic catheter while this was only the case in 8% who underwent urethroplasty.

A suprapubic catheter is also an option in frail patients not able to undergo surgery or in patients who do not want (further) urethral surgery and are willing to accept the complications of a suprapubic catheter [186]

Summary of evidence	**LE**
Patients with asymptomatic incidental (> 16 Fr) strictures have a low risk of progression and to develop symptoms.	3
Only half of the patients initially treated with a suprapubic catheter for radiation-induced bulbomembranous strictures will proceed with urethroplasty.	3

Recommendations	**Strength rating**
Do not intervene in patients with asymptomatic incidental (> 16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

6.2 Endoluminal treatment of anterior urethral strictures in males

The ability to treat the majority of strictures by less invasive and time-consuming means, offers obvious benefits particularly when specialist surgical services are not available, or patients simply prefer a more pragmatic immediately available solution.

*6.2.1 **Direct vision internal urethrotomy***

In contemporary practice, direct vision internal urethrotomy (DVIU) is commonly performed as a first line treatment of urethral strictures [187]. It is usually performed under general or spinal anaesthesia in well-resourced countries, but shown to be well tolerated under local anaesthesia with or without sedation [188-190].

6.2.1.1 Indications of “cold knife” direct vision internal urethrotomy

6.2.1.1.1 Direct vision internal urethrotomy for primary stricture treatment

In the only high-level evidence study, Steenkamp *et al*. randomised 210 patients with seemingly comparable non-obliterative strictures at all locations of the urethra to either filiform dilatation vs. DVIU with local anaesthesia on an outpatient basis [191]. They collected objective data with RUG performed at seven follow-up visits (3, 6, 9, 12, 24, 36 and 48 months). This unique study showed that urethral dilatation is equally effective as DVIU but both procedure modalities become less effective with increasing stricture length (see section 6.2.1.1.3.1).

A Cochrane systematic review in 2012 could not identify a single prospective RCT comparing DVIU (or dilatation) with urethroplasty at the anterior urethra [192]. Since then, the randomised Open-label Superiority Trial of Open Urethroplasty Versus Endoscopic Urethrotomy (OPEN) prospectively randomised patients with a recurrent bulbar stricture between open urethroplasty and DVIU but this was for recurrent bulbar strictures only and not as primary treatment [193] (see section 6.2.1.1.2). A retrospective cohort series in boys with bulbar stricture reported a patency rate of 53% for DVIU and 80% for urethroplasty. No statistical analysis was performed and no information on stricture length was available in both cohorts which makes direct comparison hazardous [194].

Patency rates vary considerably between 8% and 77% after DVIU (predominantly without prior urethroplasty) in retrospective cohort studies with minimum follow-up of one year [64, 194-203] (Table 6.1). Median time to recurrence was less than twelve months in most series [64, 195-197, 199-201].

This large variation in patency rate can be in part explained by the heterogeneous nature of the strictures and various definitions of patency used by the authors in these series. Indication to perform DVIU is dependent on various stricture characteristics that are prognostic for a successful outcome.

Table 6.1: Results of DVIU in series with minimum follow-up > 12 months

Study	N	Age (years)	Follow-up (months)	Location	Length (cm)	Previous interventions	TTR (months)	Patency rate (%)
Santucci *et al*. [195]	76	53 (range: 17-100)	18 (range: 1-30)	Bulbar: 37 (49%) Penile: 4 (5%) Penobulbar: 1 (1%) Unknown: 34 (45%)	1.5 (0.2-5)	Primary: 100%	7	8
Pansadoro *et al*. [196]	224	62 (range: 11-90)	98 (range: 60-216)	Bulbar: 142 (63%) Penile: 37 (17%) Penobulbar: 45 (20%)	1.6 (0.1-6.5)	Primary: 88% Recurrent: 12%	< 12 56% -	32 -
Al Taweel *et al*. [199]	301	37 (range: 17-82)	36	Bulbar: 227 (75%) Penile: 50 (17%) Penobulbar: 24 (8%)	1.3 (0.4-4.2)	Primary: 47% Recurrent: 53%	10 -	8.3 -
Barbagli *et al*. [198]	136	37 (IQR: 25-48)	55 (range: 36-92)	Bulbar: 100%	1-2 cm: 45% 2-3 cm: 40% 3-4 cm: 15%	Primary: 100%	25	57
Kluth *et al*. [197]	128	64 (SD: 16)	16 (IQR:6-43)	Penile: 15 (12) Bulbar: 112 (88) Unknown: 1 (1%)	NR	Primary: 66% Recurrent: 34%	8 -	52 -
Pal *et al*. [200]	186	39 (SD:15)	1st DVIU: 58 (SD: 15) 2nd DVIU: 56 (SD: 15) 3rd DVIU: 45 (SD: 15)	bulbar: 100%	NR	Primary: 69% Repeat: 31%	8.5 -	First DVIU: 30 Second DVIU: 23 Third DVIU: 13
Diamond *et al*. [194]	53	14	30 (range: 6-64)	bulbar: 100%	NR	Primary: 100%	23	53%
Launonen *et al*. [201]	34	6 (range: 0-16)	79 (range: 7-209)	Bulbar: 74% Penile: 21% Penobubar: 6%	≤ 2 cm: 85% > 2 cm: 15% -	Primary: 100%	4	26%
Redon-Galvez *et al*. [202]	67	57 (range: 15-91)	40 (range: 12-120)	Penile:9% Bulbar: 64% VUA: 21% Membranous: 6%	≤ 1 cm: 82% > 1 cm: 18%	Primary: 90% Repeat: 10%	< 24 -	63% -
Harraz *et al*. [203]	430	50 (SD: 15)	29 (range: 3-132)	Bulbar: 100%	< 2 cm	NR, prior urethroplasty excluded	NR	58%
Yürük *et al*. [64]	193	65 (SD: 13)	36 (SD: 12)	Bulbar: 100%	< 1 cm: 140 (73%) 1-2 cm: 21 (11%) 2-3 cm: 32 (17%)	0%	87% of recurrence ≤ 3 100% of recurrence ≤ 6	77% -

DVIU = Direct vision internal urethrotomy; IQR = interquartile range; N = number of patients; NR = not reported SD = standard deviation; TTR = time to recurrence.

6.2.1.1.2 Direct vision internal urethrotomy for recurrent strictures and as salvage treatment after failed urethroplasty

In the OPEN trial, a recurrent stricture was defined as at least one previous failed intervention (endoscopic urethrotomy, urethral dilatation, urethroplasty) [204]. The previous intervention was predominantly DVIU. Despite poor recruitment, 108 and 112 patients were randomised to urethroplasty and DVIU respectively in a 24-month study protocol. Both groups had a similar improvement in voiding score symptoms after intervention. However, patients undergoing urethroplasty had a 2.6 higher odds of experiencing an improvement of ≥ 10 ml/s in their maximum urinary flow compared to those undergoing urethrotomy (p=0.001) [204]. Need for re-intervention was observed in 13.8% vs. 25.9% of cases respectively allocated to urethroplasty and DVIU resulting in a 48% lower risk for re-intervention with urethroplasty (HR: 0.52; 95% CI: 0.31-0.89; p=0.017) [204]. Of note, self-dilatation was not considered a re-intervention [204]. Direct vision internal urethrotomy is also used as salvage treatment for recurrent strictures after urethroplasty. Brown *et al*. used DVIU for stricture recurrence (mean length: 4 cm; range: 1.5-7 cm) after excision and primary anastomosis (EPA), buccal mucosa grafts (BMG) urethroplasty and penile skin graft urethroplasty [205]. Patency was obtained in thirteen out of 37 cases (35%) after a single DVIU. After free graft urethroplasty (FGU), a short, veil-like stricture (or "diaphragm") might develop at the distal or proximal end of the graft. Rosenbaum *et al*. used DVIU to a selected cohort of 43 patients with a short (< 1 cm), veil-like stricture after BMG urethroplasty [206]. After a mean follow-up of twelve months, patency rate was 51%. Farrell *et al*. performed DVIU with mitomycin C (MMC) injection in seventeen patients with a short (median 2 cm; interquartile range [IQR] 1-2.5 cm) recurrence after bulbar urethroplasty (no details on technique available) and patency was achieved in twelve (71%) patients [207].

6.2.1.1.3 Predictors of failure of "cold knife" direct vision internal urethrotomy

Several groups tried to identify prognostic factors to predict which patients are most likely to fail initial treatment (Table 6.2).

6.2.1.1.3.1 Stricture length

Stricture length was identified as an important predictive factor for recurrence in several series. For bulbar strictures, Pansadoro *et al*. found a 71% and 18% patency rate for < 1 cm and ≥ 1 cm strictures respectively (p < 0.001) [196]. In the series of Al Taweel *et al*., no patient with a stricture > 1 cm who achieved patency was stricture-free, whereas this was 27% for strictures < 1 cm (p < 0.001) [199]. Barbagli *et al*. reported an estimated five-year patency rate of 71%, 51% and 39% for 1–2 cm, 2–3 cm and 3–4 cm strictures respectively (p < 0.00001)[198]. Pal *et al*. reported no patency in case of strictures > 1 cm [200]. In their prospective study, Steenkamp *et al*. reported that for each 1 cm increase in the length of the stricture the risk of recurrence was increased by 1.22 (95% CI: 1.05-1.43) [191]. In a paediatric series, a 0% patency rate was obtained for strictures > 2 cm [201]. Redon-Galvez *et al*. reported a 25% patency rate for strictures > 1 cm, whereas strictures ≤ 1 cm had a 71% patency rate (p=0.006). This difference remained statistically significant in the multivariable analysis, when adjusted for stricture location (HR: 1.75; p=0.025) [202]. A systematic review of case series calculated a weighted average patency rate of 71.2% vs. 23.2% for strictures less and more than 1 cm respectively (p < 0.0001) [208].

6.2.1.1.3.2 Stricture tightness (calibre)

Pansadoro *et al*. reported a patency rate of 69% and 34% for strictures more than and less than 15 Fr in calibre, respectively (p < 0.001) [196]. Using pre-operative maximum urinary flow (pQ_{max}) as surrogate for urethral calibre, Barbagli *et al*. stratified patients into three groups (pQ_{max} < 5 vs. 5–8 vs. > 8 ml/s) and reported an estimated five-year patency rate of 31% versus 53% vs. 83%, respectively (p < 0.00001) and the importance of pQ_{max} was confirmed in multi-variate analysis [198]. Kluth *et al*. could not confirm the significance of pQ_{max} on the outcome of DVIU [197].

6.2.1.1.3.3 Number of strictures

Pansodoro *et al*. found poorer patency rates in case of DVIU for multiple strictures compared to a single stricture at both the bulbar (18% vs. 50%; p < 0.001) and penile urethra (8% vs. 35%; p=0.013) [196]. Pal *et al*. reported a 0% patency rate in case of multiple strictures whereas this was 35% for a single stricture (p=0.03) [200].

6.2.1.1.3.4 Stricture aetiology

Harraz *et al*. identified idiopathic stricture aetiology as an independent risk factor for failure (HR: 3.11; p=0.035) [203]. On the other hand, stricture aetiology was not a predictive factor in many other series [196, 200, 201].

6.2.1.1.3.5 Stricture location

Several series have reported a better patency rate for bulbar strictures compared to penile stricture or peno-bulbar strictures [191, 196, 199]. Kluth *et al*. could not identify stricture location as an independent prognostic factor but only 12% of patients had a stricture at the penile urethra [197].

6.2.1.1.3.6 Previous interventions

Pansodoro *et al*. [196], Al Taweel *et al*. [199] and Heyns *et al*. [209] found a 0% patency rate after two or more prior failed DVIU, whereas this occured after three and four prior failed DVIUs in the series of Santucci *et al*. [195] and Launonen *et al*. [201], respectively. Kluth *et al*. identified secondary DVIU for a recurrent stricture as an independent risk factor for stricture recurrence (HR=1.78, 95% CI: 1.05-3.03, p=0.032) [197]. Pal *et al*. found significantly better patency rates after a 1st DVIU compared to a 2nd or 3rd DVIU [200].

6.2.1.1.3.7 Other factors

Two series could not identify age, diabetes, hypertension, obesity and smoking as independent predictive factors [197, 198]. However, Harraz *et al*. identified that older age at presentation and obesity are independent predictors of failure after DVIU [203].

In the absence of well-designed, adequately powered multi-centre trials it is difficult to answer the question as to which clinical factors are predictive of failure of DVIU in men with urethral strictures. However, based on the predictors evaluated above and further supported by consensus papers [210-212], one can summarise that the best candidates are previously untreated patients with a single, short (max. 2 cm) bulbar stricture. In a selected group of patients (n=60), a patency rate of 77% was reported for a single, short, primary bulbar stricture with a minimum follow-up of five years [196]. This is confirmed by a more contemporary cohort of patients with untreated short (1-2 cm) bulbar urethral strictures, in which the estimated five-year patency rate was 71% [198].

Table 6.2: Predictors for urethral patency after direct vision internal urethrotomy

Author	Location	Length	Calibre	Multiplicity	Prior DVIU
Pansodoro *et al*. [196]	Penile: 16%	< 1 cm: 71%	< 15 Fr: 34%	Single: 50%	None: 36%
	Penobulbar: 11%	> 1 cm: 18%	> 15 Fr: 69%	Multiple: 16%	1: 6%
	Bulbar: 42%	-	-	-	> 1: 0%
Steenkamp *et al*. [191] / Heyns [209]	RR for recurrence penile vs. bulbar: 1.85 (95% CI: 0.94 to 3.67, p = 0.077)	< 2 cm: 60% (@12 months)	NR	NR	None: 50-60% (@48 months)
	-	2-4 cm: 50% (@12m)	-	-	1: 0-40% (@48 months)
	-	> 4 cm: 20% (@12 months)	-	-	2: 0% (@24 months)
Santucci *et al*. [195]	NR	NR	NR	NR	0: 8%
	-	-	-	-	1: 6%
	-	-	-	-	2: 9%
	-	-	-	-	> 2: 0%
Al Taweel *et al*. [199]	Bulbar: 11%	< 1 cm: 27%	NR	NR	0: 12.1%
	Penile: 0%	1-2 cm: 0%	-	-	1: 7.9%
	Penobulbar: 0%	> 2 cm: 0%	-	-	> 1: 0%
Barbagli *et al*. [198]	NA	1-2 cm: 71% (@60 months)	pQ_{max} < 5 ml/s: 31%	NA	0: 62%
	-	2-3 cm: 51% (@60 months)	pQ_{max} 5-8 ml/s: 53%	-	1: 37%
	-	3-4 cm: 39% (@60 months)	pQ_{max} > 8 ml/s: 83%	-	-
Kluth *et al*. [197]	Location no predictor	NR	pQ_{max} no predictor	NR	0: 60%
	-	-	-	-	≥ 1: 39%
Pal *et al*. [200]	NA	< 1 cm: 45%	NR	Single: 35%	0: 30%
	-	1-1.5 cm: 0%	-	Multiple: 0%	1: 23%
	-	> 1.5 cm: 0%	-	-	2: 13%

Launonen [201]	Bulbar: 76%*	< 2 cm: 83%*	NR	NR	0: 26%
	Penile: 71%*	> 2 cm: 0%*	-	-	1: 33%
	-	-	-	-	2: 26%
	-	-	-	-	3: 11%
	-	-	-	-	4: 0%
Redon-Galvez [202]	NR	≤ 1 cm: 71%	NR	NR	NR
	-	> 1 cm: 25%	-	-	-

DVIU = Direct vision internal urethrotomy; NA = not applicable; NR = not reported.
**patency rates are reported after repetitive treatments.*

6.2.1.2 Indications of "hot-knife" direct vision internal urethrotomy

6.2.1.2.1 Laser urethrotomy

Lasers available for urological applications including Neodymium:YAG, Argon, Holmium:YAG, Potassium titanyl phosphate (KTP) and Tm:Yag and have been used for the treatment of urethral strictures. A systematic review identified four RCTs comparing laser urethrotomy and the "cold knife" urethrotomy. All studies were limited by short-term outcome evaluation and none of these four studies specified the results based on the location of the stricture. Two of these studies reported specific recurrence rates and meta-analysis showed a risk ratio (RR) for recurrence of 0.55 (95% CI: 0.18-1.66; p=0.29), 0.39 (95% CI: 0.19-0.81; p=0.01) and 0.44 (95% CI: 0.26-0.75; p=0.003) in favour of laser urethrotomy after three, six and twelve months respectively [213]. Jin *et al*. performed a systematic review including 44 case series on laser urethrotomy or "cold knife" DVIU [208]. This included nineteen articles on laser urethrotomy and 25 articles on "cold knife" DVIU. The overall weighted average stricture-free rate was 74.9% (371/495) and 68.5% (1874/2735) for laser vs. "cold knife" DVIU, respectively (p=0.004). Although significant, the results must be interpreted with caution because of heterogeneity and because no details are provided on follow-up duration. Specifically looking at first DVIU, laser and "cold knife" DVIU obtained a stricture-free rate of 58.6% and 42.7% respectively and the difference was no longer statistically significant (p=0.09). At the bulbar urethra, laser and "cold knife" DVIU yielded a stricture-free rate of 52.9% and 60%, respectively (p=0.66) [208].

After publication of this systematic review, the EAU Guideline Panel scope search identified two additional RCTs [214, 215] and one retrospective cohort series [216]. In the RCT of Yenice *et al*., patients with a primary, bulbar stricture were randomised either to "cold knife" DVIU (n=29) or holmium:YAG laser urethrotomy (n=34). After twelve months follow-up, no significant difference in patency rate was identified (79% for "cold knife" DVIU vs. 68% for laser urethrotomy, p=0.3) [215]. In their RCT, Chen *et al*. reported a better patency rate after one year with laser (n=24) compared to "cold knife" (n=22) DVIU (respectively 88% vs. 18%; $p < 0.05$). However, after two years the benefit for laser disappeared and after five years both techniques showed a low patency rate: 9% for "cold knife" DVIU vs. 12% for laser DVIU ($p > 0.05$) [214]. In both these RCTs, operation time was slightly but significantly longer with laser DVIU as compared to "cold knife" DVIU [214, 215]. Holzhauer *et al*. evaluated in a retrospective comparative study "cold knife" (n=127) with laser (n=65) DVIU at a mean follow-up of sixteen and eighteen, respectively. They reported patency rates of 42% for "cold knife" DVIU vs. 31% for laser DVIU (p=0.1) [216].

6.2.1.2.2 Plasmakinetic (bipolar) urethrotomy

Cecen *et al*. conducted an RCT comparing plasmakinetic with "cold knife" DVIU (n=136) [217]. They reported patency rates for plasmakinetic and "cold knife" urethrotomy at nine months in respectively 86% and 70% of cases (p=0.025). At eighteen months, patency rates for plasmakinetic and "cold knife" urethrotomy were 63% and 67%, respectively (p=0.643) [217]. A prospective cohort study on primary strictures < 2 cm reported a patency rate at twelve months in 23/30 (77%) cases for plasmakinetic DVIU vs. 19/30 (63%) cases with "cold knife" DVIU (p=0.04) [218]. A retrospective case series (n=27) reported a 74% patency rate for short (1-2.5 cm) strictures after a mean follow-up of fourteen months [219]. They reported negligible blood loss during the procedure and no post-operative incontinence.

Based on the conflicting results described above and taking into account the heterogeneity of series and absence of long-term follow-up, overall, the available studies do not support the efficacy of one technique of DVIU over another. Given the similar complication rates between techniques (see section 6.2.1.3), no recommendation can be made in favour of one technique over another.

6.2.1.3 Complications of direct vision internal urethrotomy

6.2.1.3.1 Complications of "cold knife" direct vision internal urethrotomy

An overall complication rate of 6.5% was reported in a systematic review of Jin *et al*. based on twelve articles including 1,940 patients [208] (Table 6.3).

Notably, erectile dysfunction (ED) was reported in 5.3% of cases in this review [208]. In addition, Graversen *et al*. reported ED in eleven out of 104 (10.6%) patients [220]. This risk appears higher in strictures located in the penile urethra and, in addition to the poor patency rates, the use of DVIU in the penile urethra must be discouraged [212, 220].

6.2.1.3.2 Complications of "hot knife" direct vision internal urethrotomy

The systematic review of Jin *et al*. reported a total complication rate of 11.8% (39/330) [208] (Table 6.3).

6.2.1.3.3 Complications of "cold knife" versus "hot knife" direct vision internal urethrotomy

In a systematic review of RCTs comparing "cold knife" DVIU vs. laser DVIU, only 1/4 series reported complications [213]. In the laser group, an 8.9% complication rate was found due to contrast extravasation to the perineum and stricture recurrence. For the "cold knife" DVIU, a 15.5% complication rate was reported related to bleeding [213]. Two later RCT's reported similar rates of urinary extravasation [214, 215] and urinary incontinence (UI) [214] with both techniques.

The systematic review of retrospective case series of Jin *et al*. found no significant differences in the incidence rates of UI, urinary extravasation and UTI between laser and "cold knife" DVIU [208]. However, urinary retention and haematuria were more frequent with laser compared to "cold knife" DVIU [208]. Conversely, In the series of Yenice *et al*. haematuria was only reported after "cold knife" DVIU but not after laser DVIU (p=0.6) [215] (Table 6.3).

Table 6.3: Complications after "cold knife" DVIU versus laser DVIU

Study/Complication	"Cold knife" DVIU (%)	Laser DVIU (%)	p-value
Jin *et al*. [208]			
Urinary extravasation	2.9	3.1	0.938
Urinary incontinence	4.1	2.1	0.259
Urinary tract infection	2.1	2.7	0.653
Urinary retention	0.4	9	< 0.0001
Haematuria	2	5.2	0.034
Epididymitis	0.5	NR	NA
Fever	2.3	NR	NA
Scrotal abscess	0.3	NR	NA
Erectile dysfunction	5.3	NR	NA
Urinary tract irritation	NR	11.4	NA
Urinary fistula	NR	1.5	NA
Dysuria	NR	5.1	NA
Yenice *et al*. [215]			
Urinary extravasation	0	2.9	0.6
Haematuria	10	0	
Chen *et al*. [214]			
Urinary extravasation	9.1	4.2	0.5
Urinary incontinence	4.5	4.2	

DVIU = direct vision internal urethrotomy; NA = not applicable; NR = not reported.

6.2.1.3.4 Complications of direct vision internal urethrotomy versus dilatation

A Cochrane review found no significant differences for overall intra-operative complications (single dilatation vs. DVIU respectively 14% vs. 11%; RR: 0.75; 95 CI: 0.36-1.55) nor for individual complications (difficulty urinating, haematuria, false passage, pain, knotting/breaking/bending filiform leader) [191, 192]. The low rate of false passage for both DVIU and dilatation (respectively 0.96 and 0.94%) might be explained by the systematic use of a filiform leader in both groups which was inserted endoscopically in the dilatation group followed by coaxial dilatators [191, 192].

A small retrospective study comparing balloon dilatation (n=31) with DVIU (n=25) showed less urethral bleeding (6.5 vs. 32%; p=0.017) and UTI (3.2 vs. 24%; p=0.037) with balloon dilatation [221].

Apart from acute peri-operative complications described above, the stricture length was reported to increase after DVIU treatment requiring complex urethral reconstruction, but the authors of this retrospective study

clearly state the limitations of the study design in the absence of consistent baseline investigations [195]. Other authors mention that repeat urethral manipulations (DVIU and/or dilatation) can increase stricture complexity and delays time to urethroplasty [222, 223].

6.2.1.3.5 Complications of "cold knife" direct vision internal urethrotomy versus urethroplasty

The OPEN-trial reported adverse events of any type in 61% and 26.1% after urethroplasty (all types) and DVIU respectively [204]. In the urethroplasty group, mouth pain (related to oral mucosa graft [OMG] harvesting) and wound infection was noted as complication in respectively 14.6% and 4.9% of cases. Erectile dysfunction was 4.9% and 2.6% after urethroplasty and DVIU respectively. Serious adverse events were reported in 8.5% and 8.7% after urethroplasty and DVIU respectively [204].

Summary of evidence	LE
Direct vision internal urethrotomy performs poorly in penile strictures. Direct vision internal urethrotomy at the penile urethra might provoke venous leakage from the corpora cavernosa with subsequent risk of erectile dysfunction.	1b
Increased stricture length is associated with higher risk of failure of DVIU.	1b
In selected patients with a primary, single, short (< 2 cm) and non-obliterative bulbar stricture, a five-year stricture-free rate of up to 77% can be expected.	3
Direct vision internal urethrotomy has a stricture-free rate of 51-71% if performed for a short (< 2 cm) recurrent stricture after prior bulbar urethroplasty.	3
There is conflicting evidence that "hot knife" (laser, plasmakinetic) DVIU would be superior compared to "cold knife" DVIU after more than one year of follow-up.	1a

Recommendations	Strength rating
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (> 2 cm) segment strictures.	Strong
Perform DVIU/dilatation for a primary, single, short (< 2 cm) and non-obliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty.	Weak
Use either "hot" or "cold knife" techniques to perform DVIU depending on operator experience and resources.	Weak

*6.2.2 **Single dilatation***

6.2.2.1 Modalities of dilatation and results

Dilatation can be done in the office, under local anaesthesia and without complex resources [211, 224].

With dilatation, the urethral mucosa at the stricture site is stretched and the scarring is disrupted. This is opposed to DVIU where the stricture is incised. However, both treatment modalities use the same principle to achieve urethral patency: a breach of the urethral mucosa at the site of the stricture in which re-epithelialisation should occur faster than wound contraction [192].

When dilators are used to dilate bulbar urethral strictures, considerable experience is required to avoid accidental perforation of the urethra at the level of the stricture. In order to reduce the risks (esp. false passage, spongiosal perforation, urethral bleeding) of "classic" blind dilatation with rigid sounds [224], other strategies have been developed and evaluated in which the dilatation is visually controlled:

- endoscopic/fluoroscopic guidewire placement and progressive dilatation with Amplatz renal dilators [224, 225];
- endoscopic/fluoroscopic guidewire placement and balloon dilatation [221, 226];
- endoscopic/fluoroscopic guidewire placement and S-curved coaxial dilators [227].

Although no direct comparative studies of blind vs. visually controlled dilatation are available, several studies have reported a low complication rate with visually controlled modifications of dilatation. The recurrence rate with short follow-up largely varies between 7.7-64.5% (Table 6.4). Chhabra *et al*. identified focal/short (< 1.5 cm) strictures and strictures at the bulbar urethra as predictors for a favourable outcome [226].

Table 6.4: Results of visually controlled dilatation

Study	Technique	N	FU (mo)	recurrence	Definition of failure	Complications			
						Haematuria	False passage	Procedural failure	UTI
Akkoc *et al*. [224]	Amplatz	26	12-21	2 (7.7%)	Need for additional intervention	3 (11.5%)	0 (0%)	NR	NR
Chhabra *et al*. [226]	Balloon + ISD (permanent)	144	24 (3-52)	21 (15.6%)	Need for additional intervention	NR	0 (0%)	3 (2.1%)	14 (9,7%)
Kallidonis *et al*. [227]	Coaxial S-curved	310	12	90 (33%)	No recurrence @1 yr with maximum one additional procedure	11 (3.5%)	0 (0%)	7 (2.2%)	33 (10.6%)
Nomikos *et al*. [225]	Amplatz + DVIU + ISD (1 yr.)	34	12	8 (23.5%)	Stricture recurrence on urethroscopy/ urethrography	2 (5.8%)	NR	NR	3 (8.8%)
Yu *et al*. [221]	Balloon	31	15 (5-36)	20 (64.5%)	Need for subsequent urethroplasty	2 (6.5%)	0 (0%)	NR	1 (3.2%)

DVIU = direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; mo = months; N = number of patients; NA = not applicable; NR = not reported; UTI = urinary tract infection; yr = year.

6.2.2.2 Effectiveness of dilatation compared with direct vision internal urethrotomy

A systematic review identified only one prospective RCT comparing dilatation with DVIU and failed to detect any differences [191, 192]. In a small (n=56) retrospective cohort study, the three-year estimated stricture recurrence-free survival was 35.5% and 28% for respectively balloon dilatation and DVIU (p=0.21) [221].

At present, there is lack of evidence to support the claim that dilatation is superior to DVIU (or *vice versa*) and therefore, the indications for single dilatation are the same as for DVIU.

Repetitive dilatation/DVIU with curative intent (see also section 6.2.1.1.3.6 Previous interventions) should be avoided as no long-term freedom of recurrence can be expected [211] and because of the significant risk of increasing stricture length and complexity [222, 223] and prolonging the time to urethroplasty (which has better patency rates rates) [223].

Summary of evidence	LE
Visually controlled dilatation after endoscopic or fluoroscopic guidewire placement has a low complication rate.	3
Repetitive dilatations/DVIU have no long-term freedom of recurrence and increase stricture complexity.	1b

Recommendations	Strength rating
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (> 2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.	Strong

6.2.3 ***Post-dilatation/direct vision internal urethrotomy strategies***

Several strategies have been developed and evaluated to prevent wound contraction, improve the stricture-free rate and time to stricture recurrence after dilatation or DVIU.

It is noteworthy that these strategies tend to stabilise the stricture rather than to keep the patient stricture-free and the reported outcomes should be understood in this respect.

6.2.3.1 Intermittent self-dilatation

6.2.3.1.1 Results

A systematic review identified six randomised and quasi-randomised trials comparing ISD with no ISD with a follow-up between eight and 24 months [228]. Stricture recurrence was reduced in men performing ISD (85/197, 43%) vs. those who did not (128/207, 62%) (RR: 0.70 [0.48-1.00]; p=0.05). There was significant heterogeneity and the quality of included studies was very low, which led the authors to conclude there is uncertainty about the estimate [228]. This review found no significant difference in adverse events between ISD and no ISD (RR: 0.60 [0.11-3.26]; p=0.56) [228]. One trial containing 48 patients found no significant difference in six vs. twelve months duration of ISD (RR: 0.67 [0.12-3.64]) and another trial (n=59) found no significant difference from using a low-friction hydrophylic vs. a polyvinyl chloride catheter (RR: 0.32 [0.07-1.40]) [228]. Other studies have been published after this systematic review of 2014. Chhabra *et al*. reported that patients complying with ISD after dilatation had a lower need for re-intervention than those who did not, 12.3% vs. 20.5% respectively (p=0.2) [226]. After a mean follow-up of 25 months, Greenwell *et al*. found a need for subsequent intervention in 13/31 (42%) men performing ISD vs. 47/95 (49%) who did not (p=0.46). The number of reoperations in patients with need for subsequent intervention was lower in the group performing ISD vs. those who did not (2.6 vs. 3.4). No major complications were reported in both groups [229].

6.2.3.1.2 Complications

The potential benefit of ISD in stabilising the stricture must be balanced against the drawbacks. Commonly reported complications are urethral bleeding (7.1%) [230] and UTI/epididymitis (4.7%-18.1%) [231, 232]. A multicentric prospective study (n=85) reported that respectively 35% and 26% of patients had moderate to severe difficulties in catheterisation and respectively 32% and 17% of patients suffered moderate to severe pain while performing ISD. This had a serious impact on QoL which was rated moderate and poor in respectively 32% and 55% of patients [30]. Younger age was identified as predictor for poor QoL, and QoL was more impaired in proximal stricture location (posterior and bulbar) [30]. In a study of 286 patients (mainly > 60 years old) performing ISD, 20% experienced problems with ISD and 33% had at least one infection annually. After a mean follow-up of 58 months 67% still continued with ISD [233]. Khan *et al*. reported eight “drop-outs” of 30 (26.7%) men randomised to ISD [232]. Of these eight “drop-outs”, two were unable to perform ISD and one stopped because of pain.

As mentioned above, repetitive dilatation (including ISD) increases stricture complexity and delays time to urethroplasty [222, 223].

6.2.3.1.3 Intermittent self-dilatation combined with intra-urethral corticosteroids

To delay wound contraction at the stricture site, intra-urethral corticosteroids (as a catheter lubricant) have been used to improve the results of ISD. In 2014, a systematic review identified three prospective randomised controlled trials comparing ISD and local steroid (triamcinolone) ointment vs. ISD without local steroid ointment [234]. These three studies included a total 67 and 68 patients randomised to local steroid, or not, with a follow-up ranging between twelve and 36 months. There were fifteen (22.4%) recurrences in the steroid group and 25 (36.7%) in the control group (OR: 0.51; 95 CI: 0.24-1.10; p=0.09) [234]. Time to recurrence was longer in the steroid group vs. the control group (weighted mean difference = 0.29 [0.08-1.00]; p=0.05). There were no difference in adverse events between groups [234].

Since 2014, two additional RCTs have been published. Ergun *et al*. evaluated patients after DVIU for primary short (< 2 cm), bulbar (82%) or posterior (18%) strictures that were further randomised between ISD (n=30) and ISD + triamcinolone ointment (n=30) for six weeks. Stricture recurrence rate after 24 months was not significantly different between ISD and ISD + triamcinolone (respectively 33.3 and 30%) [235]. On the other hand, Regmi *et al*. found a lower stricture recurrence rate (22% vs. 46%, p=0.04) in patients performing ISD + triamcinolone (n=27) vs. ISD alone (n=28) [236]. In this study, median time to recurrence was 7.4 ± 4.5 months vs. 11.9 ± 3 months in respectively ISD alone and ISD + triamcinolone (p=0.16). Both studies reported no complications related to ointment of triamcinolone [235, 236].

In a small (n=28) cohort with LS-related strictures, an intra-urethral steroid regimen was successful (no need for subsequent escalation of therapy) in 25 (89%) patients after a mean follow-up of 25 months [150]. This regimen consisted of applying clobetasol cream 0.05% as lubricant on a calibration device (10-16 Fr catheter or dilator) twice a day during a minimum of two months. As most of these patients further continued with instillation of steroids on a calibration device, this high “success” rate must be viewed with caution and should be considered as a stabilisation of the stricture rather than a cure. Eventually, twelve (42.8%) patients could reduce the interval of instillation/dilatation and three (10.7%) of them could finally stop the treatment [150].

Summary of evidence	LE
Stricture recurrence was reduced in men performing ISD versus those who did not.	1a
Intra-urethral corticosteroids in addition to ISD delays the time to recurrence.	1a

Recommendations	Strength rating
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/direct vision internal urethrotomy if urethroplasty is not a viable option.	Weak
Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak

6.2.3.2 Intralesional injections

The rationale of adjuvant intralesional injections is to reduce fibroblast proliferation and excessive urethral scaring [210].

6.2.3.2.1 Steroids

A systematic review in 2014 identified five studies comparing intra-urethral submucosal steroid injection vs. no intra-urethral submucosal steroid injection after DVIU, of which two were RCTs [234]. Meta-analysis of these two RCTs with 57 and 58 patients in, respectively, the steroid and control group showed no statistical difference in recurrence rate (OR: 0.53 [0.25-1.13]; p=0.10). Time to recurrence was significantly longer in the steroid group (weighted mean difference = 4.43; 95% CI: 2.77–6.09, p < 0.00001). There were no significant differences regarding adverse events (infection, bleeding, extravasation) between both groups (weighted mean difference = 1.59; 95% CI: 0.71–3.58, p=0.26).

6.2.3.2.2 Mitomycin C

An RCT (n=40) by Moradi *et al*. reported that MMC hydrogel significantly reduced recurrent stricture formation (10% with MMC vs. 50% without MMC; p=0.001) at one year in patients with anterior strictures < 1.5 cm and no or mild spongiofibrosis on US [237]. The authors reported no significant complications related to MMC injection [237]. Another RCT (n=151) with eighteen months follow-up in predominantly bulbar strictures reported a stricture-free rate of 86% and 63% after DVIU with and without MMC, respectively (p=0.002) [238]. The mean stricture length was less than 2 cm in both groups. No significant complications, such as necrosis of the urothelium, extravasation, or systemic absorption, were recorded in the MMC group [238].

Farrell *et al*. conducted a retrospective study in 44 patients with recurrent bulbar and BMS with a median stricture length of 2 cm (IQR: 1-2.5 cm) [207]. They reported patency in 75% after a median follow-up of 26 months. No long-term complications attributed to MMC were observed.

In a prospective case-series (n=103), Kumar *et al*. evaluated adjuvant intralesional injections of a cocktail of triamcinolone, MMC and hyaluronidase after DVIU for predominantly (78%) bulbar strictures with a median follow-up of fourteen months. A stricture-free rate of 81% was reported and none of the patients suffered local or systemic side effects related to the injection [239].

Despite the encouraging results reported with MMC, the use of MMC in urethral stricture management is still off-label and not widespread. Severe complications with MMC injection are possible. Redshaw *et al*. reported in a multi-institutional series that 4/55 (7%) patients experienced serious complications with osteitis pubis, rectourethral fistula and necrosis of the bladder floor when MMC was injected after endoscopic incision to treat BNS [240]. Given this safety concern and in the absence of well-conducted and adequately powered RCTs, MMC adjuvant to DVIU should only be used in the framework of a clinical trial.

See supplementary Table S6.1 for further information.

6.2.3.2.3 Platelet rich plasma

Rezaei *et al*. conducted an RCT comparing DVIU + platelet rich plasma (PRP) (n=44) vs. DVIU + saline (n=43) in primary, bulbar strictures < 1.5 cm in length [241]. The two-year stricture-free rate was 78% vs. 56% after DVIU with or without PRP, respectively (p=0.034). Complications were frequent but not significantly different between both groups (DVIU + PRP: 70%; DVIU + saline: 79%). All complications (urethral bleeding, haematuria, urethral pain, pelvic pain, urinary leakage and genitoperineal swelling) were classified as grade 1 according to the Clavien-Dindo system. Further validation of this treatment is needed before general clinical implementation.

Summary of evidence	LE
Intralesional injections after DVIU might improve stricture-free rates on the short-term compared to DVIU alone. Experience is limited and the use of these drugs are off-label.	1a

Recommendation	Strength rating
Do not use intralesional injections outside the confines of a clinical trial.	Weak

6.2.3.3 Urethral stents

Urethral stents are designed with the aim to oppose wound contraction after dilatation or DVIU [242, 243]. Stent insertion is a short procedure (< 60 minutes) that can be done under local or spinal anaesthesia as "one-day" surgery [242, 244, 245]. Urethral stents are classified as permanent or temporary (removable, after six to twelve months).

6.2.3.3.1 Results

Permanent stainless-steel mesh stents are no longer commercially available.

An RCT comparing dilatation/DVIU only vs. dilatation/DVIU followed by temporary stent insertion for bulbar strictures reported a significantly longer stricture-free survival time in favour of dilation/DVIU followed by stent (median 292 vs. 84 days; $p < 0.001$) [246]. Only 20.6% of patients treated with a stent developed a recurrent stricture within one year vs. 82.8% in the control group. These results are corroborated by a prospective series of Wong *et al*. who found a median stricture-free survival of two months after DVIU alone vs. 23 months after DVIU followed by temporary (three months) stent for bulbar strictures [243].

Failure and need for re-intervention are frequent (30-53%) and are usually because of stricture recurrence, stent encrustation, stent migration and urethral hyperplasia. Other complications include recurrent UTI, recurrent haematuria and genito-perineal pain (Table 6.5). Although stents are mainly used to treat bulbar strictures, they have been used for posterior stenoses as well. Stents used in the posterior urethra have a high risk (82%-100%) of causing UI and this is most pronounced in patients with previous irradiation and/or strictures extending into the membranous or bulbar urethra [247]. In the bulbar urethra, the risk of UI is higher if stent placement is adjacent to the external sphincter [248]. The use of stents in the penile urethra is anecdotal. Jung *et al*. reported stent failure in 4/7 (57%) patients with a penile stricture after a mean follow-up of eight months. Of those patients who failed, no patient with distal or pan-penile strictures was rendered stricture-free [249]. In their series, stricture recurrence after stenting of the penile urethra was significantly higher when compared to the bulbar urethra [249]. Although no direct comparison is available, temporary stents tend to have fewer and less severe complications compared to permanent stents (Table 6.7).

Table 6.5: Failure rate and complications associated with urethral stents

Study	Type of stent	Duration	N	FU (months)	Stricture length (cm)	Stricture location	Previous interventions	Failure rate	Defintion failure	Complications						
										UTI	haematuria	stent encrustation/ stone formation	stent migration	urethral hyper-plasia	Local pain	UI
Abdallah *et al*. [242]	Thermo-expandable nitinol	Temporary	23	17 (6)	3.6 (1.2)	Bulbar	DVIU/ urethroplasty: all	12 (52%)	Need for re-intervention	4 (17%)	3 (13%)	3 (13%)	5 (22%)	2 (8%)	6 (26%)	NR
Jordan *et al*. [246]	Thermo-expandable nitinol	Temporary	63	12	2.7 (1.6)	Bulbar	DVIU only: all	28 (44%)	Inability to pass 16 Fr cystoscope	31 (49%)	10 (16%)	3 (4.7%)	8 (13%)	NR	19 (30%)	12 (19%)
Temeltas *et al*. [245]	Polymer-coated	Temporary	28	29 (7-46)	1.9 (0.5-3.5)	Bulbar	DVIU only: all	10 (36%)	Stricture recurrence on urethroscopy/ graphy, Q_{max} < 15 ml/s, UTI	NR	NR	1 (3.6%)	3 (11%)	NR	0 (0%)	NR
Wong *et al*. [243]	Thermo-expandable nitinol	Temporary	22	23 (9-31)	2.4 (1-4.5)	Bulbar	DVIU only: all	7 (32%)	Inability to pass 17 Fr cystoscope, Q_{max} < 10 ml/s or recurrent obstructive symptoms	0 (0%)	NR	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	NR
Atesci *et al*. [244]	Thermo-expandable nitinol	Permanent	20	144 (120 -192)	2.5 (0.5-5.5)	Bulbar	DVIU/ urethroplasty: all	6 (30%)	Need for re-intervention	NR	NR	4 (20%)	2 (10%)	0 (0%)	8 (40%)	1 (5%)
Sertcelik *et al*. [248]	Thermo-expandable nitinol	Permanent	47	101 (84-125)	2 (0.5-5)	Bulbar (45), bulbomem-branous (2)	urethroplasty (19%)/ DVIU (64%)/ railroading (17%)	22 (47%)	Need for re-intervention	NR	NR	12 (26%)	2 (4%)	7 (15%)	20 (43%)	9 (19%)
Erickson *et al*. [247]	Self-expandable super alloy mesh	Permanent	38	28 (30)	3 (1.7)	Posterior (prostate cancer related); VAUS 24; prostatic urethra (irradition) 14	DVIU only: all	20 (53%)	Need for re-intervention	7 (18%)	3 (8%)	6 (16%)	NR	NR	6 (16%)	31 (82%)

DVIU = direct vision internal urethrotomy; FU = follow-up; N = number of patients; NR = not reported; UI = urinary incontinence; UTI = urinary tract infection; VUAS = vesico-urethral anastomotic stricture; Q_{max}= maximum flow rate

6.2.3.3.2 Treatment of stent failure

In the case of stent failure, subsequent urethroplasty (usually with stent removal) is possible, but this urethroplasty is very likely to be more complex than it would have been had it been performed initially [250-252]. Due to the fact that the stainless-steel wires are fully embedded into the urethral wall, over time the urethral spongiosum is severely damaged. Horiguchi *et al*. found that a history of urethral stenting was an independent significant predictor of increased stricture complexity (OR: 13.7, 95% CI: 1.7-318.3, p=0.01) and need for more complex urethroplasty (OR: 6.9, 95% CI: 1.1-64.5, p=0.04) [222]. The majority (62%) of patients in this study had a permanent stent and tend to be difficult to remove because they are epithelialised, usually within six months [222]. The type of urethroplasty required depends on the length of the stricture and quality of local tissues [251]. In the majority of cases, it is possible to preserve the urethral plate and to perform a one-stage substitution urethroplasty [250, 251, 253]. The patency rates after different types of urethroplasty vary greatly between 16.7-100% [250-253] and this variation probably reflects variation in complexity of the stricture, rather than that the superiority of one technique of urethroplasty over another (for further information see supplementary Table S6.2). Due to these limitations, the use of stents should be avoided if subsequent urethroplasty is considered [242, 252]. Urethral stents are not a first-line treatment for urethral strictures but can be considered in co-morbid patients who have a recurrent stricture after DVIU/dilatation and are unable to have more complex urethroplasty or who refuse urethroplasty [242, 246, 247].

Summary of evidence	LE
Permanent urethral stents have a high complications and failure rate and make subsequent urethroplasty more challenging if they fail.	3
Stents have a higher failure rate in the penile urethra.	3
Temporary stents after DVIU/dilatation at the bulbar urethra prolong time to next recurrence compared to DVIU/dilatation alone.	1b

Recommendations	Strength rating
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after direct vision internal urethrotomy to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

6.3 Open repairs (urethroplasty): site and aetiology (clinical scenario) treatment options

*6.3.1 **The role of urethroplasty in the management of penile urethral strictures***

Due to the specific aetiology and the associated problems, strictures related to failed hypospadias repair and LS will be discussed separately. However, many series reporting on the outcome of penile strictures have a mixed aetiology also including failed hypospadias repair and/or LS [254, 255]. Due to their specific location, distal penile strictures will be discussed separately.

6.3.1.1 Staged augmentation urethroplasty

Classically called “two-stage” urethroplasty, this approach may become a multi-stage urethroplasty as revision (usually due to graft contracture) after the 1st stage has been reported in 0-20% of cases [255-258]. Therefore, the term “staged” should be used instead [259]. Revision rates before 2nd stage were 0-20%, stressing that a two-stage urethroplasty might become a multi-stage urethroplasty. In general, reconstructive urologists tend to follow this approach in men with more complex urethral stricture disease (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, poor quality of the urethral plate). An interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully [260-262].

A systematic review by Mangera *et al*. has shown an average patency rate of 90.5% with the use of all types of grafts for staged penile urethroplasties with an average follow-up of 22.2 months [263]. Patency rates of staged OMG urethroplasty in specific locations vary between 73.3 and 100% [254, 255, 257, 258]. Post-operative urethrocutaneous fistula (UCF) rates were 17.2% and 2.6% in the studies of Ekerhult *et al*. and Joshi *et al*., respectively, and either not reported or unclear in the remaining studies [254, 255].

6.3.1.2 Single-stage augmentation urethroplasty

Single-stage urethroplasty offers the option for reconstruction of the stricture without the need for multiple operations, the associated peri-procedural risks and the cosmetic and functional implications that by definition follow the first part of staged urethroplasties [264-266]. There is some evidence to suggest a considerable

number of patients (50% or more in some studies) who were offered 1st stage urethroplasty never returned for the 2nd stage because they were either satisfied with their functional status after the 1st stage (this particularly applied to older men or patients with multiple failed procedures in the past) or they were disappointed with the need for another operation [264, 265].

In the systematic review of Mangera *et al*., overall patency rate for all types of single-staged graft urethroplasties is 75.7% with an average follow-up of 32.8 months [263].

The patency rate for different one-stage techniques in specific are:

- dorsal OMG (n=190): 70-100% [258, 267-272];
- ventral OMG (n=47): 55-92.6% [273, 274];
- dorsal + ventral OMG (n=10): 80% [271];
- double (dorsal + ventral) onlay with penile/scrotal skin graft /OMG (n=14/8/4): 88.5% [268];
- dorsal penile skin graft (n=44): 62-78% [268, 269];
- penile skin flap (n=315): 67-100% [268-270, 275, 276].

No high-level evidence exists to state that one technique is superior to another but it seems that the dorsal graft location is more commonly used compared to the ventral one. Mangera *et al*. reported that the patency rate was better with OMG compared to other grafts (mainly penile skin) [263]. Jiang *et al*. showed that combined (dorsal + ventral) BMG onlay had significantly better stricture-free rates for penoscrotal strictures (patency rate 88.9% vs. 60.9% with single-onlay approach); however, follow-up was significantly shorter in the double-onlay group [277]. Few studies have reported dedicated results on sexual function parameters that do not appear to be significantly impaired post-operatively [257, 278, 279].

A critical factor with respect to single-staged procedures is the careful selection of patients, as men with long and complex strictures might not be good candidates for single-stage reconstruction and attempts to offer single-staged operations in these patients might lead to high recurrence rates. Sometimes, this selection can only be done based on intra-operative findings. Therefore, any scheduled single-staged procedure might be converted into a staged one [264, 280]. Palminteri *et al*. highlighted the fact that single-stage augmentation urethroplasties in men with LS-related strictures enlarge rather than remove the diseased segment of the urethra and therefore there is always a risk of recurrence in the future [281]. The role of previous interventions (especially multiple urethrotomies or history of previous urethroplasties) remains unclear as several studies on single-staged operations do not provide information on previous procedures, or excluded patients with operations in the past [270, 279]. Although favourable outcomes in patients with previous history of urethrotomies/urethroplasties were reported by Barbagli and Kulkarni, in the study by Pfalzgraf *et al*. all recurrences post-previous urethroplasty took place in the single-stage group while Ekerhult *et al*., identified prior history of urethral operations as a risk factor for recurrence in the group of single-stage procedures [254, 257, 258, 268]. In addition to previous urethral surgery, high BMI has also been identified as a poor prognostic factor after single-stage penile urethroplasty [254].

6.3.1.3 Anastomotic urethroplasty in men with penile urethral strictures

Historically, the use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively [262, 282]. Nevertheless, it has been performed in selected patients with very short strictures (usually < 1 cm) with a 93% patency rate, with satisfactory QoL and sexual function and without any case of chordee [283].

Summary of evidence	**LE**
Stricture-free rates for single-stage penile augmentation urethroplasties range from 70%-100% for dorsal OMG augmentation, 67-100% for penile skin flap (PSF) augmentation, 55-92.6% for ventral OMG augmentation and 62-78% for dorsal SG augmentation. Overall stricture-free rates for staged OMG penile augmentation urethroplasties range from 70-100%.	2b
In staged urethroplasties, an interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully.	4
The use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively. Anastomotic urethroplasty can be offered in selected cases of very short (< 1 cm), inury-associated penile strictures.	3
In case of adverse intra-operative findings, a single-stage approach might not be feasible and must be converted into a staged approach.	3

Recommendations	Strength rating
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics.	Strong
Offer an interval of at least four to six months before proceeding to the second stage of the procedure provided that outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings.	Strong

6.3.1.4 Specific considerations for failed hypospadias repair-related strictures

The term "failed hypospadias repair" (FHR) includes a wide range of abnormalities after previous attempts for reconstruction, such as glans deformity, recurrent urethral stricture, glans/urethral dehiscence, UCF and penile chordee [284-286]. The management of FHR is challenging as the urethral plate, penile skin and dartos fascia are often deficient/non-existent. Management of these patients is often made more difficult due to incomplete health records and a lack of critical information (original meatal site, number and type of previous repairs) [260, 287]. In addition, multiple operations might need to be offered to reach satisfactory outcomes [284]. As a result, FHR should always be considered as a complex condition and it is advised that FHR management takes place in high-volume centres [285, 286, 288, 289].

"Hypospadias cripples" is a term widely used to describe the group of men with multiple previous failed attempts to correct the condition resulting in unfavourable results such as severe scarring, penile deformity and shortening, hair or stones in the urethra, UCF, chordee and functional disorders (e.g., urinary or sexual dysfunction). This term should be avoided and a more neutral one should replace it as it further stigmatises men with hypospadias who have been shown to have reduced self-esteem and confidence due to unsatisfactory cosmesis, and problematic urinary and sexual function. Moreover, it has been reported that FHR patients experience high rates of disappointment after failure of attempted repair and a sense of helplessness as they are frequently advised that their failed hypospadias is too complex to correct and they should not pursue further repair [285-287, 290, 291].

Two main approaches are applicable: single-stage or staged procedures. In general, it is advised that staged procedures should be followed when the urethral plate is inadequate for a single-stage operation. Surgeons should consent patients for both types of urethroplasty as the surgical approach might need to be modified intra-operatively depending on favourable/unfavourable intra-operative findings. Besides poor-quality of the urethral plate, these unfavourable findings include high degree of scarring and presence of concomitant LS, UCF and/or chordee. It is not uncommon for men with FHR to have scarred skin or concurrent LS and thus, skin grafts or flaps should be avoided as the risk of recurrence due to LS is very high (90% in long-term follow-up reported by Depsaquale *et al*. [36]) [292, 293].

Staged repairs (using mainly BMG) reported patency rates ranging from 71-95% [256, 290, 292, 294, 295], while single-stage repairs had patency rates from 80-100% [292, 294, 296-299]. It needs to be highlighted that, as FHR is an umbrella term that covers various clinical conditions apart from urethral stricture disease only (such as UCF, chordee, penile deformity), "success" rates as reported by the authors in their studies do not represent urethral patency rates only. Unfortunately, the number of previous operations is either not reported or refers to the whole FHR study group collectively rather than to the subgroups of staged/single-staged procedures.

A comparative analysis is reported by Barbagli *et al*. in 345 FHR patients at five-year follow-up. Overall failure-free survival rate was 48% for all urethroplasties, and in subanalysis, staged techniques had significantly lower treatment failure-free survival rates compared to single-stage techniques [300]. However, it is unclear whether these groups were comparable in terms of baseline characteristics such as age, length of stricture, number of procedures, comorbidities etc. [300]. If the patients in the staged group had a more unfavourable background, this on its own could explain the final outcome rather than the surgical approach itself.

Kozinn *et al*. reported a 16% and 14% revision rate after the 1st and 2nd stage, respectively, and observed that these revision rates were higher in the FHR group compared to non-FHR patients with penile strictures [256]. There is conflicting evidence whether FHR as aetiology is a poor prognostic factor in the outcome of urethroplasty for penile strictures [254, 301-303]. Concomitant UCF can be successfully managed at the same time of urethroplasty [300].

For further information see supplementary Table S6.3.

Summary of evidence	LE
Men with FHR have history of multiple interventions, and poor quality tissues, and might require complex procedures for a satisfactory functional and cosmetic outcome.	4
Men with FHR may have low self-esteem due to urinary and sexual dysfunction and unsatisfactory cosmesis.	2b
Men with FHR can have scarred penile skin or concurrent LS and outcomes with skin grafts or flaps can be unsatisfactory.	3

Recommendations	Strength rating
Men with failed hypospadias repair (FHR) should be considered complex patients and referred to specialist centres for further management.	Weak
Propose psychological and/or psychosexual counselling to men with unsatisfactory cosmesis and sexual or urinary dysfunction related to FHR.	Weak
Do not use penile skin grafts or flaps in failed FHR patients with lichen sclerosus or scarred skin.	Strong

6.3.1.5 Specific considerations for lichen sclerosus-related penile urethral strictures

Given the fact that LS affects the skin, the use of genital skin as a flap or graft is not advised as the risk of disease recurrence has been reported to be high (50-100%) and while most of recurrences tend to occur within the first two to three post-operative years, late recurrences have been reported [304].

Main strategies are single-stage or staged oral mucosa graft urethroplasty.

The EAU Urethral Strictures Guidelines Panel conducted a systematic review [305] to explore the role of single-stage oral mucosa graft urethroplasty in the management of LS-related urethral strictures and to compare its outcomes with alternative management options [surgical dilatations +/- intermittent self-dilatation (ISD); surgical dilatations + local steroids +/- ISD ; staged oral mucosa urethroplasty; penile skin urethroplasty; meatotomy/meatoplasty; urethrotomy (Otis, DVIU); perineal urethrostomy; urinary diversion (e.g., suprapubic catheterisation)].

In total, fifteen studies met the inclusion criteria, recruiting a total of 649 patients (366 from five non-randomised comparative studies and 283 from ten single-arm retrospective observational studies). Single-stage oral mucosa graft urethroplasty resulted in success rates ranging from 65% to 100% after a 12-67 months mean or median follow-up. For staged oral mucosa graft urethroplasty, the most commonly reported comparator, the success rates were somewhat lower and varied between 60% and 79%. Methodological issues (mainly selection bias) could explain the difference in success rates rather than the intervention itself. Complications were uncommon (0-12%) and mainly comprised Grade 1-3 events.

Due to the overall very poor quality of evidence, the systematic review did not provide a clear answer as to whether single-stage oral mucosa graft urethroplasty is superior to other management options, although careful patient selection is highlighted. In the absence of adverse local tissue conditions a single-stage approach could lead to high success rates with an improvement in voiding symptoms and QoL.

Summary of evidence	LE
Lichen sclerosus is a skin condition that can lead to scarring, and recurrence rates after skin graft/flap augmentation urethroplasties have been reported to be high (50-100%).	4
Single-stage OMG urethroplasty provides patency rates between 65 and 100% and is not inferior to staged OMG urethroplasty.	3

Recommendations	Strength rating
Do not use genital skin in augmentation penile urethroplasty in men with lichen sclerosus-related strictures.	Strong
Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with lichen sclerosus-related strictures.	Weak

6.3.1.6 Distal urethral strictures (meatal stenosis, fossa navicularis strictures)

Open repair of distal urethral strictures can be in the form of Malone meatoplasty, skin flap meatoplasty or graft (skin [SG]/OMG) urethroplasty.

For short distal meatal strictures, the Malone meatoplasty (dorsal + ventral meatotomy) provides a technique with patency rates up to 100%, and 83% patient-reported satisfaction with the cosmetic results [306].

Skin flap meatoplasty showed excellent patency rates ranging from 85-100% based on three studies comprising 53 patients [307-309]. In addition, based on their results, patient satisfaction with post-operative outcomes and cosmesis was high, there were no cases of ED and functional complaints were minimal (mainly spraying of the urine flow). Barbagli *et al*. in their study from 2008, had lower success (57%) with the use of skin flaps; however, this was in only seven patients [268].

Patency rates with the use of grafts (OMG or SG) ranged from 69-91% in 85 patients overall [268, 297, 308, 310]. Where reported, patients were satisfied with cosmesis, and mild spraying of the urine flow self-resolved. Although tubularised grafts in a single-stage procedures are not routinely recommended (see also section 9. Tissue transfer), one series reported a 89.9% patency rate for this approach ("two-in one approach") in selected patients with mainly distal penile strictures [311].

For further information see supplementary Table S6.4.

Summary of evidence	LE
Post-meatoplasty/urethroplasty patency rates in men with meatal stenosis or fossa navicularis/distal urethral strictures range between 57-100% depending on type of surgical intervention with high patient satisfaction and minimal complications.	3

Recommendation	Strength rating
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak

6.3.2 ***Urethroplasty for bulbar strictures***

6.3.2.1 "Short" bulbar strictures

The length of a "short" bulbar stricture is poorly defined. In general, "short bulbar strictures" are those amenable to stricture excision and subsequent tension-free anastomotic repair. The limit is usually around 2-3 cm but can be longer depending on the patient's anatomy and stricture location within the bulbar urethra [312].

In fit patients, the choice of urethroplasty is between EPA (transecting or non-transecting) and FGU.

6.3.2.1.1 Excision and primary anastomosis

6.3.2.1.1.1 Excision and primary anastomosis with transection of corpus spongiosum (transecting EPA)

Transecting EPA (tEPA) is based on the full thickness resection of the segment of the bulbar urethra where the stricture and surrounding spongiofibrosis is located. Reconstruction is performed by a tension-free spatulated anastomosis.

6.3.2.1.1.1.1 Patency rates

The International Consultation on Urological Diseases (ICUD) performed an extensive review of the literature and reported a composite patency rate of 93.8% for tEPA [313]. Based on this, they endorsed tEPA as treatment of choice for short bulbar strictures if other techniques have an expected patency rate below 90%. However, ED was not taken into account for this advice and, as discussed below, ED is a concern with tEPA.

After publication of the ICUD review, several other series have been published and the reported patency rates (76-97%) are in line with the findings of the ICUD review [314-326].

Usually, no need for further intervention is used to evidence that the urethra is patent. In the few studies using an anatomic definition for failure (an inability to pass a 16 Fr endoscope) tEPA urethroplasty achieves a similar patency rate, ranging between 85.5% and 97% [138, 319, 325, 327] (Table 6.12). The median time for recurrence after tEPA is between 3.5 and thirteen months [138, 316, 317].

Several authors suggested that tEPA is the technique of choice for short post-traumatic bulbar strictures with complete obliteration of the urethral lumen and full thickness spongiofibrosis [327, 328]. These strictures are a specific entity and usually the result of a straddle injury with complete or nearly complete rupture of the bulbar urethra. These obliterations are predominantly short and can be treated with tEPA yielding a patency rate of 98.5% as reported in the series of Horiguchi *et al*. [329]. They also reported an improvement in erectile function after urethroplasty measured one year post-operatively. Straddle injury (and perineal trauma) are a common aetiology in papers published about tEPA; however, separate data on the outcomes for this specific aetiology is usually lacking.

For further information see supplementary Tables S6.5 and S6.6.

6.3.2.1.1.1.2 Complications

Granieri *et al*. [318] specifically focused on complications after bulbar urethroplasty. Peri-operative complications (haematoma, neuralgia), infectious complications, anatomic complications and voiding complications were not significantly different between EPA, augmented anastomotic repair (AAR) and FGU. Erectile dysfunction after bulbar urethroplasty is usually transient, with improvement after three to six months [330]. Chordee is one of the complications attributed to EPA urethroplasty, but is rarely reported. A large series (352 patients) reported an incidence of 0.3% [327]. Another large series (94 patients) reported five cases (5.3%), with a mean stricture length of 2 cm (range 1.5-4) in patients with this complaint [314].

Other complications of tEPA are a cold feeling in the glans (1.6-3.2%) and decreased glandular tumescence (6%) [330, 331]. These latter complications (as well as ED) might be attributed to complete transection of the corpus spongiosum at the level of the stricture, thereby disrupting the antegrade blood flow of the urethra and corpus spongiosum. To spare this, the non-transecting EPA (ntEPA) has been described [332] and later modified [333].

6.3.2.1.1.2 Non-transecting excision and primary anastomosis (ntEPA)

6.3.2.1.1.2.1 Patency rates

Except for straddle injuries that are usually associated with complete obliteration of the lumen and full thickness scarring of the corpus spongiosum [313, 327], ntEPA is a good alternative for short bulbar strictures of all other aetiologies. With median follow-ups ranging between 17.6 and 37.1 months, the patency rates reported are 93.2-99%; with the lack of further intervention as success criteria [326, 328, 334]. Even with the anatomic criteria -16 Fr cystoscopy passage- the success rate achieved was 97.9% at twelve months [327] (see supplementary Table S6.7).

Two comparative analyses evaluated tEPA vs. ntEPA. Waterloos *et al*. reported patency rates of 88.4% and 93.2% respectively for tEPA and ntEPA (p=0.33) but with significantly longer follow-up for tEPA (118 vs. 32 months, $p < 0.001$). Of patients scheduled for ntEPA, 11.1% were converted to tEPA, highlighting that ntEPA is not always possible. Chapman *et al*., using anatomic success criteria (16 Fr cystoscope passage), reported patency in 93.8% of tEPA vs. 97.9% of ntEPA. Follow-up was also significantly shorter at 74.1 (SD: 45.4) months for tEPA vs. 37.1 (SD: 20.5) months for ntEPA ($p < 0.001$) [327].

6.3.2.1.1.2.2 Complications

When erectile function after urethroplasty was assessed (at six months), ntEPA had significantly lower ED rates (a decrease of > 5 points on the sexual health inventory for men [SHIM] scale) compared to tEPA (4.3 vs. 14.3%, respectively) [327]. Urethral transection performed during tEPA was the only factor associated with sexual dysfunction in multivariate analysis [327]. Other series reported ED lasting for more than six months in 2-6% of cases after ntEPA [328, 334, 335]. Grade ≥ 2 Clavian-Dindo complications were 3.6-8.1% vs. 4.3-6.8% respectively for tEPA and ntEPA, without reaching statistical significance [326, 327].

To date, no trials comparing ntEPA with FGU have been published to report on comparative patency outcomes and complications.

6.3.2.1.2 Free graft urethroplasty

Despite the very high patency rates of EPA, FGU has been performed for short bulbar strictures as well. This is mainly driven by reports of ED after EPA. A meta-analysis of ten papers [336] comparing tEPA with BMG FGU for short strictures, found that tEPA is better than BMG FGU in terms of patency rates (91.5% vs. 70%), whilst BMG FGU has less erectile complications (9% vs. 25%). However, the methodology of this meta-analysis must be disputed as it was performed on cohort studies without risk of bias assessment and without further specification of timing of assessment of ED. On the other hand, two prospective, non-randomised papers [138, 337] comparing tEPA with BMG FGU, found no significantly different patency rates for EPA compared

to BMG FGU (87-90% vs. 84-87%, respectively) and no significant differences in erectile complications for tEPA compared to BMG FGU (6.7% vs. 2.2%, respectively). However, the operation technique used was dependent upon the length of the stricture, with tEPA utilised for shorter strictures (< 2 cm) and BMG for longer (> 2 cm) [337] or when a tension-free anastomosis was not possible [138]. Appropriate choice of procedure for stricture length and other patient and stricture parameters appear to equalise outcomes. Another prospective trial [338] involving both penile and bulbar strictures could not find any influence on erectile function of urethral transection. A prospective study on ejaculatory function following different urethroplasties by Erickson *et al*. [339] found no overall difference in ejaculatory score pre- and post-operatively, although patients with a poor score pre-operatively improved significantly and those with a good score pre-operatively did not decrease post-operatively.

Dogra *et al*. [278] looked prospectively at sexual function in 87 patients after different urethroplasties (EPA, penile/bulbar substitution) and found a 20% reduction in sexual function in all groups, which resolved after six months.

Details on where to place the graft during FGU are discussed below.

Summary of evidence	**LE**
For short post-traumatic strictures tEPA has good patency rates.	3
For short bulbar strictures not related to straddle injury tEPA, ntEPA and FGU have the same patency rates, but ntEPA and FGU have less erectile dysfunction than tEPA.	3

Recommendations	**Strength rating**
Use transecting excision and primary anastomosis (tEPA) for short posttraumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis.	Strong
Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury.	Weak

6.3.2.2 "Longer" bulbar strictures

6.3.2.2.1 Free graft urethroplasty

For strictures not amenable to EPA, FGU is the technique of choice and buccal mucosa is, at the moment, the most widely used graft. Other grafts (and flaps) are possible and discussed in the tissue transfer chapter. Patency rates of FGU of the bulbar urethra are 88-91% with twelve to 40 months follow-up [263, 340].

During bulbar urethroplasty, the bulbospongiosus muscle is usually separated at the midline which may cause damage to the muscle and perineal nerves. This might subsequently provoke post-void dribbling and ejaculation disorders. In order to reduce this, the muscle and nerve-sparing perineal approach has been introduced [341]. Although it is mostly used in graft urethroplasty, this approach is also possible for EPA as well [342]. Elkady *et al*. [335] randomised 50 patients between a muscle and nerve-sparing perineal approach vs. a classic perineal approach and found no difference in operative time (100 vs. 105 min), but significantly less dribbling (4% vs. 36%, p=0.01), and significantly less ejaculatory changes (8% vs. 40%, p=0.02) in the nerve and muscle-sparing group. Fredrick *et al*. [342] did the same in 50 patients in a multicentric study with bulbar urethroplasty but could not find a statistical difference regarding post-void dribbling and ejaculatory changes. Due to the limited and conflicting evidence, no recommendation can be made about the routine use of nerve and muscle-sparing modification during bulbar urethroplasty.

See supplementary Table S6.8 for further information.

6.3.2.2.2 Augmented anastomotic repair

Augmented anastomotic repair is also an option for these strictures. It has been mainly performed in cases where the stricture was just too long (+/- 2-4 cm) for tension-free EPA [324]. It can also be performed for longer strictures with a shorter (nearly) obliterative segment [343]. In this case, only the most obliterative segment is excised, the urethral plate is anastomosed and the urethra is further reconstructed with an onlay graft [343]. Patency rates after AAR vary between 91.1 and 91.9% with twelve to 28 months follow-up [318, 324] (see supplementary Table S6.9).

A non-transecting alternative has also been described to overcome the previously mentioned inconveniences related to spongiosal transection (augmented non-transecting anastomotic bulbar urethroplasty [ANTABU]). With this technique, Bugeja *et al*. [344] reported a 100% patency rate in sixteen patients after a median follow-up of thirteen months. One patient (6.7%) suffered permanent ED.

Summary of evidence	LE
For strictures not amenable to EPA, FGU provides a 88-91% patency rate.	1b
Augmented anastomotic repair provides good patency rates for bulbar strictures with a nearly obliterative segment.	3

Recommendations	Strength rating
Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment.	Weak

6.3.2.2.3 Location of the graft during urethroplasty for bulbar strictures

The best location for graft positioning into the bulbar urethra remains to be determined. There are many techniques described with ventral, lateral, dorsolateral or dorsal graft as an onlay or an inlay. Onlay means from the outside onto the urethra, inlay means from the inside after opening the urethra.

Regarding the site of graft placement, the Panel has conducted a systematic review assessing the literature from 1996 onwards, including studies with at least 20 patients and a minimum of twelve months follow-up [345]. This yielded one RCT, four non-randomised comparative series and 36 case series comprising 3,683 patients. The RCT of Vasudeva *et al*. compared ventral (n=40) with dorsal (n=40) onlay BMG urethroplasty and reported a patency rate of 90 and 92.5% respectively at twelve months follow-up (p=0.51) [340]. The non-randomised comparative studies could not identify any significant differences in patency rates for dorsal onlay vs. ventral onlay, dorsal inlay vs. ventral onlay or dorsal onlay vs. ventral onlay vs. dorsolateral onlay. Case series reported a patency rate of 62.1-98.3% for dorsal onlay, 74.3-94.4% for ventral onlay and 78.4-92% for dorsal inlay. There are no arguments to assume a higher risk of ED with one of the four techniques. Post-void-dribbling was reported in 0-28.1% with dorsal onlay and in 20-21% with ventral onlay. Other complications were also similar in incidence between techniques. Urethrocutaneous fistula and urethral diverticulum were only reported with the ventral onlay technique although this consisted of only two and one cases, respectively.

Double ventral-dorsal onlay, proposed by Palminteri *et al*. [139] for high-grade strictures, yielded a patency rate of 91% after 22 months follow-up.

Summary of evidence	LE
Location of the graft has no impact on patency rates.	1b

Recommendation	Strength rating
Use dorsal, dorsal-lateral or ventral approach according to surgical practice, expertise and intra-operative findings.	Strong

6.3.2.3 Staged urethroplasty for bulbar urethral strictures

6.3.2.3.1 Indications

Staged urethroplasty may be considered when:

- there are locally adverse conditions such as fistula, false passage, abscess, cancer [280, 346, 347];
- there has been a previously unsuccessful complex urethroplasty including failed hypospadias repair [256, 346];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [346];
- the stricture is radiotherapy induced [256];
- the stricture is consequent to LS [256] (this is controversial and for some groups LS is a contraindication for a staged urethroplasty [302]; Kozinn *et al*. recommend leaving at least ten months between 1st stage and 2nd stage re-tubularisation in patients with LS to allow graft complication to develop) [256];
- there is severe spongiofibrosis [348].

6.3.2.3.2 Outcomes

Patency rates of 33.3-94.6% at mean follow-up of 11.2-50 months have been described for staged urethroplasty in series which include men with bulbar urethral stricture disease [256, 302, 325, 348-350]. Grafts (mesh graft, preputial skin, oral mucosa) can be used in staged augmentation as well as marsupialisation [325,

348]. In patients affected by LS, a 52.2% patency rate for staged urethroplasty was reported whereas this was 86% for single-stage buccal mucosa urethroplasty ($p < 0.01$) [302]. It is highly likely that different stricture and patient characteristics contributed to the differences reported and this should be kept in mind when interpreting the data. Of note, 19-45.5% of patients planned for staged urethroplasty declined to proceed to 2nd stage re-tubularisation [256, 349].

Early complications after staged procedures include wound dehiscence, UTI, epididymitis, scrotal abscess and penile numbness. Specific to 2nd stage Johanson urethroplasty UCF occurs in 3-15%. The actual incidence of UCF is probably higher as many small fistulae close spontaneously with conservative management and are not formally reported [302, 325, 348].

Late complications of 1st stage urethroplasty include a need for revision in up to 19% - consequent to recurrence of LS in graft(s) (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%) [256]. Late complications of 2nd stage urethroplasty include post-micturition dribble in 14-18%, SUI in up to 16%, penile curvature in up to 9%, ED in up to 4%, urethral diverticulum formation in 1% and cold glans [302, 348, 350]. Stress urinary incontinence (SUI), penile curvature and ED appear to be particularly associated with mesh graft stage urethroplasty [348, 350].

After their procedure, 86% and 96.6% of men with respectively mesh graft and buccal mucosa graft staged urethroplasty were satisfied. The patient groups included in the review were too small to detect significant differences [348]. All are retrospective series – with heterogenous indications, stricture locations (not exclusively bulbar), stricture lengths and patient groups. It is consequently difficult to draw meaningful conclusions from the little data that are available.

See supplementary Table S6.10 for more information.

Summary of evidence	LE
Staged urethroplasty for bulbar strictures and for strictures involving the bulbar urethra yields patency rates of 33.3-90% depending upon patient and stricture characteristics and patient satisfaction is high with all types of staged urethroplasty.	3
Lichen sclerosus is a relative contraindication for staged urethroplasty in the literature with lower long-term urethral patency rates of 52.2% compared to urethral patency rates of 64.3% in non-lichen sclerosis patients.	3
Up to 45.5% of men elect not to proceed to 2nd stage re-tubularisation after successful 1st stage.	3
Up to 19% of men required revision of their 1st stage urethroplasty.	3

Recommendations	Strength rating
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single stage urethroplasty and who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single stage urethroplasty is possible.	Weak
Consider staged procedure in patients unsure about perineal urethrostomy versus urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

6.3.2.4 Risk factors for adverse outcomes

In four series specifically dedicated to risk factors for failure after urethroplasty using multivariate analysis, there is conflicting evidence about several factors (aetiology, comorbidity, stricture length, prior therapy) that might be predictive for failure after urethroplasty (Table 6.6). Advanced age does not appear to be a risk factor for urethroplasty failure in the majority of studies, with the exception of Viers *et al*. 2017 [354] retrospective case series which found that the risk for recurrence was significantly higher beyond the age of 60 (< 50 yrs 94%, > 70 yrs 74%) in 184 patients having a wide variety of urethroplasties. Previous radiation therapy was also found to be a risk factor for stricture recurrence in both Viers' [354] retrospective case series and Ahyai's 2015 series [355] – with only a 71% patency rate at a median follow-up of 29 months in those with previous radiotherapy. Based on these data, a clear and evidence-based recommendation cannot be formulated.

Table 6.6: Risk factors for failure after urethroplasty based on multivariable Cox regression analyses

Study	N	Population	Comorbidity HR (95% CI)	Length HR (95% CI)	Aetiology HR (95% CI)	Prior stricture therapy HR (95% CI)
Breyer *et al*. 2010 [351]	443	Mixed	NS	NS	NS	Prior DVIU: 1.7 (1.0-3.0) Prior urethroplasty: 1.8 (1.1-3.1)
Kinnaird *et al*. 2014 [352]	604	Mixed	NS	≥ 5 cm: 2.3 (1.2-4.5)	Iatrogenic: 3.4 (1.2-10.0) LS: 5.9 (2.1-16.5) Infectious: 7.3 (2.3-23.7)	NS
Chapman *et al*. 2017 [319]	596	Isolated bulbar strictures	Overall comorbidity: 2.4 (1.1-5.3) Obesity: 2.9 (1.3-6.5)	1.2 (1.1-1.3)	Infectious: 3.7 (1.3-10.6)	NS
Verla *et al*. 2020 [353]	474	Anterior strictures	NS	NS	NS	NS

CI = confidence interval; HR = hazard ratio; LS = Lichen sclerosus; N = number of patients; NR = not reported NS = not significant.

6.3.2.5 Management of recurrence after bulbar urethroplasty

Kahokehr *et al*. [324] followed nearly 400 patients after urethroplasty and found a recurrence rate of 6% (n=25). Ninety-two percent of the failed cases were treated successfully with DVIU and only 8% needed another open reconstruction. However, they did not mention characteristics of the recurrent cases nor the duration of follow-up.

Rosenbaum *et al*. [356] and Javali *et al*. [357] retrospectively analysed the outcomes of BMG FGU for ReDo urethroplasty in 51 and 21 patients respectively using the other cheek as donor side. Patency rates were 82-86%, which is in the range of primary cases.

Vetterlein *et al*. [358] compared primary (no previous open urethroplasty) vs. ReDo (previous open urethroplasty with BMG) vs. secondary (previous open urethroplasty without use of BMG) cases in a retrospective series of 534 patients with BMG FGU. The patency rates in primary and ReDo cases were comparable (87%) whilst the outcome in secondary cases was worse (71%).

A small series (n=37) reported on the use of EPA for revision surgery after failed urethroplasty in strictures of 2.1 (range 1-3.5) cm length on average. Patency rates using EPA after failed primary EPA (51%) and after any other technique of urethroplasty (49%) were 95 and 94% respectively with a mean follow-up of 30 months [317].

Summary of evidence	LE
Buccal mucosa free graft urethroplasty after failed urethroplasty achieves the same patency rates as primary cases.	3

Recommendation	Strength rating
Use oral mucosa free graft urethroplasty for ReDo urethroplasty in case the of a long stricture.	Strong

6.3.3 ***Urethroplasty for penobulbar or panurethral strictures***

The possibilities for reconstruction are various and often include combinations of different techniques or grafts other than OMG. The patency rates are usually lower than in shorter reconstructions (Table 6.7). Hussein *et al*. [359] performed a RCT comparing skin grafts vs. skin flaps in strictures of mean length 15 cm and found no difference in patency rates (72% vs. 79%) or complications.

Warner *et al*. [302] performed a multi-institutional review in 2015 including 466 patients with stricture length > 8 cm and found an overall patency rate of 77.5%.

As discussed previously, Kozinn *et al*. [256] reported on the outcome of staged urethroplasty in a cohort of which 54.9% had panurethral strictures (Table 6.7).

Kulkarni *et al*. [360] proposed a one-stage completely perineal approach with invagination of the penis and one-sided urethral dissection. After 59 months the overall patency rate was 83.7% in 117 men with a mean stricture length of 14 cm.

Another option in patients refusing or unfit for complex reconstructive surgery is PU (see section 6.3.4 Perineal urethrostomy).

Table 6.7: Study characteristics and patency rates of series on penobulbar strictures

Author	Study	Length in cm (min, mean, range)	Technique	N	FU months (mean, range)	Patency
Hussein *et al*. 2011 [359]	RCT	NR, 15, 9-21	Skin graft vs. flap	37	36, 12-60	72 vs. 79%
Hussein *et al*. 2016 [361]	Prospective	NR, 8, NR	BM vs. skin dorsal onlay	69	56, NR	90 vs. 84%
Warner *et al*. 2015 [302]	Retrospective review	> 8, 12.5, 8-24	BM/staged/skin	466	20, 12-344	77.5%
El Dahshoury *et al*. 2009 [362]	Retrospective	NR, 18, 15-20	Skin flap	30	24, NR	87%
Mathur *et al*. 2010 [363]	Retrospective	NR, 12, 8-16.5	Tunica albuginea graft	86	36, NR	89%
Meeks *et al*. 2010 [364]	Retrospective	NR, 11, 4-24	Abdominal skin graft	21	28, 11-52	81%
Kulkarni *et al*. 2012 [360]	Retrospective	NR, 14	BM dorsal onlay	117	59, NR	83.7%
Tabassi *et al*. 2014 [365]	Retrospective	NR, 14.4, NR	BM dorsal onlay	117(37)	19, NR	84%
Xu *et al*. 2017 [298]	Retrospective	> 8, 12, 8-20	BM/LM/combination	81	>12, 41, 15-86	83%
Alsagheer *et al*. 2018 [366]	Retrospective	> 8, 11.3	BM onlay vs. skin flap	50	NR, 16, NR	70 vs. 77%
Kozinn *et al*. 2013 [256]	Retrospective	NR, 9.6, 4-17	Staged urethroplasty	91	15, 12-69	90.1%

BM = buccal mucosa; LM = lingual mucosa; FU = follow-up; N = number of patients; NR = not reported; RCT = randomised controlled trial.

Summary of evidence	LE
Publications about panurethral urethroplasties generally come from high volume centres.	4
Different materials and techniques might be needed for reconstruction.	3

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

6.3.4 ***Perineal urethrostomy***

6.3.4.1 *Indications*

Perineal urethrostomy offers a permanent or temporary solution for restoration of voiding in men with complex urethral stricture disease in whom:

- there are no further options to restore urethral patency either due to multiple previous failed urethroplasties [302, 346] or multiple co-morbidities precluding a more expansive surgical undertaking after failed endoscopic management [367];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [346];
- following urethrectomy and/or penectomy for cancer [368].

6.3.4.2 *Types of perineal urethrostomy*

Johanson described an inverted anterior scrotal funnel PU in 1953. This was later modified by Gil-Vernet and Blandy to utilise a posteriorly based scrotal flap. Both these techniques utilise an inverted U or lambda incision. The Gil-Vernet-Blandy PU has been further modified with the addition of dorsal and/or ventral free OMG augment to allow use of PU in men with strictures consequent to radiotherapy [369] or LS [258] and/or in men with PU stenosis or stricture extending into the proximal bulbar or membranous urethra ("augmented Blandy") [367].

More recently, the '7 flap' PU utilising a unilateral posteriorly based scrotal flap has been developed for use in the very obese, or in men of all BMI with stricture extension into the proximal bulbar or membranous urethra [370]. Initially this was performed with transection of the distal bulbar urethra but latterly the technique has been modified to a non-transection technique with loop mobilisation of the bulbar urethra ("loop PU") [371]. The "7-flap" utilises a midline incision – which has been shown to have a significantly reduced side-effect profile in terms of superficial wound infection (1.9% c.f. 18.6%) and superficial wound dehiscence (11.9% c.f. 23.3%) than the inverted U or lambda incision [372, 373] and may be associated with improved urethroplasty (and by inference PU) outcomes, at least in the short term (0% failure c.f. 6.2% failure at six months) [372]. Operative time is similar for all types of PU with mean operative time varying between 97.2 minutes to 112 minutes [368, 374].

The utilisation of PU is increasing [375] – constituting 4.5% of 403 procedures for complex urethral stricture disease in a tertiary centre in 2008 and 38.7% in 2017 [376]. Perineal urethrostomy patients are generally older than those having urethroplasty with a median of 62.6 years of age for men having PU in Fuchs *et al*. 2018 series compared with a median of 53.2 years for men having anterior urethroplasty [376]. Between 18.7% and 73.4% of men having staged urethroplasty for complex anterior urethral stricture decline to proceed to 2nd stage re-tubularisation after a successful 1st stage and remain voiding from the PU of their 1st stage urethroplasty [256, 346, 349].

6.3.4.3 *Outcomes*

6.3.4.3.1 Patency rates

Patency rates of 70-95% at mean/median follow-up of 20–63 months have been described [302, 346, 354, 367-369, 371, 374, 376]. All reports are retrospective series – all of which are heterogenous in terms of indications and patients. There is consequently little data available to determine which is the best technique for PU.

McKibben *et al*. reported a patency rate of 92.9% in 42 patients for "7-flap" PU at median follow-up of 53.6 months, whilst they had a 100% patency rate with loop PU in 20 patients at a median follow-up of thirteen months [371].

Lumen *et al*. in 2015 reported a 74.3% patency rate for Johanson PU compared with an 87.5% patency rate for Gil-Vernet-Blandy PU (p=0.248), but with a significantly longer follow-up after Johanson PU (median 36 vs. nine months) [368]. Barbagli *et al*. published the largest series of PU patients to date – including 173 men (all of whom had been planned to have a staged urethroplasty for their complex anterior urethral stricture disease and 127 (73.4%) of whom declined to proceed with 2nd stage re-tubularisation). The median follow-up in this series was 62 months and the patency rate was 70% - confirming that patency rates for PU (and indeed for all urethroplasty [269, 322] reduce with time [346].

See supplementary Table S6.11 for further information.

6.3.4.3.2 Complications

Perineal urethrostomy complications occur in 2.5-11.4% and include superficial wound dehiscence, scrotal abscess, UTI and urosepsis, bleeding, and transient scrotal pain and numbness [302, 368, 377]. The majority of

complications are Clavien-Dindo grades 1 (2.9-18.8%) and 2 (0-2.9%). Grade 3 complications are rare and only occur in 5.7-6.2%. In the medium-term 22.2-30.8% of men with PU report post-micturition dribble [368].

6.3.4.3.3 Patient reported outcomes

Barbagli *et al*. reported that 168/173 (97.1%) of men were satisfied or very satisfied with the outcome of their Gil-Vernet-Blandy PU and would have the procedure again at median 62 months follow-up. Of these, 166/173 (95.9%) felt they had excellent or good results from their Gil-Vernet-Blandy PU, 145/173 (85%) felt it caused them no problems and 141/173 (82%) felt it caused their partner no problems [346]. The Trauma and Urologic Reconstructive Network of Surgeons (TURNS) collaborative found no significant change in sexual function and a significant improvement in urinary symptoms following PU in a small group of patients [378] whilst Lumen *et al*. found satisfactory or acceptable International Prostate Symptom Score (IPSS) outcomes in 26/32 (81.25%) of men with Johanson or Gil-Vernet-Blandy PU at a median follow-up of 32 months and nine months, respectively.

McKibben *et al*. found a mean patient global impression of improvement (PGI-I) of 1.3 in nineteen patients with either loop PU or "7-flap" PU [371] at median 31 months follow-up.

6.3.4.3.4 Risk factors for patency failure of the perineal urethrostomy

Lichen Sclerosus, trauma and infection urethral strictures have poorer outcomes from PU, with PU patency failure in 36.7-67% at a median 62 months follow-up [346, 377]. Worse outcomes were also observed in patients with previous failed urethroplasty and multiple previous endoscopic and open treatments [346, 368, 369].

Barbagli *et al*. found that stricture length was inversely related to PU patency, as was patient age [346]. Conversely Viers *et al*. found outcomes worsened with age, reporting patency rates of 100% in men < 50 years old compared with 83% in men aged 60-69 years old [354]. Lopez *et al*. found increased risk of PU failure in men with ischaemic heart disease which makes sense and would be a putative explanation for the age-related worsening of outcomes noted by Viers *et al*. [377].

Failure of PU is most commonly treated with surgical revision of PU using V-Y plasty, augmentation or complete ReDo but can also be managed with periodic dilatation or urinary diversion [346, 367, 368].

For further information see supplementary Table S6.11.

Summary of evidence	LE
Perineal urethrostomy provides very good short- and long-term outcomes for men with complex urethral stricture disease.	1a
Perineal urethrostomy provides very good short and long-term outcomes for men who are unable to have complex reconstruction due to co-morbidities.	2b
All types of PU yield equivalent very good outcomes.	4
Augmented Gil-Vernet-Blandy or "7-flap" PU yield very good outcomes in men with extension of their urethral stricture disease into the proximal bulbar or membranous urethra.	2
"7-flap" PU yields very good results in obese men.	3

Recommendations	Strength rating
Offer perineal urethrostomy as a management option to men with complex anterior urethral stricture disease.	Strong
Offer perineal urethrostomy for men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose type of perineal urethrostomy based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet-Blandy perineal urethrostomy or "7-flap" perineal urethrostomy in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider "7-flap" urethroplasty in obese men.	Weak

*6.3.5 **Posterior urethra***

6.3.5.1 Non-traumatic posterior urethral stenosis

6.3.5.1.1 Treatment of non-traumatic posterior urethral stenosis

Several treatment modalities including conservative management (see section 6.1 Conservative options), endoluminal, open or minimally invasive surgical procedures are currently available, depending on patient's goals and health status.

6.3.5.1.2 Endoluminal management of non-traumatic posterior urethral stenosis

6.3.5.1.2.1 Dilatation of non-traumatic posterior urethral stenosis

This can be done under loco-regional anaesthesia [379-383]. Dilatation is used for VUAS [379-384] or radiation-induced BMS [112, 385] and in the majority of reported cases, patients were not previously treated for their stricture (see supplementary Table S6.12). Patency rates vary widely between 0% and 89% [112, 379-385]. The risk of *de novo* UI was low (0-11%) and no other complications were reported. It is of note that most series report on visually controlled dilatation [379-383] in VUAS without complete obliteration.

6.3.5.1.2.2 Endoscopic incision/resection of non-traumatic posterior urethral stenosis (Table 6.8)

Incisions can be performed at multiple locations according to surgeon's preference [386]. However, aggressive incisions at the six and twelve o'clock positions should be avoided because of the risk of respectively rectal injury and urosymphyseal fistulation [182, 387-389]. The risk of urosymphyseal fistulation is especially a concern after previous radiotherapy [390]. Direct vision internal urethrotomy is mainly performed in patients with primary or recalcitrant VUAS although one series performed it in a mix of patients with VUAS and BNS [391] and two series reported it for radiation-induced BMS [112, 385]. Direct vision internal urethrotomy/dilatation for non-irradiated BMS are usually included in series reporting on anterior strictures (see section 6.2 Male endoluminal treatment of anterior urethral strictures). Patency after a 1st "cold/hot knife" DVIU ranges between 25-80% [379, 382, 384, 386, 391-396]. Laser incision yields a 69-100% patency rate [382, 384, 397, 398]. In a retrospective and unbalanced series, LaBossiere *et al*. found better patency rates for laser incision as compared to dilatation, "cold knife" DVIU and transurethral resection (TUR) [382]. Redshaw *et al*. reported inferior patency rates for "cold knife" incision vs. "hot knife" incision followed by MMC for BNS (50 vs. 63%; p=0.03) [240] (see supplementary Table S6.13). Urinary incontinence largely varies between 0 and 53% but some series have not assessed urinary continence before DVIU [392, 394]. In series where pre-DVIU continence data were available, *de novo* urinary continence after DVIU ranges between 0% and 10% [379, 384, 393, 395, 397]. Noteworthy, of 21 patients that were incontinent pre-DVIU in the series of Giannarini *et al*., eleven (52%) patients became continent and eight (38%) patients experienced improvement after DVIU [393]. In the series of Lagerveld, 1/5 (20%) patients noticed improvement of UI after DVIU [397]. As most recurrences will occur early [393, 394], it is advised to wait for three to four months after DVIU [386, 394, 399] to proceed with incontinence surgery if necessary, although others wait for twelve months [400]. The presence of recurrence must be ruled out by cystoscopy prior to incontinence surgery [386, 394, 399, 400].

Another option is to resect the stenosis. Popken *et al*. reported a 47% patency rate with TUR for untreated VUAS and no patient suffered *de novo* SUI [395]. Kranz *et al*. compared the results of TUR in 87 and 60 patients with respectively VUAS after RP and BNS after TURP. After a median follow-up of 27 (range: 1-98) months, patency rate was 40.2% for VUAS and 58.3% for BNS (p=0.031). The rate of *de novo* incontinence was significantly higher in patients treated for VUAS compared to BNS (13.8 vs. 1.7%; p=0.011) [401]. Kravchick *et al*. reported a higher incontinence rate after TUR compared to "cold knife" DVIU and dilatation for VUAS (50% vs. 13% vs. 0%, respectively; p=0.005) [383]. However, the number of patients were small and a selection bias of more severe cases towards TUR might be possible [383]. Alternatively, thermal damage to the adjacent external sphincter during TUR (especially with monopolar current) might be the cause of incontinence [383]. Brodak *et al*. compared TUR by bipolar resection (n=22) with holmium laser incision and vaporisation (n=17). After a mean follow-up of 42 months, two (9.1%) and four (23.5%) patients suffered a recurrence with bipolar and laser resection respectively (p=0.37). After six months, patients treated with bipolar resection had a significant better Q_{max} compared to laser treatment (13 vs. 6.1 ml/s; $p < 0.001$) [398]. Bipolar plasma vaporisation produced an 82% patency rate at a mean 24 months follow-up in 28 patients with VUAS who previously failed endoscopic treatment [402].

Cut-to-the-light technique for a complete obliterative stricture is not advised because of the very-low likelihood of durable patency and for the risk of false passage towards the rectum [399, 403, 404].

Repetitive DVIU was often able to stabilise the stricture [112, 379, 382, 385, 391-393, 401], but ultimately 6-10% required urinary diversion [394] or chronic suprapubic cystostomy [385, 391].

Transurethral resection can be performed for prostatic obstruction due to sloughing after high-energy treatments (HIFU, cryoablation) [96]. Transurethral resection for obstructive necrotic debris after radiotherapy is possible but is of limited role. Risk of recurrence is 50% and risk of *de novo* UI is 15-25% [96].

Table 6.8: Results of endoluminal incision/resection for posterior non-traumatic stenosis

Study	Modality	Type	N	Previous treatment (%)	FU (months)	Patency° (%)	Urinary incontinence (%)	Complications (%)
Merrick *et al*. [385]	Dilatation/ "Cold knife" DVIU	Radiation-induced BMS	29	0	NR	69	NR	NR
Sullivan *et al*. [112]	Dilatation (n=15) / "Cold knife" DVIU (n=20)	Radiation-induced BMS	39	0	16 (2-48)	51	11	NR
Brede *et al*. [394]	"Cold knife" DVIU	VUAS	63	Dilation 33 Incision 38 Both 29	11 (1-144)	73	52*	NR
Yurkanin *et al*. [392]	"Cold knife" DVIU	VUAS	61	Dilatation 100	31 (1-77)	87	12**	NR
Giannarini *et al*. [393]	"Cold knife" DVIU	VUAS	43	0	48 (23-80)	74	0	NR
Ramchandani *et al*. [379]	"Cold knife" DVIU	VUAS	10	0	NR	80	10	0
Hayashi *et al*. [384]	"Cold knife" DVIU	VUAS	6	Dilatation: 100	NR	50	NR	NR
	Holmium laser DVIU	VUAS	3	Dilatation + DVIU: 100	11-37	100	0	NR
Lagerveld *et al*. [397]	Holmium laser DVIU	VUAS	10	None: 40 Endoscopic (dilatation +/- DVIU +/- ISD): 60	18 (3-29)	100	0	0
Ramirez *et al*. [391]	"Hot knife" DVIU	VUAS: 74% BNS: 26%	50	None: 22	16	72	9	NR
Gousse *et al*. [396]	"Hot knife" DVIU	VUAS	15	None	15 (6-26)	80	100***	NR
Bang *et al*. [386]	"Hot knife" DVIU	VUAS	37	NR	13 (2-33)	65	100***	NR
Popken *et al*. [395]	"Cold knife" DVIU	VUAS	6	None	12-72	50	0	NR
	TUR	VUAS	15	None		47	0	NR
Kranz *et al*. [401]	TUR	VUAS	87	NR	27 (1-98)	40.2	13.8	NR
	TUR	VUAS	60	NR		58.3	1.7	NR
Brodak *et al*. [398]	TUR (bipolar)	BNS	22	DVIU 45	42 (14-72)	91	NR	NR
	Holmium laser DVIU	VUAS	17	DVIU: 12		76	NR	NR
Ozturk *et al*. [402]	TUR (bipolar)	VUAS	28	Dilatation: 75 DVIU: 25	24 (6-66)	82	0	0
LaBossiere *et al*. [382]	Holmium laser DVIU	VUAS	70	NR	10	69	NR	NR
	"Cold knife" DVIU	VUAS	8	NR		25	NR	NR
	TUR	VUAS	36	NR		39	NR	NR

BNS = bladder neck stenosis; DVIU = Direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; NR = not reported; TUR = transurethral resection; VUAS = vesico-urethral anastomosis stricture.

°patency rate after 1st endoluminal treatment evaluated in the study.

** requiring incontinence surgery (artificial urinary sphincter or male sling).*

*** slightly problematic urinary incontinence by questionnaire post DVIU (no data on pre DVIU continence).*

****all incontinent pre-operatively.*

6.3.5.1.2.3 Post-dilatation/direct vision internal urethrotomy strategies for non-traumatic posterior urethral stenosis

6.3.5.1.2.3.1 Intermittent self-dilatation for non-traumatic posterior urethral stenosis

As for anterior strictures, ISD can be offered to patients for recurrent posterior stenosis after dilation/DVIU in order to stabilise the stenosis. This is especially relevant for patients unfit/unwilling to undergo surgery or in patients with radiation-induced BMS [112, 382, 385, 405]. Although ISD may be acceptable to many urologists and patients, it usually is associated with a reduced QoL and poor patient compliance [30].

6.3.5.1.2.3.2 Intralesional injections for non-traumatic posterior urethral stenosis

In order to stabilise the luminal fibrosis and consequently to reduce the risk of recurrence, injection of antifibrotic agents at the time of endoluminal treatment has been proposed. The majority of patients in these studies were patients with recalcitrant/recurrent non-obliterative VUAS/BNS. Two series used corticosteroids [383, 399], whilst the others used MMC [240, 400, 403-406]. Patency rates with corticosteroid injections range between 50 and 100% [383, 399]. Patency rates with MMC vary between 50 and 79% [240, 400, 403-406]. No trials comparing endoluminal treatment with or without adjuvant intralesional injections were identified.

See supplementary Table S6.13 for further information.

Complications are low across most studies, but all studies were retrospective in nature. Redshaw *et al*. also reported grade 3 complications in four out of 55 (7%) patients, including osteitis pubis (n=2), bladder neck necrosis (n=1) and rectourethral fistula (n=1) in one multi-institutional study [240]. Three of these patients ultimately required urinary diversion with additional faecal diversion in one patient [240]. Given the severity of these complications, although rare, MMC should not be used outside the framework of a clinical trial [407].

6.3.5.1.2.3.3 Urethral stent for non-traumatic posterior urethral stenosis

Stents have been used anecdotally in the posterior urethra [247, 248, 382]. Patency rate are relatively low (47-60%) [247, 248, 382] at the cost of a high-risk for UI (19-82%) [247, 248].

Summary of evidence	**LE**
For non-obliterative VUAS and radiation-induced BMS, visually controlled dilatation and DVIU yield a patency rate of respectively 0-89% and 25-100% with a low complication rate. It can be performed under loco-regional anaesthesia.	3
During DVIU, deep incision might provoke injury to the rectum at the six o' clock position and might provoke urosymphyseal fistulation at the twelve o'clock position.	3
For BNS, TUR and "hot-knife" incision yield a patency rate of respectively 58.3 and 72% with a low complication rate.	3
Repetitive endoluminal treatments in non-obliterative VUAS, radiation-induced BMS or BNS have the ability to stabilise the posterior stenosis and are easy to perform compared to reconstructive surgery.	3
Any form of endoluminal treatment might be associated with *de novo* UI (up to 25%) or worsening of existing UI (up to 15%).	3
Vesico-urethral anastomosis stricture, BMS and BNS with complete obliteration are not included in present series and endoluminal treatment is unlikely to be successful.	3
Urethral stents at the posterior urethra have a rather low patency rate (47-60%) and incontinence rate (19-82%).	3

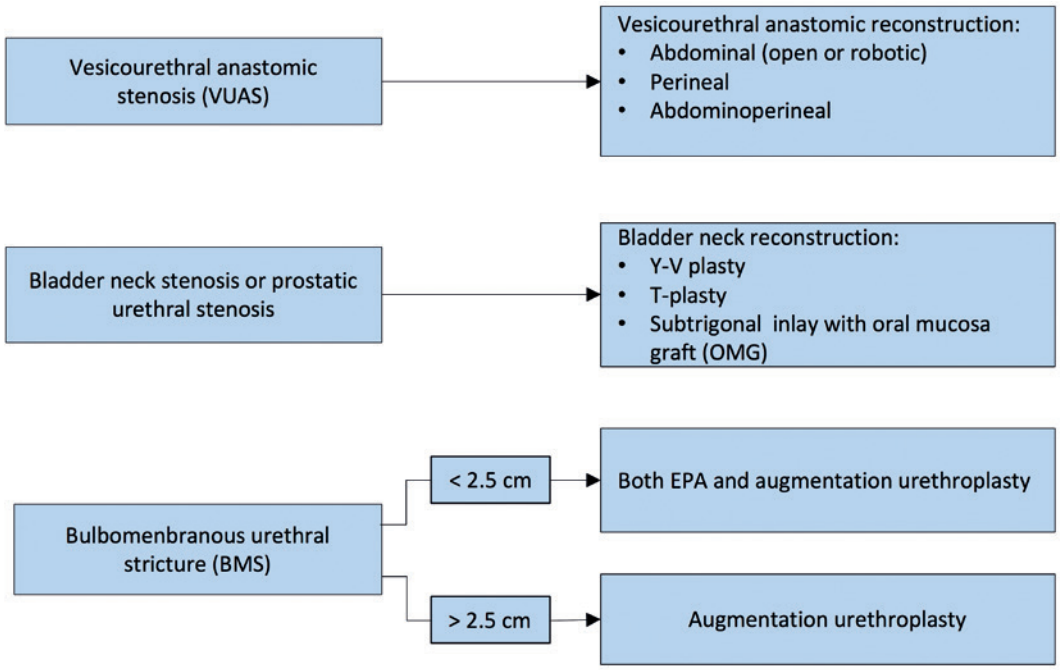
Recommendations	**Strength rating**
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as 1st line-treatment for a non-obliterative vesico-urethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous strictures (BMS).	Weak
Do not perform deep incisions at the six and twelve o' clock position during DVIU for VUAS or radiation-induced BMS.	Strong
Perform transurethral resection (TUR) or "hot-knife" DVIU as 1st line-treatment for patients with non-obliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repetitive endoluminal treatments in non-obliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of *de novo* urinary incontinence (UI) or exacerbation of existing UI after endoluminal treatment.	Weak

Do not perform endoluminal treatment in case of VUAS, BMS and BNS with complete obliteration.	Strong
Do not use stents for strictures at the posterior urethra.	Weak

6.3.5.1.3 Lower urinary tract reconstruction for non-traumatic posterior urethral stenosis

If endoluminal treatment (repeatedly) fails or in case of a completely obliterated posterior stenosis [403, 404, 408, 409], lower urinary tract reconstruction may be considered in fit patients motivated to undergo surgery (Figure 6.1). The choice of lower urinary tract reconstruction will depend upon the length, location, calibre and aetiology of the stenosis, continence status, bladder function, previous radiotherapy, patient's preference and surgeon's expertise.

Figure 6.1: Options for lower urinary tract reconstruction of non-traumatic posterior urethral obstruction (stenosis/stricture)



6.3.5.1.3.1 Redo vesico-urethral anastomosis for vesico-urethral anastomotic stenosis after radical prostatectomy

After excision of the stenosis, ReDo vesico-urethral anastomosis (ReDo VUA) can be performed. This may be performed via a retropubic, perineal, combined abdominoperineal or robot-assisted approach. Nikolavsky *et al*. proposes a retropubic approach for VUAS involving the bladder neck, a perineal approach for short VUAS with intact bladder neck and an abdominoperineal approach for long segment (> 3 cm) VUAS with bladder neck involvement [408]. The ReDo VUA must be performed in a tension-free fashion which can be achieved either by mobilisation of the bladder (retropubic approach), mobilisation of the bulbar urethra with corporal splitting and inferior pubectomy if necessary (perineal approach) or both (abdominoperineal approach)[408, 410]. Dinerman *et al*. reported a robot-assisted abdominoperineal approach in a case with 4.5 cm long complete obliteration [411]. Kirshenbaum *et al*. reported a pure robot-assisted abdominal approach. Regardless of the approach, the procedure is technically demanding due to the location deep under the pubic symphysis, and the proximity of the external sphincter [410]. As a consequence, the surgical morbidity must be taken into account. As most patients with VUAS were healthy enough to undergo RP, most patients will likewise remain fit and eligible for VUAS surgical reconstruction [408, 410].

Table 6.9: Outcomes of ReDo vesico-urethral anastomosis

Study	N	Approach (%)	Previous RT (%)	FU (months)	Length (cm)	Patency (%)	Incontinence (%)	Complications (%)
Nikolavsky *et al*. [408]	12	Perineal: 25 Abdominal: 67 Abdominoperineal: 17	25	76 (14-120)	2.5 (1-5)	67	58	Persistent extravasation due to anastomotic dehiscence grade 3b: 8.3 (prior RT)
Mundy *et al*. [410]	17	Transperineal	0	NR	NR	88	100	NR
	6		100	NR	NR	67	100	NR
Schuettfort *et al*. [412]	22	Transperineal	0	45 (4-77)	NR	91	100*	Rectal injury: 4 Lower leg paresthesia: 4
	1		100		NR	0	100*	
Pfalzgraf *et al*. [413]	20	Retropubic	NR	63 (15-109)	NR	60	65**	UTI: 5 Fever: 5 Renal failure: 5 (all grade 2)
Giudice *et al*. [414]	10	Perineal: 5 Abdominal: 4 Combined: 1	NR	30 (4-106)	NR	80	70	NR
Dinerman *et al*. [411]	1	Robot-assisted abdominoperineal	0	12	4.5	100	0***	0
Kirshenbaum *et al*. [409]	5	Robot-assisted abdominal (±VY-plasty)	0	14 (5-30-)	NR	60	0	Pubovesical fistula: 20 grade 3b

FU = follow-up; N = number of patients; NR = not reported; RT = radiotherapy; UTI = Urinary tract infection.

* *incontinent before ReDo VUA.*

** *de novo incontinence in four out of eleven patients.*

****social continent (1 pad/day).*

ReDo VUA in non-irradiated patients yields patency rates of 60-91% (Table 6.9) [408-410, 412-414]. Prior radiotherapy is a risk factor for failure [410, 412]. In addition, radiation-induced bladder toxicity might provoke reduced bladder capacity, low bladder compliance, bladder spasms and pain, and urethral necrosis making reconstruction futile (see below) [390, 410, 415]. ReDo VUA should only be done in patients with adequate bladder function and in the absence of (peri)-urethral pathology (urethral necrosis, calcification, fistulation). Flaps (gracilis flap, peritoneal flap) to support and protect the anastomosis may be beneficial in irradiated patients [408].

With the transperineal approach, UI is inevitable, as this approach disrupts the external sphincter [409, 410, 412, 414]. With the retropubic approach, Pfalzgraf *et al*. reported *de novo* incontinence in only four out of eleven (36%) patients [413]. In the series of Nikolavsky *et al*. where a retropubic approach was predominantly used, incontinence rate was 58% [408]. Kirshenbaum *et al*. reported no incontinence in five patients treated by robot-assisted retropubic approach [409]. Giudice *et al*. reported incontinence in one out of four patients treated with the retropubic approach [414]. Therefore, some authors [96, 408, 409] have proposed a preference for the retropubic approach in patients with good pre-operative urinary continence, although both approaches have never been directly compared for UI. In addition, the lack of perineal dissection by a retropubic approach will preserve the perineal anatomy and vascularisation which makes subsequent artificial urinary sphincter (AUS) less demanding [409]. Artificial urinary sphincter implantation should be deferred because of the risk of VUAS recurrence and difficulty of treating any recurrent VUAS with the cuff of the AUS in place [394, 410]. The exact timing of AUS placement is not consensual in the literature but most advise waiting at least three to six months to ensure stability of the VUA patency [390, 407, 410, 412, 413].

Due to the complexity of this pathology the EAU Urethral Strictures Panel advises that VUAS reconstruction should be performed only in experienced high-volume centres, particularly after prior radiotherapy or other energy ablative treatments.

Summary of evidence	LE
ReDo VUA has patency rates of 60-91% in non-irradiated patients and 67% in irradiated patients with obliterative VUAS or VUAS refractory to endoluminal treatment.	3
Urinary incontinence is inevitable after transperineal ReDo VUA. Artificial urinary sphincter placement can be offered after three to six months if patency of ReDo VUA is ensured.	3
De novo incontinence with retropubic ReDo VUA is 0-58%.	3

Recommendations	Strength rating
Perform ReDo vesico-urethral anastomosis (VUA) in non-irradiated patients and irradiated patients with adequate bladder function with obliterative vesico-urethral anastomosis stricture or vesico-urethral anastomosis stricture refractory to endoluminal treatment.	Weak
Warn patient that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage, after at least three to six months.	Strong
Offer ReDo VUA by retropubic approach if the patient is pre-operatively continent.	Weak

6.3.5.1.3.2 Posterior stenosis after surgery for benign prostatic obstruction

6.3.5.1.3.2.1 Bladder neck reconstruction for bladder neck stenosis after surgery for benign prostatic obstruction

The bladder neck is augmented by advancement of local bladder flaps (Y-V or T-plasty) with or without resection of scar tissue. They are used for BNS refractory to endoscopic treatments [409, 416-418]. Patency rates vary between 83% to 100% with fourteen to 45 months follow-up [409, 416-418]. There is a trend to perform bladder neck reconstruction by minimally invasive approach (laparoscopic, robot-assisted)[409, 417, 418]. *De novo* incontinence rate ranges from 0% to 14% [409, 416-418]. Satisfaction among patient is high with 88.5% of patients stating that they are pleased with the surgery, with an improvement of QoL in 75% of patients [416, 418]. Recently, a robot-assisted augmentation technique with subtrigonal buccal mucosa inlay has been successfully reported in a case report, but this technique requires further investigation [419].

See supplementary Table S6.14 for further information.

6.3.5.1.3.2.2 Bulbomembranous strictures after surgery for benign prostatic obstruction

Bulbomembranous urethral strictures (BMS) after TURP or simple prostatectomy are managed as bulbar strictures and can be treated by EPA or augmentation urethroplasty with a graft, taking into account the length and tightness of the stricture [79, 420]. As reconstruction is in the proximity of the external sphincter and the bladder neck was already damaged during BPO surgery, the risk of incontinence (up to 25%) is present [79].

Summary of evidence	LE
Bladder neck reconstruction with Y-V or T-plasty for treatment refractory BNS has patency rates of 83-100%.	3
Incontinence occurs in up to 14% with bladder neck reconstruction and up to 25% after reconstruction of BMS after previous surgery for BPO.	3

Recommendations	Strength rating
Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis (BNS).	Weak
Warn patients about *de novo* urinary incontinence after reconstruction for BNS or bulbomembranous urethral strictures with previous benign prostatic obstruction surgery as aetiology.	Strong

6.3.5.1.3.3 Radiation/high-energy induced posterior strictures

6.3.5.1.3.3.1 Bulbomembranous strictures secondary to radiation/high energy sources

The major challenge in treating radiation-induced strictures is the consequent tissue damage with impaired healing capacity, involving not only the stricture itself but also the adjacent proximal and distal areas of the scar [410, 421]. Additionally, proximity of the stricture to the external sphincter can further complicate surgery [79]. Due to these challenges, patients with radiation-induced BMS have long been considered poor candidates for urethral reconstruction, and have been treated with urinary diversion if endoscopic treatments failed or were not possible [410].

Most radiation-induced BMS are short and in these cases EPA is possible [79, 184, 422, 423]. Reported patency rates vary between 67% and 95% [79, 184, 423, 424]. *De novo* UI was reported in 33-36% of cases [79, 184, 423, 424] and this seems to be higher compared to the rates reported for bulbar and traumatic-posterior strictures (see sections 6.3.2 and 6.3.5). Chung *et al*. reported *de novo* incontinence in twelve out of 36 (33%) patients with EPA for radiation-induced BMS vs. four out of 33 (12%) patients with EPA for PFUI (p=0.05) [424].

Excision and primary anastomosis has the advantage of avoiding the use of a graft or a local flap in an area of poor vascular health. However, EPA will not be possible for BMS with a long bulbar segment and in these cases, augmentation urethroplasty will be necessary despite the aforementioned concerns [184, 423, 425, 426]. Glass *et al*. used a cut-off of 2.5 cm to proceed with augmentation urethroplasty, whilst this was 2 cm by Meeks *et al*. [423, 426]. Some authors have even used augmentation urethroplasty as their standard technique for radiation-induced BMS [355]. Both dorsal [420, 425] and ventral onlay [355, 426] have been described to treat radiation-induced BMS. In the absence of a robust vascular graft bed, the support by a gracilis flap has been proposed during ventral onlay graft urethroplasty [426, 427]. Patency rates with augmentation urethroplasty vary between 50 and 83% [184, 355, 423, 425] with *de novo* incontinence ranging between 11 and 50% [184, 355, 425] (see supplementary Table S6.15). Rourke *et al*. reported a patency rate of 91% vs. 75% for respectively EPA and augmentation urethroplasty but this difference did not reach statistical significance (p=0.31) [425]. Of note, strictures treated with augmentation urethroplasty were significantly longer compared to those treated by EPA (respectively 6.1 vs. 2.1 cm; $p < 0.001$). They reported no significant differences in *de novo* urinary incontinence (26 vs. 25%; p=1), new onset ED (35 vs. 0%; p=0.06) or other adverse events (30% vs. 33%; p=1) [425].

6.3.5.1.3.3.2 Prostatic strictures secondary to radiation/high energy sources

Radiotherapy and high-energy modalities (cryoablation, HIFU) might provoke prostatic necrosis, sloughing and obstruction [96]. Cases refractory to TUR and with good bladder capacity might be salvaged by prostatectomy taking into account the morbidity associated with salvage RP (rectal injury, VUAS, incontinence) [96, 421]. Mundy *et al*. treated nine patients with patency in six, (67%) and one (11%) needing an AUS for severe incontinence [410].

Cases with impaired bladder function, urethral necrosis and/or peri-urethral pathology should be considered for supravesical diversion, especially if a suprapubic catheter is not tolerated due to bladder pain or spasms [390, 407, 410, 415].

Recently, a "pull-through" procedure has been reported as an alternative to cutaneous diversion for reconstruction of the devastated posterior urethra associated with a defunctionalised bladder after radiation where tissue vascularity and quality is poor [428]. This novel technique of total lower urinary tract reconstruction combines salvage cystectomy, ileal neobladder formation and urethral pull-through. An AUS was implanted in a 2nd stage. All eight patients maintained a patent posterior urethra after a median follow-up of 58 (range 16-84) months. Five patients experienced low-grade complications after the 1st stage, but no high-grade complications were reported. Four out of eight (50%) patients experienced cuff erosion with need for removal and subsequent reimplantation. After a median of two revision surgeries (range 0 to 4), all patients achieved social continence enhancing QoL [428]. This technique requires further validation before its use can be recommended.

Summary of evidence	**LE**
Patency rates with EPA and augmentation urethroplasty are respectively 67-95% and 50-83% in case of radiation-induced BMS.	3
Radiation-induced BMS longer than 2-2.5 cm are rarely amenable for EPA.	3
De novo incontinence and new onset ED after urethral surgery for radiation-induced BMS are reported in respectively 11-50% and 0-35% of cases.	3
Salvage prostatectomy is able to achieve patency in 67% of patients for prostatic strictures after irradiation or high-energy treatments but morbidity is substantial.	4

Recommendations	**Strength rating**
Use either excision and primary anastomosis (EPA) or augmentation urethroplasty for short (< 2.5 cm) radiation-induced bulbomembranous strictures (BMS) refractory to endoscopic treatment depending on surgeon's experience.	Weak

Perform augmentation urethroplasty for long (> 2.5 cm) radiation-induced BMS.	Weak
Warn patients about the risk of *de novo* incontinence and new onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to irradiation or high-energy treatment.	Weak

6.3.5.1.4 Extirpative surgery and urinary diversion for non-traumatic posterior urethral stenosis

In complex and/or recurrent cases [408], lower urinary tract reconstruction is not possible or not indicated due to severe necrosis, calcification and significant morbidity, especially severe pain [407]. Intractable haematuria or fistulation might be other reasons to abandon the urethral outlet. Typically, the patient has a history of pelvic irradiation or high energy prostate cancer treatment and several previous attempts to achieve cure. Moreover, and equally important, any of the options used to deal with a devastated posterior urethra are dependent upon good bladder capacity, compliance and function allowing for bladder preservation as well as healthy distal ureters [390, 407]. The last resort therapeutic option is urinary diversion (continent or incontinent) with or without cystectomy [410, 415]. Different techniques have been described and the choice between them largely depends on the bladder capacity, presence of local symptoms, performance status and expectations of the patient. Cystectomy during urinary diversion is able to palliate symptoms of intractable bladder pain, spasms and haematuria which are especially prevalent after pelvic radiotherapy [429-432]. The satisfaction rate was reported to be 100% and the overwhelming majority of patients would have undergone this extirpative surgery an average of thirteen months sooner in a study of fifteen patients by Sack *et al*. [433]. In a report by Faris *et al*., 27% of the patients also required bowel diversion due to intractable gastrointestinal morbidity, highlighting the complexity of this pathology [415].

Summary of evidence	**LE**
Urinary diversion can improve QoL in patients with a devastated lower urinary tract with a high satisfaction rate.	3
Cystectomy is able to palliate symptoms of intractable bladder pain, spasms and haematuria.	3

Recommendations	**Strength rating**
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak
Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms and/or haematuria.	Weak

6.3.5.2 Post-traumatic posterior stenosis

The acute and early management of PFUIs is discussed in the EAU Guidelines on Urological Trauma. A non-obliterative stenosis is the result of a partial injury at the membranous urethra, or occurs after unsuccessful early realignment of a partial or complete injury. An obliterative stenosis is the consequence of a complete injury with a distraction defect between the ruptured urethral ends. The gap between these ends fills up with dense fibrotic tissue [6].

The deferred management of PFUI is at earliest three months after the trauma. After that period, the pelvic haematoma has nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [434] and the patient is clinically stable and able to lie down in the lithotomy position [434, 435].

6.3.5.2.1 Endoluminal treatment for post-traumatic posterior stenosis

6.3.5.2.1.1 Endoluminal treatment as primary treatment for post-traumatic posterior stenosis

Endoluminal treatment (dilation, DVIU) of an obliterative stenosis using the cut-to-the light principle will not be successful [43] and has a risk of creating a false passage towards the bladder base or rectum [436]. For a non-obliterative, short (≤ 1.5 cm) stenosis, one attempt of endoluminal treatment (endoscopic incision or dilation) can be performed. Kulkarni *et al*. reported a 92.3 and 96.5% stricture-free rate with “cold knife” and holmium laser urethrotomy, respectively (median follow-up respectively 61 and 57 months) [437]. These results are challenged by Barbagli *et al*. who reported a 51% stricture-free rate with holmium laser urethrotomy but with no data on length of follow-up available [438]. Cai *et al*. compared patient outcomes between bipolar plasma vaporisation and “cold knife” DVIU in 53 patients with posterior traumatic (80%) and iatrogenic (20%) urethral strictures with significantly different stricture-free rates of 81.5% vs. 53.8% at a mean follow-up of 13.9 months, respectively [439]. No severe complications were reported in either group. A statistically significant shorter operative time was found in the bipolar group [439]. Barratt *et al*. calculated a composite

stricture-free rate of 20% after all types of endoscopic treatments (but with a mix of obliterative and non-obliterative stenoses) [43]. *De novo* UI was reported in 4% of cases [43]. Repetitive endoluminal treatments are unlikely to be curative and must be discouraged as this delays the time to definitive cure and can lead to more complications [440, 441].

6.3.5.2.1.2 Endoluminal treatment after failed urethroplasty for post-traumatic posterior stenosis

In case of a non-obliterative and short (≤ 1 cm) recurrence after failed urethroplasty, endoluminal treatment can be performed [442, 443]. Although a 1st and 2nd DVIU can be successful with a stricture-free rate of 22.9-77.3% and 0-60% respectively, three or more incisions are never successful (see supplementary Table S6.16) [442-446]. Therefore, repetitive endoluminal treatments (dilations and/or endoscopic incisions) can only be considered as a palliative option [443, 447].

Summary of evidence	LE
Endoluminal treatment of obliterative stenoses is not successful and may create false passages towards bladder or rectum.	3
Endoluminal treatment of short, non-obliterative, stenoses has a 20-96.5% stricture-free rate.	3
A 1st DVIU has stricture-free rates of 22.9-77.3% for a short and non-obliterative recurrence after excision and primary anastomosis.	3

Recommendations	Strength rating
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, non-obliterative stenosis.	Weak
Do not perform more than two direct vision internal urethrotomies and/or dilatations for a short and non-obliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

6.3.5.2.2 Urethroplasty for post-traumatic posterior stenosis

In view of the complexity and difficulty of urethroplasty and the fact that the best results are obtained with its first attempt, this surgery must be performed in high-volume centres [448-450]. It has been calculated that to achieve and maintain sufficient experience in the reconstruction of PFUI, one centre per twelve million inhabitants is sufficient (for well-resourced countries) [449].

6.3.5.2.2.1 First urethroplasty for post-traumatic posterior stenosis

6.3.5.2.2.1.1 Indication and technique of urethroplasty for post-traumatic posterior stenosis

Progressive perineal EPA is the standard treatment for an obliterative stenosis and for a non-obliterative stenosis as first attempt, or after failure of primary endoluminal treatment [43, 451].

Although both a midline and inverted U-incision are possible to gain access to the posterior urethra, a midline incision is associated with a significant reduction in trauma to the superficial perineal and posterior scrotal nerves and vessels, in the rate of surgical site infections (3.1 vs. 16.4%) and reduced length of hospitalisation [373].

A combined transpubic abdomino-perineal approach is only necessary in complicated cases such as those with associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury [436]. Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure [452]. Although also considered complex situations, iatrogenic recto-urethral fistula (after misdirected endoscopic treatment), traumatic recto-urethral fistula < 5 cm from the anus, UCF and urinoma cavity can usually be corrected by a progressive perineal approach only [436, 453].

6.3.5.2.2.1.2 Patency rate after urethroplasty for post-traumatic posterior stenosis

The overall patency rate after deferred EPA is 85.7% [43]. Complete excision of scar tissue is a strong predictor for freedom of stricture whereas number (3-5 vs. 6-7) and size (3.0 vs. 4.0 cm) of sutures are not [454]. One retrospective cohort study showed a significantly improved patency rate if dorsal anterior urethral spatulation was performed compared to ventral anterior urethral spatulation [455]. Another retrospective study showed an improved patency rate after eversion of the urethral mucosa of both urethral ends before anastomosis ("valgus urethral mucosa anastomosis") [456]. The findings of both studies have yet to be confirmed in a prospective fashion.

To preserve the antegrade arterial inflow of the bulbar urethra and reduce the surgical trauma of "classic" deferred EPA, bulbar artery sparing EPA has been described [457]. Initial patency rates vary between 88.5-100% with 20-45 months of follow-up (see supplementary Table S6.17) [457-459]. Xie *et al*. only used this technique for distraction defects less than 2.5 cm [459]. No evidence exists to date whether bulbar artery sparing EPA is superior to the "classic" EPA in terms of patency rate and potency and continence rates.

In case of a very deep location of the proximal urethral end that makes anastomotic suturing impossible, Badenoch described a pull-through technique which has a 33.3-96.5% patency rate after 43-126 months of follow-up (see supplementary Table S6.18 for further information) [437, 460, 461]. With the aim to reduce stricture recurrence, Wong *et al*. advise a 1.5 cm segment overlap of the bulbar stump within the prostatic urethra during the pull-through technique [460]. To facilitate the suturing at the proximal part of the urethra located deep under the pubic bone, the robotic approach is under exploration but there is no evidence so far of improved outcome with this approach [462].

Patency rate in children varies between 75 and 89.8% (Table 6.10). The statement that EPA in children is associated with poorer results [463] cannot therefore be generally accepted [464].

Table 6.10: Outcomes of EPA in children

Study	N	Follow-up (months)	patency rate	Erectile dysfunction	Incontinence	Abdomino-perineal
Podesta *et al*. [465]	49	78 (60-264)	44 (89.8%)	3 (6.1%)	9 (18.4%)	21 (43%)
Waterloos *et al*. [466]	7	57 (8-198)	6 (85.7%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Singh *et al*. [463]	5	26 (12-42)	4 (80%)	NA	0 (0%)	0 (0%)
Singla *et al*. [467]	28	36 (3-58)	21 (75%)	-	1 (3.6%)	1 (3.6%)
Voelzke *et al*. [468]	18	13 (1-71)	16 (88.9%)	-	-	1 (5.6%)

N = number of patients; NA = not applicable.

6.3.5.2.2.1.3 Sexual function, urinary continence and rectal injury after urethroplasty for post-traumatic posterior stenosis

Regarding erectile function, a prospective study by Hosseini *et al*. found no significant difference before, and three or six months after EPA for posterior traumatic stenosis [469]. Another prospective study by Tang *et al*. also demonstrated no significant overall change in ED after urethroplasty. However, in the subgroup of patients with pre-operative non-vascular ED, a significant post-operative increase in ED was observed [470]. A meta-analysis of retrospective studies showed a significant decline of the rate of ED from 43.27% before to 24.01% after posterior urethroplasty ($p < 0.001$) [471]. Assessment of erectile function and its definitive treatment (e.g., penile prosthesis) should be performed two years after the trauma because of the potential return of normal erectile function within that time [472, 473].

After deferred EPA, antegrade ejaculation is present in 98.3-100% of cases [474, 475]. Decreased ejaculatory volume and/or diminished ejaculatory force were reported in 17.2-18.7% of cases but it cannot be assessed whether this is due to the trauma or due to the surgery [474, 475].

Continence after PFUI and urethroplasty is generally attributed to a competent bladder neck [43]. On the other hand, as most ruptures occur at the bulbomembranous junction just below the external sphincteric mechanism, at least a part of the external sphincter mechanism can be spared during urethroplasty [476]. Therefore, incontinence is rare with deferred EPA (6.8%) and is usually due to incompetence of the bladder neck although an incompetent bladder neck will not necessarily result in incontinence after urethroplasty [43, 476].

Rectal injury is a relative rare (0-10.2%) but a severe complication after deferred EPA (see supplementary Table S6.19) [434, 446, 452, 455, 477-481]. The risk of rectal injury tends to be higher in complicated cases or cases with previous urethral manipulations [434, 477, 482] .

6.3.5.2.2.2 ReDo-urethroplasty for post-traumatic posterior stenosis

In case of a recurrent stenosis, a repeat ("ReDo") urethroplasty is possible. In the majority of cases, especially if not all consecutive length-gaining manoeuvres have been used during the 1st EPA, another EPA can be performed [465, 477, 478, 483, 484]. The Badenoch pull-through technique is again an option if no adequate mucosa-to-mucosa suturing is possible (See supplementary Table S6.18) [460, 461]. In case of excessive dead space after resection of the fibrosis, gracilis muscle [482] or omental flaps (laparoscopically harvested if urethroplasty was performed using perineal approach only) [436, 480] have been advised to fill up this space

and support the anastomosis. These flaps, or alternatively bulbospongious muscle or local subcutaneous dartos flaps, are also useful to separate the suture lines in case of a concomitant recto-urethral fistula [436, 448, 453, 482]. If the urethra cannot be anastomosed in a tension-free fashion despite the aforementioned manoeuvres or in cases of ischemic narrowing/necrosis of the bulbar urethra, options are a tubed preputial island flap, staged BMG urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty [448, 478, 483, 485]. In case of entero-urethroplasty, the sigmoid colon is preferred above ileum (which is in turn better than stomach) because of the proximity of the vascular pedicle to the perineum. Entero-urethroplasty should only be done in the presence of a competent bladder neck because subsequent implantation of an AUS is nearly impossible [485].

Patency rate of different types of ReDo-urethroplasty varies between 37.5-100% (Table 6.11) [443, 448, 450, 477, 478, 480, 483-485]. An alternative is to abandon the normal urinary outlet and opt for Mitrofanoff-vesicostomy, PU (if local perineoscrotal skin is suitable) or permanent suprapubic diversion [478, 485].

Table 6.11: Outcome of different types of ReDo-urethroplasty

Study	Type	N	Follow-up (months)	Patency rate
Bhagat *et al*. [483]	Progressive perineal EPA	28	29 (12-108)	36 (83,72%)
	Transpubic EPA	12		
	Tubed preputial flap	1		
	Staged BMG + local flap	2		
Fu *et al*. [477]	Progressive perineal EPA	55	36 (18-47)	33 (60%)
Garg *et al*. [478]	Progressive perineal EPA	40	31 ± 11	30 (75%)
	Transpubic EPA	2	25	2 (100%)
	Tubed preputial flap	1	25	1 (100%)
	Staged BMG + local flap	2	17	1 (50%)
	Radial forearm free flap	1	15	1 (100%)
Gupta *et al*. [484]	Progressive perineal EPA	52	54 (10-144)	42 (80.8%)
Koraitim M. [443]	Progressive perineal EPA	4	168 (12-300)	4 (100%)
	Transpubic EPA	5		5 (100%)
Kulkarni *et al*. [480]	Progressive perineal EPA	15	18 (6-24)	14 (93.3%)
Kulkarni *et al*. [448]	Progressive perineal EPA	541	68 (12-240)	412 (79.1%)
	Tubed preputial flap	37		30 (81%)
	Staged BMG flap	10		6 (60%)
	Staged BMG + local flap	15		13 (86.6%)
	Entero-urethroplasty	2		2 (100%)
	Radial forearm free flap	3		3 (100%)
	Pedicled anterolateral thigh flap	1		1 (100%)
Mundy *et al*. [485]	Entero-urethroplasty	11	NA	7 (63.6%)
Podesta *et al*. [465]	Transpubic EPA	4	120 (72-204)	4 (100%)
Singh *et al*. [450]	Progressive perineal EPA	8	31 (13-90)	3 (37.5%)
Singh *et al*. [463]	Progressive perineal EPA	37	26 (12-42)	32 (86.5%)
Singla *et al*. [467]	Progressive perineal EPA	1	NA	1 (100%)
	Tubed preputial flap	2	NA	2 (100%)

BMG = buccal mucosa graft; EPA = excision and primary anastomosis; N = number of patients; NA = not applicable.

Summary of evidence	LE
The best results are obtained after the 1st urethroplasty.	4
The overall stricture-free rate after EPA is 85.7%. By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed.	3
After failed endoluminal treatment, EPA is the standard treatment for a non-obliterative stenosis.	3
Both a midline and inverted U perineal incision equally gain access to the posterior urethra but a midline incision is associated with less anatomical damage to local vessels and nerves, reduced risk of surgical site infection and hospital stay.	2b

Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure.	4
By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed except for very long distraction defects and in case of complicated situations, which include associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	3
If the urethra cannot be anastomosed in a tension-free fashion or in case of ischaemic narrowing/ necrosis of the bulbar urethra, options are a tubed preputial island flap, staged buccal mucosa graft urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty.	3
In case of excessive dead space after resection of the fibrosis, local flaps have been advised to fill up this space and support the anastomosis. These flaps are also useful to separate the suture lines in case of a concomitant recto-urethral fistula.	3

Recommendations	Strength rating
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis.	Strong
Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdomino-perineal reconstruction.	Strong
Reserve abdomino-perineal reconstruction for complicated situations including very long distraction defect, para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	Weak
Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant recto-urethral fistula.	Weak

7. DISEASE MANAGEMENT IN FEMALES

7.1 Signs and symptoms of female urethral strictures

The symptoms of female urethral strictures are non-specific and therefore generally non-diagnostic. Female urethral stricture presents with mixed filling and voiding symptoms with frequency in 60.2%, urgency in 51%, poor flow in 42%, incomplete emptying in 42%, UI in 36% (stress, urge or mixed), nocturia in 26%, UTI in 20% and straining to void in 16%. It very rarely presents with urethral pain (3%), terminal dribble (1%), haematuria (1%) or renal failure (1%) (see supplementary Table S7.1) [10, 18, 119, 121, 122, 127, 129, 131, 133, 486-489].

There is often a significant delay in diagnosis of FUS from time of development of symptoms with mean delays of 4.3-12 years described (range 1-30 years) [124, 131].

7.2 Diagnosis of female urethral strictures

Twenty-four studies detail investigations leading to a diagnosis of FUS (see supplementary Table S7.2) [8, 10, 119-122, 125-131, 133, 488-497]. In all cases a full history was taken and a detailed pelvic examination was performed to assess for prolapse, masses, scars and vulval dermatological disorders such as LS, lichen planus or vulvo-vaginal atrophy. Flow rate and US PVR assessment was evaluated in eighteen (75%) and seventeen (71%) studies respectively. Lateral VCUG was performed routinely in fifteen studies (63%) and as required in one study (4%). Cystourethroscopy was performed routinely in thirteen studies (54%) and as required in two studies (8%). Urodynamics (UDS) were performed routinely in four studies (17%) and as required in seven studies (30%) whilst video-urodynamics (VUDS) were performed routinely in three studies (13%) and urethral calibration (to < 14 Fr) also in three studies (13%). Pelvic MRI was performed as required in four series (17%) whilst transrectal US (TRUS) and renal US were each performed routinely in two series (8%) and intravenous urography (IVU) in ten (4%).

Flow rate and PVR assessment make inherent sense as initial non-invasive screening tools and allow for simple monitoring of effect of treatment. Voiding cystourethrography and/or VUDS will permit diagnosis of BOO [18, 496], visualisation of ballooning above the proximal end of the FUS [129], and delineation of alternate or co-existent diagnoses such as detrusor overactivity (DO) and SUI [122], although VCUG, VUDS and UDS require the ability to insert a 6 Fr catheter and may not be possible without preliminary urethral dilatation in all cases of FUS [489]. Likewise, passage of a cystourethroscopy will require a preliminary dilation in the majority of cases even when a paediatric uretero-renoscope is utilised [120]. Cystourethroscopy will allow for formal identification of the distal end of the FUS and will also allow for exclusion of a functional cause of BOO [129]. Magnetic resonance imaging is performed mainly to exclude alternate pathology such as urethral diverticulum and urethral carcinoma and also allows assessment of the degree of urethral fibrosis associated with FUS [489, 498]. Proponents of TRUS utilise it in lieu of MRI and also for visualisation of the dilated urethra above the proximal end of the FUS [499].

7.3 Treatment of female urethral strictures

*7.3.1 **Minimally invasive techniques for treatment of female urethral strictures***

Several minimally invasive treatments have been reported; these include urethrotomy, dilatation, meatotomy and meatoplasty. Meatotomy and meatoplasty are essentially the same procedure in the female urethra and the term 'meatoplasty' will be used throughout this document.

7.3.1.1 Urethrotomy for treatment of female urethral strictures

No papers were found detailing the use and outcomes of urethrotomy specifically for the management of FUS. Internal urethrotomy or dilation was used by Massey and Abrams [500] to treat a variety of pathologies, including FUS, causing symptoms of obstructed voiding, and resulted in symptomatic improvement in 80% of patients. As this study included women with a variety of complaints and did not assess urodynamic parameters, the results in the patient subset with true urethral stricture are unclear. If utilised, urethrotomy in the female urethra involves incisions at three, nine and occasionally twelve o'clock [500].

7.3.1.2 Urethral dilatation for treatment of female urethral strictures

With this treatment, the urethra is dilated to between 30 Fr and 41 Fr Some patients will continue with ISD. Romman *et al*. 2012 [488] and Popat & Zimmern [489] also described suture plication of bleeding areas of the meatus if required post-urethral dilatation.

Four studies described the results after 12-59 months follow-up of, in total, 183 patients having dilatation only. Patency rates ranges from 7.5 to 51% (see Table 7.1) [122, 123, 488, 489]. In another four studies that included, in total, 31 patients that continued to perform ISD, stabilisation of the stricture with "patency" was obtained in 37.3-100% of cases at 12-21 months of follow-up (see Table 7.1)[8, 127, 130, 494].

New onset SUI (0.8%) and other complications are very rare after dilation (see supplementary Table S7.3). Due to the low complication rate, the minimally invasive nature of the technique and the reasonable success rate, it is acceptable to start with urethral dilation as a first-line treatment for an uncomplicated FUS.

7.3.1.3 Meatoplasty for treatment of female urethral strictures

Meatal stenosis is extremely rare, with only 2/58 (3%) of females evaluated for voiding dysfunction found to have true meatal stenosis [501]. Only three meatoplasty papers were identified containing 60 patients (see supplementary Table S7.4): one [502] detailed meatoplasty outcomes in a series of 58 girls whilst the 2nd was from a study analysing outcomes of various forms of FUS treatment that included one case of meatoplasty [503], and the third was a case report [127]. The patency rate of meatoplasty in girls is excellent with 97% of the 58 girls in Hesing's series having a successful outcome with no reported side effects at twelve months. Forty-eight of 50 patients experienced resolution of their recurrent UTIs and improved voiding symptoms one year after meatoplasty [502]. None of these studies reported incontinence or other acute complications. For short meatal strictures, meatoplasty is the first-line treatment option.

*7.3.2 **Urethroplasty for treatment of female urethral strictures***

Twenty-five papers report the outcomes of urethroplasty for FUS disease in 231 patients in total after the scope search of the Panel. The Panel have analysed the outcomes of these urethroplasty according to flap or graft type as: vaginal graft, vaginal flap, labial/vestibular graft, labial/vestibular flap and buccal or lingual graft.

In female urethroplasty, a dorsal approach is via a stricturotomy at twelve o'clock, a ventral approach is via a stricturotomy at six o'clock and circumferential is a full circumference reconstruction.

7.3.2.1 Vaginal graft augmentation urethroplasty for treatment of female urethral strictures

There were four studies reporting vaginal graft urethroplasty including 37 patients [10, 492, 497, 504]. All 37

vaginal graft urethroplasties were performed via a dorsal approach in women with a mean/median age of 47.5-60.6 years (range 35-70). In these studies, patency rates of 73-100% were reported after 22-27 months follow-up (Table 7.1). No complications and no new onset UI were reported.

See supplementary Table S7.5 for further information.

7.3.2.2 Vaginal flap augmentation urethroplasty for treatment of female urethral strictures

Vaginal flap urethroplasty was reported in 70 women and was always via a ventral approach, utilising an inverted U vaginal flap inlay in five studies (n=52) [121, 122, 125, 486, 487], a lateral C vaginal flap in three studies (n=17) [119, 127, 131] and one vaginal island flap urethroplasty in one patient [125]. At a mean/median follow-up time of 30-80.7 months, patency rates of 67-100% were reported (Table 7.1). Eight (11.4%) patients had a simultaneous pubo-vaginal sling (PVS), four (5.7%) had a simultaneous Martius fat pad flap interposition and one (1.4%) had a simultaneous excision of urethral diverticulum. Five (7.1%) patients developed new onset UI, two (2.9%) developed UTIs and two (2.9%) described temporary intravaginal direction of their urinary stream.

See supplementary Table S7.6 for further information.

7.3.2.3 Labial/vestibular graft augmentation urethroplasty for treatment of female urethral strictures

There were four papers detailing the outcomes of 31 patients having labial or vestibular graft urethroplasty (see supplementary Table S7.7); nineteen had ventral labial minora graft [126, 133, 491] and twelve had dorsal labial graft [130]. At a mean follow-up of 15-24 months, patency rates of 75-100% were reported with ventral grafting whilst this was 100% with dorsal grafting at six to fifteen months follow-up (Table 7.1). One (5.2%) ventral graft patient developed a UTI post-surgery. There were no other complications (including UI).

7.3.2.4 Labial/vestibular flap urethroplasty for treatment of female urethral strictures

There were two papers detailing the outcomes of nineteen patients having labial/vestibular flap urethroplasty: two had a ventral labia minora flap [505] and seventeen had a dorsal vestibular flap [11]. At a follow-up of 24 months the two ventral flap patients (100%) remained stricture-free whilst fifteen (88%) dorsal flap patients remained stricture-free at a mean of twelve months follow-up (Table 7.1 and supplementary Table S7.8). There were no adverse short- or long-term effects reported in either group.

7.3.2.5 Buccal and lingual mucosal graft augmentation urethroplasty for treatment of female urethral strictures

There were twelve papers detailing the outcomes of 73 patients, all treated with BMG except in the series of Sharma *et al*. who used lingual mucosa graft (LMG) in fifteen patients at the dorsal urethra [120]; 44 patients with dorsal onlay oral (buccal or lingual) mucosa graft (DOOMG) [120-122, 125, 128, 490, 496, 504, 506]; 27 with ventral onlay BMG (VOBMG) [121, 129, 507, 508] and two with circumferential BMG urethroplasty [121]. At a mean/median follow-up of 6-28 months, 62.5-100% of DOOMG urethroplasty patients were stricture-free whilst 50-100% of VOBMG patients were stricture-free at a mean of 10-24 months follow-up. Both circumferential BMG patients were stricture-free at a mean of 21 months follow-up (Table 7.1). Seven (15.9%) DOOMG patients suffered a low-grade short-term adverse effect and no patients in any subgroup developed sustained new onset UI.

For further information see supplementary Tables S7.9, S7.10 and S7.11.

7.3.2.6 Anastomotic urethroplasty

Anastomotic urethroplasty has only been described in two cases in the literature – both in women with very short mid-urethral stricture and both of whom were stricture-free at four and 24-months follow-up respectively. None of them suffered from UI post-operatively [121, 493] (see supplementary Table S7.12).

Table 7.1: Summary of available evidence on treatment of female urethral strictures

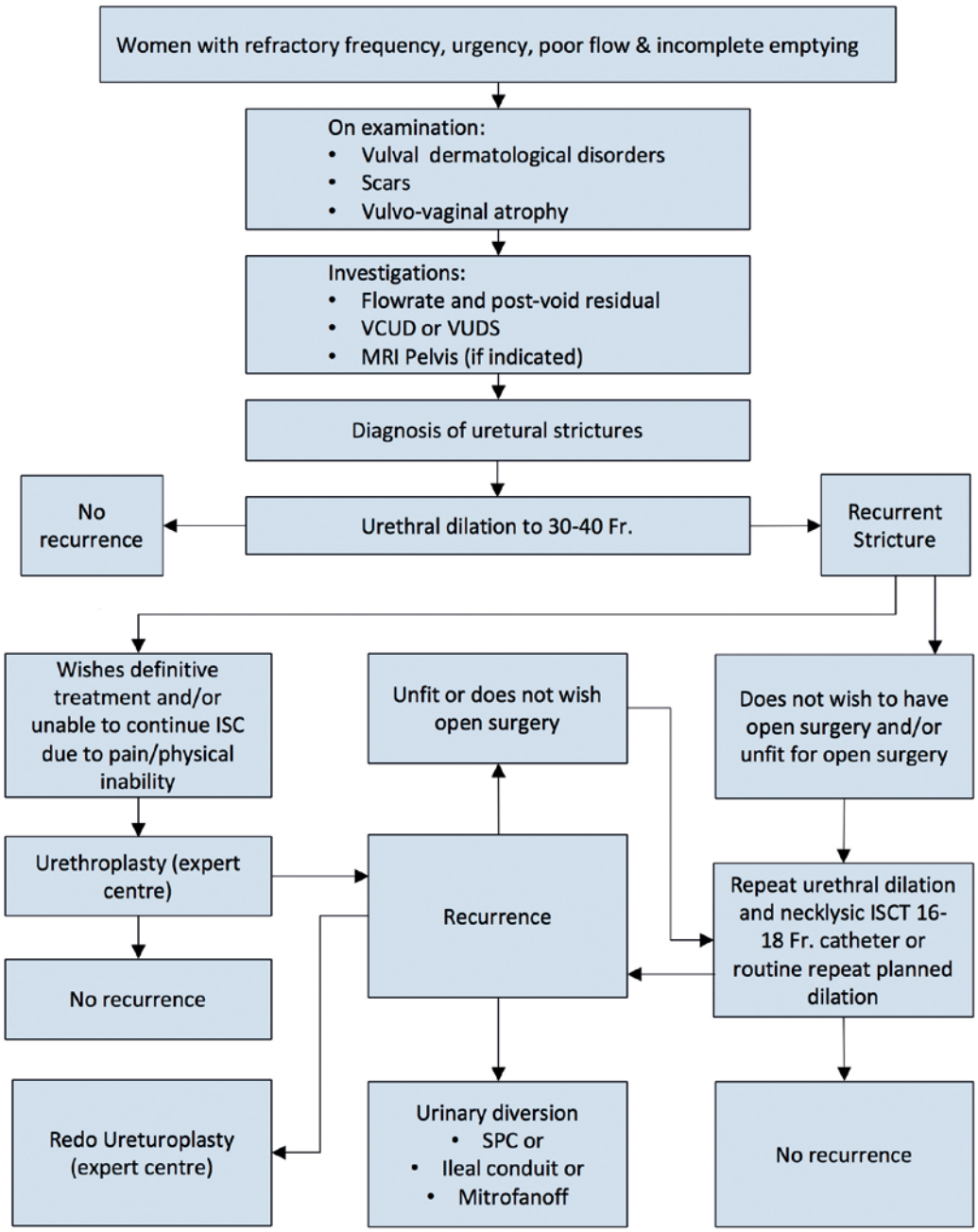
Treatment	No. of studies	N	Patency rate (%)	UI (%)	Mean/Median FU Months	Refs
Urethral Dilatation	4	183	7.5-51	0	12-59	[122, 123, 488, 489]
Urethral Dilatation + ISD/ planned repeat dilatation	4	31	37.3-100*	1.9	12-21	[8, 127, 130, 494]
Dorsal Vaginal graft urethroplasty	4	37	73-100	0	22.4-27	[10, 492, 497, 504]
Ventral Vaginal flap urethroplasty	8	70	67-100	7	30-80.7	[119, 121, 122, 125, 127, 131, 486, 487]
Ventral Labial/Vestibular graft urethroplasty	3	19	75-100	0	15-24	[126, 133, 491]
Dorsal Labial/Vestibular graft urethroplasty	1	12	100	0	6-15	[130]
Ventral Labial/Vestibular flap urethroplasty	1	2	100	0	24	[505]
Dorsal Labial/ Vestibular flap urethroplasty	1	15	88	0	12	[11]
Dorsal BMG urethroplasty	9	44	62.5-100	0	6-28	[120-122, 125, 128, 490, 496, 504, 506]
Ventral BMG urethroplasty	4	27	50-100	0	10-24	[121, 129, 507, 508]

FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; UI= urinary incontinence.

Summary of evidence	LE
Female urethral stricture symptoms are long standing and non-specific, the most commonly reported are frequency, urgency, poor flow, incomplete emptying and urinary incontinence. It is important to exclude FUS in female patients with LUTS.	3
Urethral dilatation alone to 30-41 Fr provides low stricture-free rates of mean 35% at mean follow-up 36.3 months.	3
Urethral dilatation and ISC or planned repeat dilatation provides stricture-free rates of 75%.	3
Urethroplasty provides stricture-free rates of 81-92%. No one particular type of urethroplasty is superior to another.	3
Meatotomy/meatoplasty for short meatal strictures has a success rate of 95% at twelve months follow-up.	3

Recommendations	Strength rating
Perform flow rate, post-void residual and voiding cystourethrogram or video-urodynamics in all women with refractory lower urinary tract symptoms.	Strong
Perform urethral dilatation to 30-41 Fr as initial treatment of female urethral stricture (FUS).	Weak
Perform repeat urethral dilatation and start planned weekly intermittent self-dilatation (ISD) with a 16-18 Fr catheter for the 1st recurrence of FUS.	Weak
Perform urethroplasty in women with a 2nd recurrence of FUS and who cannot perform ISD or wish definitive treatment. The technique for urethroplasty should be determined by the surgeon's experience, availability and quality of graft/flap material and quality of the ventral versus dorsal urethra.	Strong
Treat meatal strictures by meatotomy/meatoplasty.	Weak

Figure 7.1: Women with refractory frequency, urgency, poor flow and incomplete emptying



ISC = intermittent self-catheterisation; MRI = magnetic resonance imaging; VUDS = video-urodynamics.

8. DISEASE MANAGEMENT IN TRANSGENDER PATIENTS

8.1 Treatment of strictures in trans men

In trans men, stricture treatment depends on the time after neophallic reconstruction, stricture location, stricture length and quality of local tissues [509].

8.1.1 Management of strictures early after neophallic reconstruction

Urethral surgery on tissues in the acute phase of inflammation and wound healing is not indicated and should be postponed until any healing problems of the neophallus have been resolved and scar tissue formation in the urethra has been stabilised. This usually takes six months [27, 140]. Endoscopic incision for short (< 3 cm)

urethral strictures has been performed, mainly at the anastomotic site, with a maximum stricture-free rate of only 16.7% when performed within six months after neophallic reconstruction [510]. Insertion of a suprapubic catheter is the first-line treatment in cases of obstructive symptoms severely affecting the patient's QoL, recurrent UTI or retention. The alternative is perineostomy, which is a specialist procedure and should be performed by a urologist familiar with transgender urethral anatomy. The perineostomy may be closed at the time of formal urethral reconstruction [140].

*8.1.2 **Treatment of meatal stenosis in trans men***

Intermittent urethral dilatation is an option, as palliative treatment, for low-grade meatal stenosis with the interval of dilatation depending on the interval of stricture recurrence. Patients with high-grade meatal stenosis, those who refuse ISD, or those who want a durable solution should be offered simple meatotomy. Patency is 75% (mean follow-up 39 months) but the drawback is that the meatus will be in a hypospadiac position [140]. Alternatively, a staged urethroplasty can be offered [140].

*8.1.3 **Treatment of strictures at the neophallic urethra***

Endoscopic incision of a short stricture at the neophallic urethra has been reported but evidence is very scarce and the long-term results seem to be disappointing (34% patency rate after median follow-up of 51 months) [510].

Single-stage graft urethroplasty is only possible if the graft can be supported and covered by the healthy surrounding fatty tissue of the neophallus. Experience is very limited and reported patency rate is 50% after a mean follow-up of 102 months [140].

The standard treatment for these strictures is staged urethroplasty with or without graft augmentation [140, 509] (BMG or full thickness SG) [27, 140]. A patency rate of 69.7% has been described with these techniques (mean follow-up: 25 months) [140].

For complex (e.g., fully obliterated) or recurrent strictures at the neophallic urethra, a complete urethral substitution of this part needs to be performed. Different suitable flaps have been described (radial forearm free flap, superficial circumflex iliac artery free flap, pedicled groin flap). Double-face grafts with the ventral graft supported by rotating a part of the neoscrotum or by a gracilis flap have been successfully reported in a very limited number of patients [509].

*8.1.4 **Treatment of strictures at the anastomosis neophallic urethra-fixed part of the urethra***

Short, non-obliterative, strictures can be treated by endoscopic incision. A first endoscopic incision has a 45.5% patency rate but this dropped to 0% in case of three or more attempts (median follow-up of 51 months) [510]. Therefore, repetitive endoscopic incisions should be discouraged unless with palliative intent.

For very short (< 1 cm) low-grade strictures, Heineke-Mikulicz urethroplasty is an option reporting a 57.9% patency rate after a mean follow-up of 44 months [140].

If endoscopic incision fails or if the stricture is nearly or completely obliterative, options are EPA or graft augmentation urethroplasty. In case of short (< 2-3 cm) strictures, EPA yields a 57.1% patency rate (mean follow-up of 35 months) [27, 140]. If EPA is not possible, usually for strictures longer than 2 cm, a ventral onlay BMG urethroplasty demonstrated a 50% patency rate (median follow-up of 9.5 months) [511]. In case of insufficient ventral tissue during graft urethroplasty, it is advised to support this graft by a local fasciocutaneous flap [512]. An alternative (especially after failure of the previous techniques) can be a staged approach but no data are currently available [511].

*8.1.5 **Treatment of strictures at the fixed part of the urethra***

This part of the urethra has a more reliable blood supply and the dorsal part of the urethra is supported by the corporal bodies of the clitoris. Therefore, single-stage dorsal inlay graft urethroplasty is possible for strictures at this site. Experience however is very limited [140, 509].

Staged repair with or without a dorsal graft is a reliable treatment for these rare strictures [140].

*8.1.6 **Definitive perineostomy in trans men***

The vast majority of trans men have a strong desire to void in a standing position [509]. Therefore, definitive perineostomy should only be offered to those with refractory strictures or to patients with strictures who do not wish to have complex reconstructive surgery [27, 140].

8.2 Peri-operative care after treatment of strictures in trans men

Anecdotally, after endoscopic incision and urethroplasty, the urethral catheter is maintained for two to three weeks [510, 511]. Peri-catheter urethrography is advised before catheter removal as it might be challenging to reinsert the urethral catheter in case of urinary extravasation [511].

8.3 Strictures in trans women

It is acceptable to start with dilation of a short and non-obliterative stricture in trans women although no long-term data about the effectiveness are available [28, 513]. If this is not possible or if it fails, a short (< 1 cm) meatal stricture can be treated by Y-V meatoplasty with an 85% stricture-free rate [514]. Somewhat longer (1-2 cm) meatal strictures can be treated by a neovaginal advancement flap (inverted U or "7-flap") with no recurrence observed after 37 months median follow-up [515].

Summary of evidence	LE
After neophallic reconstruction, local tissues go through the different stages of wound healing and stable wound healing is usually achieved after six months.	3
After two attempts, endoscopic incision is no longer successful in trans men.	3
Two-stage urethroplasty for strictures at the neophallic urethra has a stricture-free rate of 69.7%.	3
Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women has a stricture-free rate of 85%.	3

Recommendations	Strength rating
Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty.	Strong
Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent.	Strong
Perform staged urethroplasty for strictures at the neophallic urethra if open reconstruction is indicated.	Weak
Perform Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women if open reconstruction is indicated.	Weak

9. TISSUE TRANSFER

9.1 Comparison of grafts with flaps

One small RCT (LS excluded) comparing OMG with PSF found no significant difference in urethral patency rate [516]. Penile skin flaps had a higher urogenital morbidity (superficial penile skin necrosis, penile torsion, penile hypoesthesia and post-void dribbling) and longer operation time compared to OMG. Furthermore, patient dissatisfaction was significantly higher with penile flaps [516]. Another small RCT (LS excluded) comparing penile skin grafts with PSF confirmed these findings with longer operation time and more superficial penile skin necrosis in the group of the flaps whereas the urethral patency rate was similar between both groups [359]. Several retrospective series also found a comparable urethral patency rate between PSF and grafts [268, 270, 275, 517] (Table 9.1).

Table 9.1: Comparative studies of grafts versus flaps used in urethroplasty for anterior urethral strictures

Study	Type of study	Follow-up (mo.)	Flap		Graft		p-value*
			Type	Urethral patency	type	Urethral patency	
Barbagli *et al*. [268]	Retrospective	55	LIF	12/18 (67%)	OMG/PSG	36/45 (80%)	0.32
Dubey *et al*. [516]	RCT	22-24	LIF	22/26 (84.6%)	BMG	24/27 (88.9%)	0.70
Fu *et al*. [270]	Retrospective	>12	All types	166/199 (83.4%)	LMG	80/94 (85.1%)	0.71
Hussein *et al*. [359]	RCT	36	TIF	15/19 (78.9%)	PSG	13/18 (72.2%)	0.25
Lumen *et al*. [275]	Retrospective	42-43	All types	23/29 (79.3%)	OMG/PSG	63/75 (84%)	0.57

Sa *et al*. [517]	Retrospective	28 (18-60)	TIF	28/34 (82.3%)	BMG	67/82 (81.7%)	0.851

BMG = buccal mucosa graft; Excl. = excluded; LIF = longitudinal island flap; LMG = lingual mucosa graft; LS = lichen sclerosus; mo = months; NR = not reported; OMG = oral mucosa graft; PSG = penile skin graft; TIF = transverse island flap; RCT = randomized controlled trial.
** if not reported: recalculated by EAU Urethral Strictures Panel with chi²-statistics.*

Due to their robust vascular pedicle, flaps can be used as a tube as well as a patch in a single-stage approach [448]. Castagnetti *et al*. showed that grafts used as a tube have significantly higher complication rates as compared to onlay grafts (OR: 5.86; 95% CI: 1.5-23.4) [518]. A review by Patterson *et al*. also reported high (circa 50%) complication and recurrence rates for tubularised grafts [519]. Iqbal *et al*. have shown an encouraging 87% stricture-free rate in 23 patients who were offered single-stage circumferential skin flap urethroplasty [279]. Therefore, if there is a need to reconstruct a complete urethral segment with a tissue-transfer tube in a one-stage operation, flaps are usually the preferred option. As flaps carry their own vascular supply to the reconstruction site, they do not rely on the local vascularisation of the recipient site. Therefore, they need to be considered in case of poor urethral vascularisation (e.g., after irradiation or dense scarring after previous urethroplasty) [275, 520]. In addition, flaps survive well in the presence of active urinary infection [521].

Grafts and flaps should not be considered competitors in urethral surgery. A combination of a flap with a graft is possible for complex, multifocal or penobulbar strictures [275, 522, 523].

Summary of evidence	LE
Flaps have a higher urogenital morbidity, but a comparable patency rate compared to grafts.	1b
Grafts have a significantly higher complication rate compared to flaps when complete tubularisation in a single-stage approach is needed.	1b
Flaps do not rely on the local vascularisation of the recipient site.	3

Recommendations	Strength rating
Use a graft above a flap when both options are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak

9.2 Comparison of different types of flaps

Different local flaps have been described. Penile skin flaps are generally hairless, although the ventral penile skin can be hair-bearing around the raphe in some ethnic groups/phenotypes. They can be harvested as a transverse preputial skin flap [524], a transverse distal PSF [362, 521, 525, 526] or as a longitudinal island flap [527]. Urethral patency rates vary between 74.2 and 100% [270, 362, 521, 524-527]. Complications include skin necrosis (0-3.8%), fistula (0-7%), penile deformity (0-7%), post-void dribbling (0-79%) and sacculation (0-16.5%) (see supplementary Table S9.1). As there are no direct comparative series available about these flaps it is not possible to determine which performs better.

Hair-bearing perineal and scrotal flaps have been described as well. Fu *et al*. demonstrated that PSF had a significantly better urethral patency rate compared to scrotal and perineal skin flaps (respectively 87.7%, 69% and 66.7%) [270]. The hair-bearing perineal and scrotal skin flaps are associated with hairball formation and chronic infection which may cause failure of the repair. A study of Blandy with long-term follow-up reports 3% revision for calculi and 3% revision for diverticula [528].

An alternative is to epilate the needed scrotal skin prior to tissue transfer [529, 530] or to patch an OMG to the underlying dartos tissue of the scrotum after incision of the scrotal skin and use this patch as a flap in a second attempt [448].

Summary of evidence	LE
Hair-bearing flaps have a lower urethral patency rate compared to non-hair-bearing flaps.	3

Recommendation	Strength rating
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong

9.3 Comparison of different types of grafts

Buccal mucosa is at present the most commonly used graft. Urethral patency rates of buccal mucosa vary between 75.6% and 91.7% with 16-75 months of follow-up (see supplementary Table S9.2) [531-537].

Penile skin is another popular graft, especially in uncircumcised men where the foreskin is an abundant source of graft material.

In case of LS, Trivedi *et al*. demonstrated a significantly higher urethral patency rate when using non-genital mucosal grafts for reconstruction (82.6%) compared to genital skin grafts (4%) [538]; therefore, the use of genital skin in LS cases is not indicated.

There is no RCT comparing buccal mucosa with penile skin. A secondary analysis of a meta-analysis comparing dorsal with ventral onlay graft urethroplasty found a superior urethral patency rate for buccal mucosa compared to penile skin (88.1% vs. 79%; $p < 0.001$). In this secondary analysis, no data were available about the stricture aetiology, stricture length, follow-up duration or other potential confounders between both groups [539]. A pooled analysis of non-RCTs comparing buccal mucosa (n=483) with penile skin (n=428) found a better urethral patency rate for buccal mucosa (respectively 85.9% vs. 81.8%). However, the results might be biased because of the longer follow-up time and longer stricture length in the penile skin group [540]. Lengthy skin grafts (up to 20 cm) can be taken from the foreskin in a spiroid fashion which is clearly more difficult with oral mucosa grafts.

The main disadvantage of BMG harvesting is the oral morbidity and because of this morbidity, lingual mucosa has been proposed as alternative. A systematic review and meta-analysis of comparative studies comparing LMG with BMG (four prospective, two retrospective studies) showed no significant differences in urethral patency rate and overall long-term complication rate [541-543]. These studies revealed that LMG was associated with more difficulties in eating/drinking, speaking, tongue protrusion and dysgeusia [541, 542]. In 13.8-20%, speaking problems remained after six months [541, 542]. A retrospective study of Xu *et al*. reported difficulties in tongue movements, numbness over the donor site and speaking difficulties in 6.2%, 4.9% and 2.5% of patients, respectively after twelve months [298]. On the other hand, BMG harvesting provoked more oral tightness which was present in up to 24% of patients after six months [541, 542]. Chauhan *et al*. showed that immediate and early donor site complications were more common in the BMG group, except for bleeding being more common in the LMG group. Numbness (61%), difficulty in chewing (54%), swelling (48%) and articulation (40%) were the most common problems during the first week. Late donor site complications were rare [544]. Pal *et al*. describes more short-term complications (difficulty in tongue movement and slurring of speech) in the LMG group, compared to the BMG group. Long-term complications (after three months) at the donor site (persistent pain, perioral numbness, tightness of mouth, salivary disturbance, scarring of the cheeks) were only seen in the BMG group [545]. For long strictures, buccal mucosa can be combined with lingual mucosa [298].

The use of lower lip mucosa was described, especially when smaller grafts are needed, and has similar qualities to lingual mucosa. However, a narrative review based on the experience from retrospective series showed that these grafts have a higher post-operative donor site morbidity and can lead to permanent sequelae (persistent discomfort, neurosensory deficits, salivary flow changes and important aesthetic changes) at the donor site, which have not been described with lingual mucosa [546].

Beyond the oral mucosa and penile skin graft, a multitude of other autologous grafts have been described. These include: postauricular skin [523, 547], abdominal skin [364], split-thickness mesh graft from the thigh [348], inguinal skin [297] and colonic mucosa [548] (Table 9.2). Manoj *et al*. only used the postauricular skin when both genital skin and oral mucosa were not usable [547]. Marchal *et al*. used postauricular skin in addition to oral mucosa to reconstruct lengthy strictures [523]. Meeks *et al*. reported the use of abdominal skin graft mainly in patients with lengthy strictures where OMG harvesting would be insufficient, in case of prior OMG urethroplasty or if OMG was refused by the patient [364]. Pfalzgraf *et al*. reported a comparable urethral patency rate for split-thickness mesh graft and BMG (respectively 84 and 83%), but more penile deviation (9% vs. 0%) and lower satisfaction (83.3 vs. 96.7%) with split-thickness mesh graft [348]. Xu *et al*. used colonic mucosa for lengthy (> 10 cm) strictures. Urethral patency rate was 85.7% but graft harvest requires an abdominal procedure and 1/35 (2.9%) patient developed a colonic-abdominal fistula [548]. Due to the limited experience with grafts other than oral mucosa and penile skin, they should only be considered if oral mucosa and penile skin are not available, indicated or desired.

Table 9.2: Outcome of case series of other autologous grafts

Study	Type of graft	N	Follow-up (months)	Stricture length (cm)	Urethral patency (%)
Bastian *et al*. 2012 [297]	Inguinal skin	34	70 (3-86)	8 (1.5-14)	91
Manoj *et al*. 2009 [547]	Postauricular skin	35	22 (3-48)	8.9 (3-15)	89
Meeks *et al*. 2010 [364]	Abdominal wall skin	21	28 (11-52)	11 (4-24)	81
Pfalzgraf *et al*. 2010 [348]	Split thickness skin graft	57/68	32	NR	84
Xu *et al*. 2009 [548]	Colonic mucosa	35	53.6 (26-94)	15.1 (10-20)	85.7

N = number of patients; NR = not reported.

Summary of evidence	LE
Patency rates of buccal mucosa and lingual mucosa are comparable.	1a
Different types of oral grafts have different types of oral morbidity and some of the oral complications might last in the long-term.	1a
Patency rates with penile skin grafts are 79-81.8% versus 85.9-88.1% with buccal mucosa.	3
In LS related strictures, the use of genital skin graft is associated with poor patency rates (4%).	3

Recommendations	Strength rating
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal versus lingual versus lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong

9.4 Tissue engineered grafts

9.4.1 Cell-free tissue engineered grafts

These grafts are derived from cadaveric or animal sources (e.g., porcine small intestine submucosa (SIS), acellular bladder matrix, acellular dermal matrix), are completely cell-free and serve as a scaffold for host cell ingrowth [549]. The main advantage suggested for their use is the off shelf availability [549].

A small RCT (n=30) comparing acellular bladder matrix with BMG reported a urethral patency rate of respectively 66.6% and 100%. The poorer results of acellular bladder matrix were the most apparent in cases of an unhealthy urethral bed [550]. Palminteri *et al*. reported a global urethral patency rate with SIS graft in 19/25 (76%) cases [551]. In this series SIS graft urethroplasty failed in all cases with a stricture length > 4 cm [551]. On the other hand, Xu *et al*. reported adequate urethral patency in 26/28 patients (92.8%) after a median follow-up of 25 months. Of note, only one patient in this series underwent previous urethroplasty suggesting only minor spongiofibrosis in the remaining patients [552]. Other series have included only a limited number of patients with short follow-up. In these series, urethral patency rates vary between 20 and 100% [549].

Summary of evidence	LE
Patency rate of cell-free tissue engineered grafts decreases with large stricture length and unhealthy urethral bed.	1b

Recommendation	Strength rating
Do not use cell-free tissue engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty or stricture length > 4 cm.	Weak

9.4.2 Autologous tissue engineered oral mucosa grafts

These grafts contain a matrix seeded with autologous oral mucosa cells. Production requires a small oral mucosa biopsy (@ 0.5 cm^2) and the graft is further manufactured in the lab. The main advantage suggested is the reduction of oral donor site morbidity whereas the main disadvantages are costs and the strict time frame between manufacturing and implantation of the graft [549].

The clinical use of autologous tissue-engineered OMG was evaluated in a prospective, multicentre study including 99 patients [553]. Estimated 12- and 24-months urethral patency rate was 67.3 and 58.2%, respectively. Oral adverse events were minimal. No comparative studies with acellular grafts or native OMGs are available nor are there any data about the cost-effectiveness [549].

Summary of evidence	LE
Safety, patency rate and cost-effectiveness of autologous tissue-engineered grafts is currently under research.	3

Recommendation	Strength rating
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

9.5 Management of oral cavity after buccal mucosa harvesting

The post-operative morbidity of closure vs. non-closure of the buccal mucosa harvesting site has been evaluated by a number of prospective RCTs.

The results are summarised in Table 9.3. Based on these findings, no clear recommendation can be provided whether or not to close the harvesting site and the decision can be left to the treating physician.

Oral rinsing with chamomile [554] or chlorhexidine [542, 555] solution has been suggested in the first post-operative days without any evidence that this reduces pain or other oral complications.

Table 9.3: Effect of non-closure compared to closure on oral morbidity after buccal mucosa harvesting

Study	Early oral pain	Eating/ drinking problems	Altered taste	Altered salivation	Oral tightness	Perioral numbness	Oral bleeding	Slurred speech
Soave *et al*. [554]	=	=	=	=	=	=	=	=
Rourke *et al*. [556]	=	↓	NR	NR	↓	↓	=	NR
Muruganandam *et al*. [557]	↓	=	NR	=	=	=	=	NR
Wong *et al*. [555]	=	↑	NR	NR	=	=	=	NR
Lumen *et al*. [542]	↑	NR	NR	NR	NR	NR	NR	NR

↓ = less morbidity with non-closure; ↑ = more morbidity with non-closure; = = no significant difference; NR = not reported

10. PERI-OPERATIVE CARE OF URETHRAL SURGERY

10.1 Urethral rest

After any form of urethral manipulation (urethral catheter, ISD, dilatation, DVIU), a period of urethral rest is necessary in order to allow tissue recovery and stricture "maturation" before considering urethroplasty. This improves the ability to identify the true extent of the fibrotic segments during subsequent surgery. If the patient develops incapacitating obstructive symptoms or urinary retention, a suprapubic catheter should be inserted. Terlecki *et al*. propose diagnostic evaluation after two months and urethroplasty after three months of urethral rest. These timings are based on the general principles of wound healing [558]. In their study, it has been shown that these periods allow for reliable stricture evaluation during urethrography which is, in turn, important to ensure selection of the most appropriate urethroplasty technique [558]. Utilising this strategy, similar outcomes were obtained compared to patients with stable previously unmanipulated strictures [558]. However, the optimal duration of urethral rest for all patients is not known and the degree of associated infection and inflammation should be taken into account as well with longer periods of rest in those with greater degrees of infection and inflammation.

Summary of evidence	LE
After any form of urethral manipulation, a minimum period of three months urethral rest is necessary to allow for tissue healing before performing urethroplasty.	3

Recommendation	Strength rating
Do not perform urethroplasty within three months of any form of urethral manipulation.	Weak

10.2 Antibiotics

Post-operative wound infection and UTI are common post-operative complications and infection at the site of reconstruction may contribute to failure of urethroplasty. The vast majority of reconstructive urologists perform urine culture one to two weeks prior to surgery [559]. Urine culture is superior to urine-analysis which can be omitted in the pre-operative evaluation [559]. If infection or colonisation is present, a therapeutic course with antibiotics is recommended pre-operatively. In case of an indwelling catheter general principles would suggest at least an attempt to suppress the colonisation with pre-operative antibiotics [559]. These practices are in accordance to the strong recommendations of the EAU Guidelines on Urological Infections:

- "Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa."
- "Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions."

An intra-operative prophylactic regimen with antibiotics (according to local antibiotic resistance profiles) is effective in reducing the rate of post-operative surgical site and UTIs [559]. Although most urologists continue with post-operative antibiotics upon and even beyond catheter removal, there is no evidence that such a prolonged administration would reduce the infective complication rate [559]. The EAU guidelines on urological infections do not routinely recommend the use of antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. There is no evidence that this recommendation would not apply to catheter removal after urethral surgery.

Summary of evidence	LE
An intra-operative prophylactic regimen with antibiotics is effective in reducing the rate of post-operative surgical site and urinary tract infections.	4

Recommendation	Strength rating
Administer an intra-operative prophylactic regimen with antibiotics at time of urethral surgery.	Strong

10.3 Catheter management

After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period and it should be removed within 72 hours [560].

After one-stage urethroplasty and closure of the urethral plate after staged urethroplasty, urinary extravasation at the site of reconstruction must be avoided [561]. For this purpose, urinary diversion by either transurethral catheter or suprapubic catheter with urethral stent can be used. With respect to the type of catheter material, a prospective randomised (but underpowered) trial comparing silicone vs. hydrogel coated latex transurethral catheters showed no significant difference in the time to stricture recurrence nor in the overall recurrence rate [561]. The size of the urethral catheter utilised usually varies varies between 14 Fr and 20 Fr [562, 563]. Systematic use of anticholinergic drugs has not shown a significant reduction in the rate of involuntary pericatheter voiding whilst catheterised [564].

After urethroplasty an indwelling catheter is commonly left *in situ* for two to three weeks [563, 565]. After three weeks of urethral catheterisation, an extravasation rate of 2.2%-11.5% at urethrography has been reported after different types of urethroplasty [565-568]. However, success with early catheter removal under three weeks has also been reported. A study after EPA for non-complicated anterior strictures demonstrated no significant difference in extravasation (6.8 vs. 4.5%) and recurrence rates (4.9 vs. 5.2%) between catheter removal at one or two weeks respectively [569]. Poelaert *et al*. reported an extravasation rate of 3.5% vs. 8.3%, when the catheter was removed ≤ 10 days or > 10 days respectively after all types of urethroplasty (n=219) (p=0.158) [562]. Importantly, patients who had a duration of catheterisation of > 10 days had longer and more complex strictures [562].

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation [565, 567]. Importantly, some authors have identified urinary extravasation as a predictive factor for stricture recurrence [562, 570]. Other series, however, could not confirm the prognostic significance of urinary extravasation but they included any form of extravasation (including minor leaks) [567, 568]. Grossgold *et al*. found that high-grade leaks (defined as length ≥ 1.03 cm and width ≥ 0.32 cm) were significantly associated with higher restricture rates. This study also found length of extravasation ≥ 1.03 cm alone to be an independent predictor of restricture [570]. In cases of persistent and significant urinary extravasation, the catheter should be maintained or reinserted and the examination repeated after one week [565]. However, low-grade ("wisp-like") extravasation does not appear to affect long-term restricture rate and the catheter can be removed in these cases without subsequent urethrogram [567, 570]. In case of any doubt about the significance of extravasation, it is safe to keep the catheter in for an additional week and ReDo the assessment.

The assessment of urinary extravasation is achieved by either pericatheter retrograde urethrography (pcRUG), classic RUG or VCUG [565]. Voiding cystourethrography (after catheter removal) is the most physiologic examination as it shows the urethra under normal intra-urethral pressures and using this test residual urethral narrowing is most accurately identified. This has been found to be a strong prognostic factor for failure in a series evaluating bulbar FGU [568]. In contrast, pcRUG is associated with supraphysiological intra-urethral pressures and a potentially higher chance of false positive results [565, 570]. Although there is no evidence that one imaging modality is superior to the other, pcRUG should be performed if there is a high-risk of leakage as it avoids the need for catheter reinsertion through a recently reconstructed urethra in case of a positive exam. High risk of leakage depends on the complexity of urethroplasty (e.g., stricture length > 10 cm, panurethral repair) [567, 570]. External clinical signs of impaired wound healing (e.g., abscess formation, wound dehiscence) are also associated with a high risk (71.4%) of leakage [562]. In cases of attempted VCUG where the patient is not able to void during fluoroscopy after catheter removal, RUG should be performed [570].

Although limited evidence for urethroplasty care in trans men exists, one study advised a three week period of transurethral catheterisation with pcRUG upon catheter removal [511].

After perineostomy or the 1st stage of staged urethroplasty, the catheter can be removed without need for urethrography after three to five days [346, 567].

Summary of evidence	LE
Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation with urethrography to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation.	2b
After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period.	3
Early catheter removal may be appropriate for a subset of patients with short, uncomplicated, strictures.	3

Recommendations	Strength rating
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Remove the catheter within 72 hours after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Consider 1st urethrography seven to ten days after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Weak

11. FOLLOW-UP

11.1 Rationale for follow-up after urethral surgery

The rationale for following-up patients after urethral stricture surgery is to detect and manage any complication or recurrence. As with any surgical procedure, following urethroplasty some patients will present with complications at short to medium follow-up: approximately 38% with bulbar urethroplasties [318] and up to 54% for all anterior urethroplasties [571]. Most of these complications (92%) would be classified as Clavien

grade 1 or 2 [318]. Even though urethroplasty techniques provide the highest chances for successful treatment of urethral strictures, some patients will experience recurrence [322]. For further details on particular outcomes in each urethral segment, please review the individual chapters of this Guideline.

Summary of evidence	LE
After urethroplasty surgery, recurrent strictures appear with different frequency depending on stricture features and urethroplasty techniques.	3

Recommendation	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong

11.2 Definition of success after urethroplasty surgery

The “traditional academic” definition of post-operative success after urethroplasty has been considered as “The lack of any post-operative intervention for restricture” [572]. This definition, despite being widely used [302, 318] is problematic as it ignores asymptomatic or even symptomatic recurrences in patients not willing to undergo further surgeries [572]. There is some variation as to what is considered intervention with some groups accepting endoscopic treatments as success, while considering failure only as the requirement for a ReDo urethroplasty [303].

A more objective definition of success is the “anatomic success”, defined as “Normal urethral lumen during RUG or cystoscopy, regardless of patient symptoms”. Using this definition, stricture recurrence or anatomical failure is considered by some groups as urethral narrowing found to be endoscopically impassable – without force – with a 16 Fr flexible endoscope [138, 573]. This definition is certainly more strict, with up to 35% of cystoscopic recurrences after bulbar urethroplasty remaining asymptomatic, and thus would have been considered as successful if a “lack of further intervention” definition was used [138]. Other groups consider cystoscopic recurrence as any stricture that is visible on post-operative cystoscopy, even the so-called “large-calibre re-strictures” (> 17 Fr) [136]. Not all anatomic recurrent strictures would need further treatment [572]. It was suggested to intervene when the anatomic recurrence is associated with recurrence of symptoms, stricture-related high post-void residuals or a stricture calibre of < 14 Fr – even if these are asymptomatic [572].

Over the last ten years, the evaluation of urethral surgery outcomes has shifted towards a “patient-reported definition of success”. The aim of any urethral intervention is to allow patients to return to a normal state of voiding while maintaining QoL [574] or to minimise symptoms, reduce disability, and improve HRQoL by restoring normal urinary function [575]. Even if the surgeon reconstructed a wide and patent urethra, if patients experience pain, sexual dysfunction or perceive their urinary function as not improved, they will not rate their outcome as successful [572]. On a multivariate analysis including both patient-reported and clinical parameters, urine flowmetry parameters failed to demonstrate significant contribution to satisfaction [576]. Kessler *et al*. reported that only 78.3% of patients with clinical success described themselves as (very) satisfied. More dissatisfaction significantly appeared with penile curvature, penile shortening, worsening of erectile function and impairment of sexual life [577]. Conversely, 80% of patients defined as clinical failures considered themselves as (very) satisfied with their outcomes [577]. Regardless of anatomic success after urethroplasty, post-operative pain, sexual dysfunction and persistent LUTS were independent predictors of patient dissatisfaction [576]. Improvement in voiding function (i.e., statistical improvement on IPSS) alone does not predict patient satisfaction after urethroplasty [578]. On a multivariate analysis including both patient-reported and clinical parameters, after adjusting for disease recurrence and age, persistence in voiding symptoms (weak stream), genitourinary pain, and post-operative sexual function alterations were the greatest independent drivers of post-operative dissatisfaction [576]. In addition, penile shortening (OR: 2.26; CI: 95% 1.39-3.69) and chordee (OR: 2.26; CI: 95% 1.44-4.19) were independent predictors of patient dissatisfaction after urethroplasty [578] (Table 11.1).

Table 11.1: Predictors of patient dissatisfaction after urethral surgery

Predictor/Symptoms	Measure of effect	Authors
Weak/very weak urinary stream	< 0.001	Kessler TM *et al*. J Urol 2002 [577]
Penile curvature	0.001	
Penile shortening	0.001	
Worsening of erectile function	0.001	
Impairment of sexual life	< 0.001	
Sexual activity alteration	OR: 4.36 (1.54 – 12.37)*	Bertrand LA *et al*. J Urol 2016 [576]
Erection confidence (SHIM)	OR: 1.53 (1.12 – 2.07)*	
Inability to ejaculate (MSHQ)	OR: 1.52 (1.15 – 2.01)*	
Urethral pain	OR: 1.71 (1.05 - 2.77)*	
Bladder pain	OR: 2.74 (1.12 – 6.69)*	
Urinary strain (CLSS)	OR: 3.23 (1.74 – 6.01)*	
Hesitancy (IPSS)	OR: 2.01 (1.29 – 3.13)*	
Voiding quality of life (IPSS)	OR: 1.96 (1.42 – 2.72)*	
Haematuria	10	Maciejewski CC *et al*. Urology 2017 [578]
Urinary extravasation	9.1	

** p < 0.05; ** p < 0.001.*
SHIM = Sexual Heath Inventory for Men; MSHQ = Male Sexual Health Questionnaire;
CLSS = Core Lower Urinary Tract Symptom Score; IPSS = International Prostate Symptoms Score.

Due to this evident discrepancy between surgeon's assessment and patient assessment, PROMs have been developed for the follow-up after urethroplasty [153, 575].

A complete approach for urethral surgery outcomes would combine both anatomic, endoscopic, and patient-reported success [320, 572]. As a Panel, we suggest using a functional definition of success in clinical practice, namely "lack of symptoms and/or need for further interventions".

Collecting standardised documentation of the patient's subjective assessment of their symptoms and objective anatomic outcomes would be limited for academic purposes, in order to allow comparison of surgical outcomes among reconstructive urologic surgeons and centres. Those objective and subjective outcomes measures should therefore be assessed and reported (simultaneously but separately) when evaluating urethroplasty results [572].

11.3 Follow-up tools after urethral surgery

*11.3.1 **Diagnostic tools for follow-up after urethral surgery***

11.3.1.1 Calibration during follow-up after urethral surgery

The difference between calibration and urethral dilatation is usually subjective as soft strictures may be dilated during calibration [579]; therefore, urethral calibration should be used with caution for follow-up after urethroplasty. Dedicated calibration bougies should be used and not dilatators.

11.3.1.2 Urethrocystoscopy during follow-up after urethral surgery

Urethrocystoscopy has been considered the most useful tool to confirm the presence or absence of a recurrent stricture [136, 580], as up to 35% of patients with re-strictures remain asymptomatic [138]. Also, the cystoscope could be a measure to calibrate the strictured lumen, bearing in mind the most commonly used endoscopes: 15.7 Fr (5 mm diameter) or 17.3 Fr (5.5 mm diameter) [580]. Urethrocystoscopy allows differentiation of recurrences as diaphragm/cross-bridging – responding to simple intervention, or significant urethral restrictures – requiring repeated interventions or ReDo surgeries [581]. Endoscopic assessment at three months after anterior urethroplasty can predict the risk for further re-intervention at one year. Compared to normal endoscopy, large calibre (> 17 Fr) restrictures have a HR of 3.1 (1.35-7.29) for repeat intervention while small calibre (< 17 Fr) restrictures have a 23.7 HR (12.44-45.15) adjusted for age, stricture length, location and aetiology [136]. The main problem with using urethrocystoscopy for routine follow-up is the low compliance of patients as only 54% of patients underwent endoscopy at one year after urethroplasty, even when it was a part of a study protocol [138].

11.3.1.3 Retrograde urethrogram and voiding cystourethrogram during follow-up after urethral surgery

Retrograde urethrogram combined with VCUG are commonly used to confirm suspected recurrence [582, 583] or as part of a routine protocol to assess post-operative urethral patency [584, 585].

11.3.1.4 Urethral ultrasound – Sonourethrography during follow-up after urethral surgery

The use of SUG as a follow-up tool is not very common. It would be a reliable tool for diagnostic recurrent strictures [582].

11.3.2 ***Screening tools for follow-up after urethral surgery***

These tools are used to assess whether there is suspicion of stricture recurrence and need for subsequent diagnostic evaluation (see section 5. Diagnostic evaluation).

11.3.2.1 Flow-rate analysis during follow-up after urethral surgery

Evaluating the Q_{max} is the commonest follow-up tool. Different cut-off points from Q_{max} 15 ml/s or 12 ml/s were suggested to consider the intervention as a failure or to trigger a confirmatory test for recurrence [584]. There is no clear threshold, and 19% of patients with Q_{max} < 14 ml/s would still have a patent urethra, allowing passage of 15 Fr cystoscope [139].

Flow rates may be affected by operator error, BPO/LUTS, bladder dysfunction, and variations in bladder capacity. Further limitations of uroflowmetry include the need for a minimum voided volume of 125 to 150 ml to reach a voided flow rate that reliably predicts an abnormality [579]. Even in controlled settings, the percentage of patients with adequate pre- and post-operative uroflowmetry analysis is only 31% [585]. Comparing both pre- and post-operative Q_{max} levels was suggested, and a difference in Q_{max} of 10 ml/s or less is found to be a reliable screen tool for recurrence (sensitivity 92%, specificity 78%). This measure also has strong reproducibility (R=0.52) [585]. Unfortunately, this improvement after urethroplasty is significantly different between age groups, with less than 10 ml/s average change in those over 65 years old, probably affected by BPO and/or bladder dysfunction [586]. Another parameter to consider is the shape of the voiding curve, recording it as flat (obstructed) or bell-shaped [587]. An obstructive voiding curve demonstrated 93% sensitivity to predict recurrent strictures, while a combination of urinary symptoms and obstructive voiding curve achieved 99% sensitivity and 99% NPV [587].

11.3.2.2 Post-void residual ultrasound measure during follow-up after urethral surgery

Post-void residual US measure is significantly increased in patients with recurrent strictures compared with those without recurrences [582]. Unfortunately, PVR measurement is affected by abdominal ascites, bladder diverticula and/or poor bladder function [579], with some studies reporting inconsistent correlation with obstruction in the presence of BPO. Also US measures of PVR are user dependent, showing high interobserver variability. Combined with other tests – uroflowmetry, IPSS, and SUG – PVR achieves adequate predictive values [582], but currently there is no literature support for its solo use to assess urethral stricture recurrence [588].

11.3.2.3 Symptoms questionnaires during follow-up after urethral surgery

The IPSS questionnaire, despite being designed for BPO, showed significant improvement after successful urethroplasty and inverse significant correlation with Q_{max} [578, 589]. The mean improvement of IPSS is around -11 points (range -19 to -5) [586].

Table 11.2: Post-urethroplasty changes in IPSS values

Author	N	Mean pre-operative value	Mean post-operative value	Change	Significancy
Morey AF *et al*. 1998 [589]	50	26.9	4.4	NR	p < 0.0001
DeLong J *et al*. 2013 [586]	110	NR	NR	-11 (IQR -19 - -5)	p < 0.001
Maciejewski CC *et al*. 2017 [578]	94	18.7 (+/- 9)	5.8 (+/- 5)	NR	p < 0.0001

N = number of patients; NR = Not reported; IQR = Interquartile range.

Combination of IPSS and Q_{max} analysis was suggested to diagnose recurrences. Using an IPSS cut-off point of 10 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 34% of patients, while only 4.3% of strictures < 14 Fr would have been missed. Using an IPSS cut-off point of 15 points associated with Q_{max} >15 ml/s would prevent further invasive studies in 37% of cases, while 6% of strictures < 14 Fr would have been missed [590].

The Visual Prostate Symptom Score (VPSS) was also used to diagnose recurrent urethral strictures, offering a significantly shorter time to completion compared with IPSS, especially in cases of illiteracy or limited education. Visual Prostate Symptom Score showed a good correlation with IPSS, Q_{max} and urethral diameter. A combination of VPSS > 8 with Q_{max}< 15 ml/s had a NPV of 89% and a PPV of 87% for recurrent urethral strictures [591].

Post-micturition dribble, assessed by the specific question of the USS-PROM questionnaire, was present in 73% of patients pre-operatively and 40% after anterior urethroplasty, while only 6.3% was *de novo*. Incidence was not predicted by stricture location nor urethroplasty type [143].

*11.3.3 **Quality of life assessment, including disease specific questionnaires during follow-up after urethral surgery***

Urethral stricture affects QoL evaluated by EQ-5D-3L questionnaire. Pre-operative anxiety and depression was found in 29% of patients. *De novo* AD after urethroplasty is uncommon (10%), and has two predictors: decreased sexual function and poor reported image of overall health [592]. A more recommended approach is the assessment of the condition-related QoL [593]. The USS-PROM proved useful to assess outcomes in anterior urethroplasty patients [575]. Its use also received criticism, as some of the individual generic QoL questions do not improve after successful urethroplasty, as they are not condition-specific [594]. Currently, there is another version of PROM, being developed and validated by a North American collaborative group, including questions related to the sexual consequences of urethral stricture disease [154]. PROM questionnaires should be implemented in each visit to check for functional success, as they are able to show improvement over time.

The Core Lower Urinary Tract Symptom Score (CLSS) questionnaire was used to assess pre- and post-urethroplasty pain in the bladder, penis/urethra, and perineum/scrotum. Most of the parameters improved after urethroplasty, but up to 29% of patients reported worsening of perineal pain after surgery [595].

Sexual function should be evaluated by validated tools if not assessed in a - PROM. The international index on erectile function (IIEF), SHIM, O´Leary Brief Male Sexual Function Inventory (BMFSI), SLQQ (Sexual Life Quality Questionnaire), Male Sexual Health Questionnaire (MSHQ) have all been used after urethroplasties for evaluation of erectile and ejaculatory functions. Other non-validated tools were suggested such as the Post-Urethroplasty Sexual Questionnaire (PUSQ) [596] or specific questionnaires for genital appearance (length, curvature) or sensitivity [597].

Summary of evidence	LE
Retrograde urethrography and urethrocystoscopy are able to identify anatomical success after a urethroplasty.	2a
A significant gap was demonstrated between objective and subjective outcomes after urethroplasties. PROM questionnaires are specific tools to assess subjective outcomes and patient satisfaction after urethroplasty surgeries.	2a
Validated questionnaires proved useful to assess the consequences of urethral surgery on sexual function.	2a

Recommendations	Strength rating
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use PROM questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong

11.4 Ideal follow-up interval after urethral surgery

The optimal follow-up strategy must allow for an objective determination of anatomic and functional outcomes to assess surgical success whilst avoiding excessive invasive testing that leads to unnecessary cost, discomfort, anxiety and risk [572].

After anterior urethroplasty, 21% of recurrences are clinically evident, and cystoscopically confirmed, after three months [598] and 96% after one year [581]. Early recurrences are more frequent in patients with LS and older age, in longer strictures and when skin grafts were used [598].

11.5 Length of follow-up after urethral surgery

The median time of recurrence after bulbar urethroplasty is approximately ten months [324]. In case series, between 55.4% [598] and 96% [581, 584] of all recurrences are detected during the first year of follow-up after urethral surgery. Twenty-three percent of bulbar stricture recurrences are detected during the second year of follow-up, and the percentage of recurrences decreases after the second year [322].

On the other hand, long-term follow-up studies highlighted the role of length of follow-up as a predictor for stricture recurrence after bulbar urethroplasty [322, 599]. Late recurrences – later than five years after urethroplasty – could be observed in up to 15% of cases [139, 322]. This should be considered mainly after augmentation urethroplasties, especially in case skin grafts were used [583]. Certainly, patients should be instructed to seek urological evaluation if they experience late recurrent symptoms [599].

11.6 Risk stratified proposals during follow-up after urethral surgery

Cost of follow-up after urethroplasty is higher in the first year after the procedure [600]. In a literature review it ranged between 205 to 1,784 US Dollars, with higher costs associated to posterior urethral repairs [600].

As the risk of recurrence and side effects are related to the type of stricture and urethroplasty, a different follow-up schedule was proposed and shown to be cost-effective in the USA, potentially saving up to 85% of costs after five years [573]:

- Urethroplasties with a low risk of recurrence (EPA urethroplasty without history of radiotherapy, hypospadias or LS features) could be safely followed up based on monitoring of symptoms, using self-administered IPSS questionnaire, every three months for one year, and annually thereafter.
- Urethroplasties with standard risk of recurrence (urethroplasty using grafts, flaps, and/or post-irradiation, hypospadias and/or LS patients) could combine IPSS questionnaire + flowmetry every three months for one year, and annually thereafter. Additionally, RUG at three and twelve months should be performed.

In this protocol, urethrocystoscopy is only performed if required [573]. Another suggested follow-up protocol includes urethrocystoscopy or RUG/VCUG at three months post-operatively, in order to rule out early failures, especially in case of graft use. If there is evidence of good anatomical outcome in these tests, flowmetry and questionnaire results at three months should be considered as the new baseline. Thereafter, follow-up could be safely and routinely performed with non-invasive tests (flowmetry – evaluating Q_{max} and the shape of curve – and questionnaires. Any deterioration should be further investigated with a urethrocystoscopy [588].

A recently suggested protocol also included assessment of LUTS, sexual function (erectile and ejaculatory), and lower urinary tract pain, that need to be compared with pre-operative findings which should include a PROM questionnaire [572]. Cystoscopy and flowmetry should be performed between three to six months post-operatively, and flowmetry findings should be considered as the new baseline for longitudinal follow-up. Future significant decline (25-30%) in Q_{max} or Q_{max}-(average flow rate) should trigger new cystoscopy to rule out anatomic recurrence, even in patients who are symptom-free [572]. A routine cystoscopy at twelve to fifteen months should be performed at the surgeon's discretion, based on risk assessment of three aspects: higher-risk patients, evidence of partial urethral narrowing at three month assessment, low-volume surgeons [572].

Summary of evidence	LE
The higher percentage of recurrences presents during the first twelve months, after urethoplasty surgery.	2a
Risk-adjusted follow-up protocols are cost-effective and safe for the patients.	3

Recommendations	Strength rating
Offer a routine follow-up of at least one year after urethroplasty.	Strong
Adopt a risk-adjusted follow-up protocol.	Weak

11.7 Follow-up protocol proposal after urethroplasty

*11.7.1 **Surgeries with low risk of recurrence***

- Anastomotic urethroplasties in the bulbar/(bulbo)membranous segment with no history of radiotherapy, hypospadias or balanitis xerotica obliterans (BXO)/LS features.

Table 11.3: Follow-up protocol for urethroplasty with low risk of recurrence

Surgery	3 months	12 months	24 months*
Uroflowmetry	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+**	On indication	On indication

**Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.*
***The Panel suggests performing an anatomic assessment at three months.*

*11.7.2 **Surgical management options with standard risk of recurrence***

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias or BXO/LS features;
- Penile urethroplasties;
- Non-traumatic posterior urethroplasties;
- Graft or/and flap – substitution – urethroplasties.

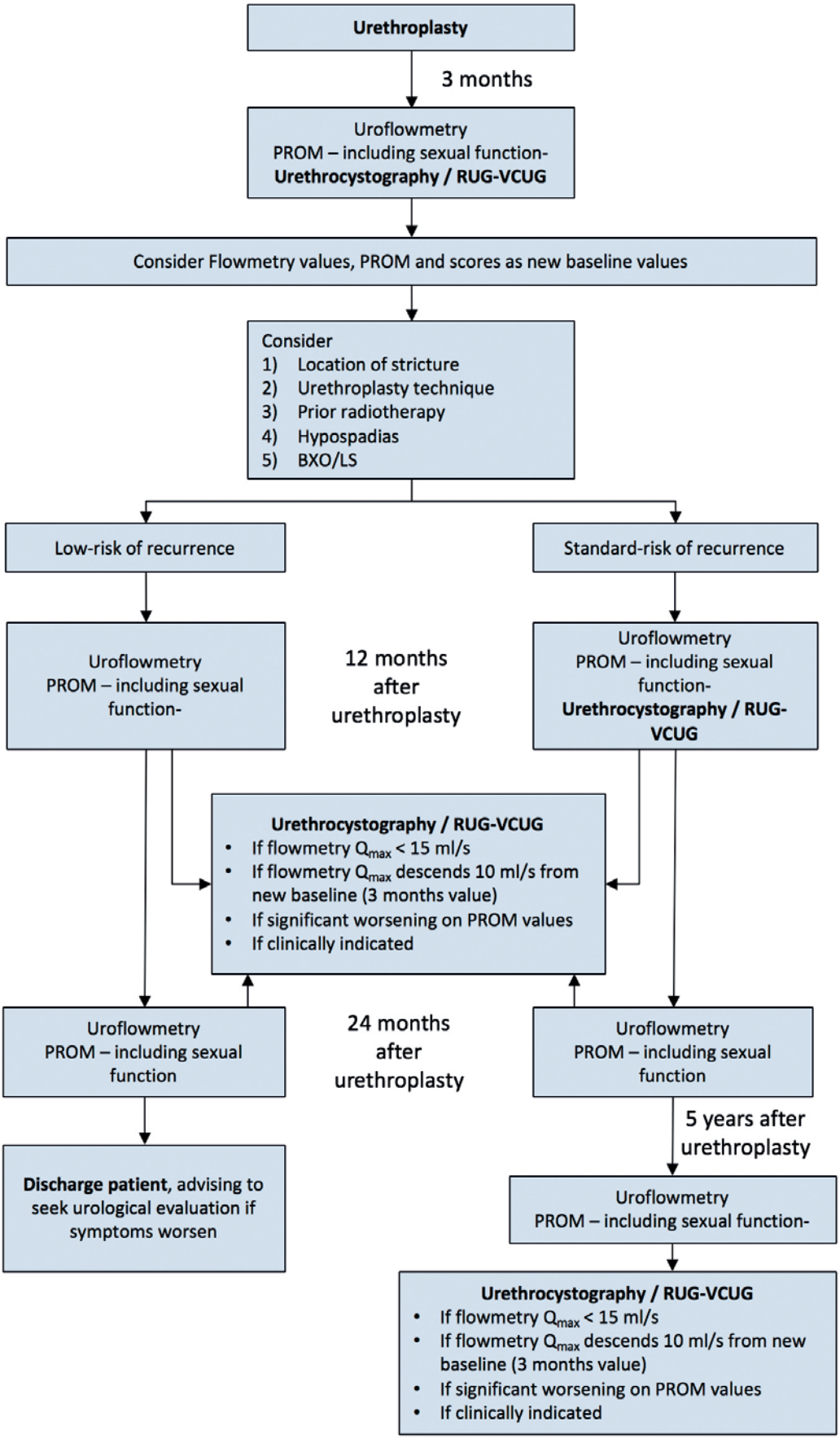
Table 11.4: Follow-up protocol for urethroplasty with standard risk of recurrence

Surgery	3 months	12 months	24 months	5 years *
Uroflowmetry	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+	+	+	On indication

** Follow-up could be discontinued after five years, advising the patient to seek urological evaluation if symptoms worsen. A longer follow-up period should be considered after penile and subtitution urethroplasties. Academic centres could increase the length of follow-up for reseach purposes.*

Please see Figure 11.1 for further guidance.

Figure 11.1: Follow-up after urethroplasty



BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

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13. CONFLICT OF INTEREST

All members of the Urethral Strictures Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

14. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2021. ISBN 978-94-92671-13-4.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, the Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

References to individual guidelines should be structured in the following way:
Contributors' names. Title of resource. Publication type. ISBN. Publisher and publisher location, year.

OPTILUME® DCB CLINICAL PROGRAM

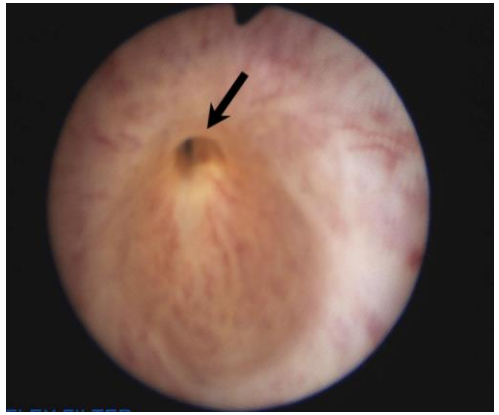
UROTRONIC

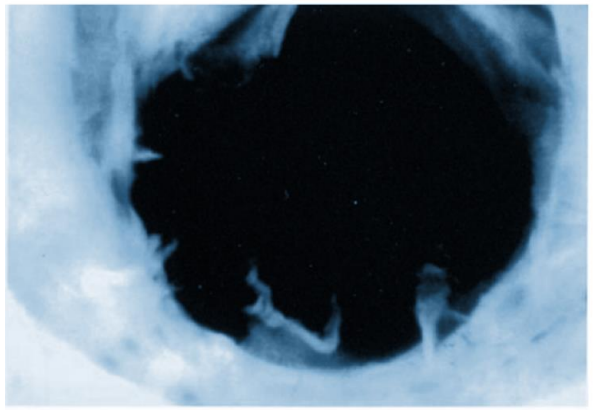
Optilume® Urethral DCB Mode of Action

Step 1

Mechanical Dilation

- Plastically deforms and opens the lumen
- Creates micro-fissures for drug uptake

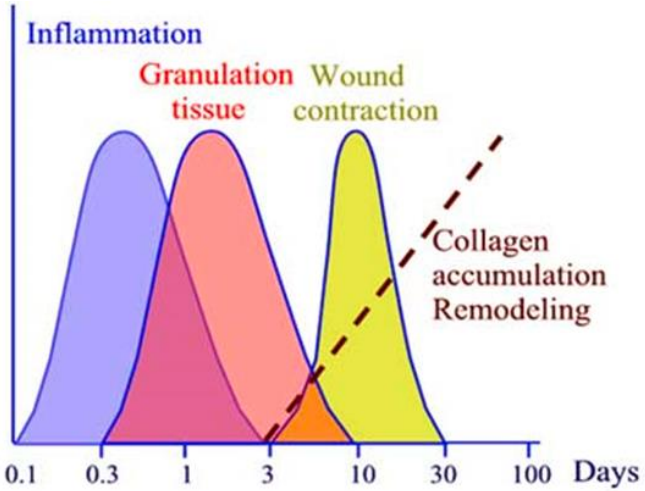




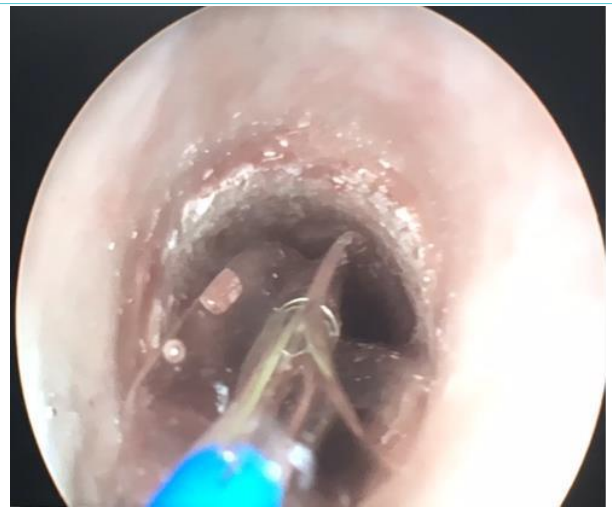
Step 2

Drug Delivery

Inhibits cell division
+
Inhibits cell growth
=
Inhibits stricture recurrence



Orderly phases of wound healing



ROBUST I

Design: Single arm, prospective, multicenter

Geography: Latin America

Number of Sites: 4

Total Enrollment: 53

Procedure:

- Optilume® DCB Pre-dilation
  - ✓ Plain balloon: 31/53 (59%)
  - ✓ DVIU: 8/53 (15%)
  - ✓ Balloon + DVIU: 14/53 (26%)

ROBUST II

Design: Single arm, prospective, multicenter

Geography: United States

Number of Sites: 5

Total Enrollment: 16

Procedure:

- Optilume® DCB Pre-dilation
  - ✓ None: 9/16 (56.3%)
  - ✓ Plain balloon: 3/16 (18.8%)
  - ✓ DVIU: 2/16 (12.5%)
  - ✓ Balloon + DVIU: 1/16 (6.3%)

ROBUST III

Design: Randomized (2:1), prospective, single blind, multicenter

Geography: United States and Canada

Number of Sites: 22

Total Enrollment: 127

- Optilume® DCB: 79
- Standard of Care: 48

Procedure:

- Optilume® DCB Pre-dilation
  - ✓ Plain balloon: 72/79 (91.1%)
  - ✓ DVIU: 3/79 (3.8%)
  - ✓ Balloon + DVIU: 4/79 (5.1%)
- Standard of Care
  - ✓ Plain Balloon: 28/48 (58.3%)
  - ✓ DVIU: 12/48 (25.0%)
  - ✓ Rigid Rods: 8/48 (16.7%)

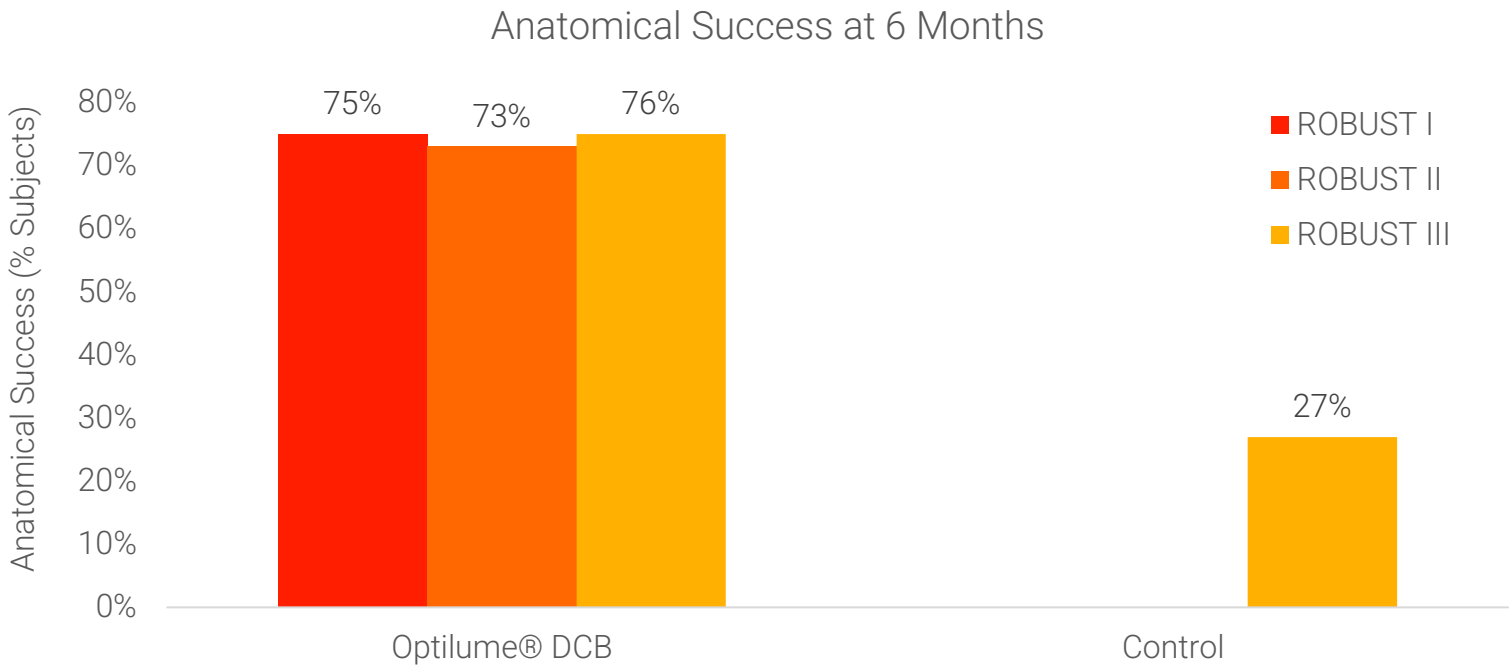
ROBUST Clinical Program – Stricture Characteristics

	ROBUST-I	ROBUST-II	ROBUST III*
Stricture Characteristics	**Stricture Length**: 0.9cm ± 0.5cm (53) Proportion ≥2cm: 1/53 (1.9%) **Prior Dilations**: 1.7 ± 0.8 (53) Proportion with ≥2: 43% **Anatomical location** Bulbar: 53/53 (100%) Penile: 0/53 (0%) **Etiology** Idiopathic: 2/53 (3.8%) Iatrogenic: 24/53 (45.3%) Traumatic: 27/53 (50.9%) Inflammatory: 0/53 (0.0%) **Retention at Baseline**: 27/53 (50.9%) **Prior Radiation**: 0/53 (0.0%)	**Stricture Length**: 2.1cm ± 0.7cm (16) Proportion ≥2cm: 13/16 (81.3%) **Prior Dilations**: 4.1 ± 4.9 (16) Proportion with ≥2: 100% **Anatomical location** Bulbar: 16/16 (100%) Penile: 0/16 (0%) **Etiology** Idiopathic: 11/16 (68.8%) Iatrogenic: 2/16 (12.5%) Traumatic: 3/16 (18.8%) Inflammatory: 0/16 (0.0%) **Retention at Baseline**: 1/16 (6.3%) **Prior Radiation**: 0/16 (0.0%)	**Stricture Length**: 1.6cm ± 0.8cm (79) Proportion ≥2cm: 40/79 (50.6%) **Prior Dilations**: 3.1 ± 1.62 (79) Proportion with ≥2: 100% **Anatomical location** Bulbar: 71/79 (89.9%) Penile: 8/79 (10.1%) **Etiology** Idiopathic: 42/78 (53.8%) Iatrogenic: 21/79 (26.9%) Traumatic: 14/79 (17.9%) Inflammatory: 1/79 (1.3%) **Retention at Baseline**: 26/79 (32.9%) **Prior Radiation**: 9/79 (11.4%)

Stricture characteristics represent a difficult patient population for all studies, particularly so for ROBUST II and ROBUST III.

Similar stricture characteristics were seen in both Optilume® DCB and Control arms in ROBUST III

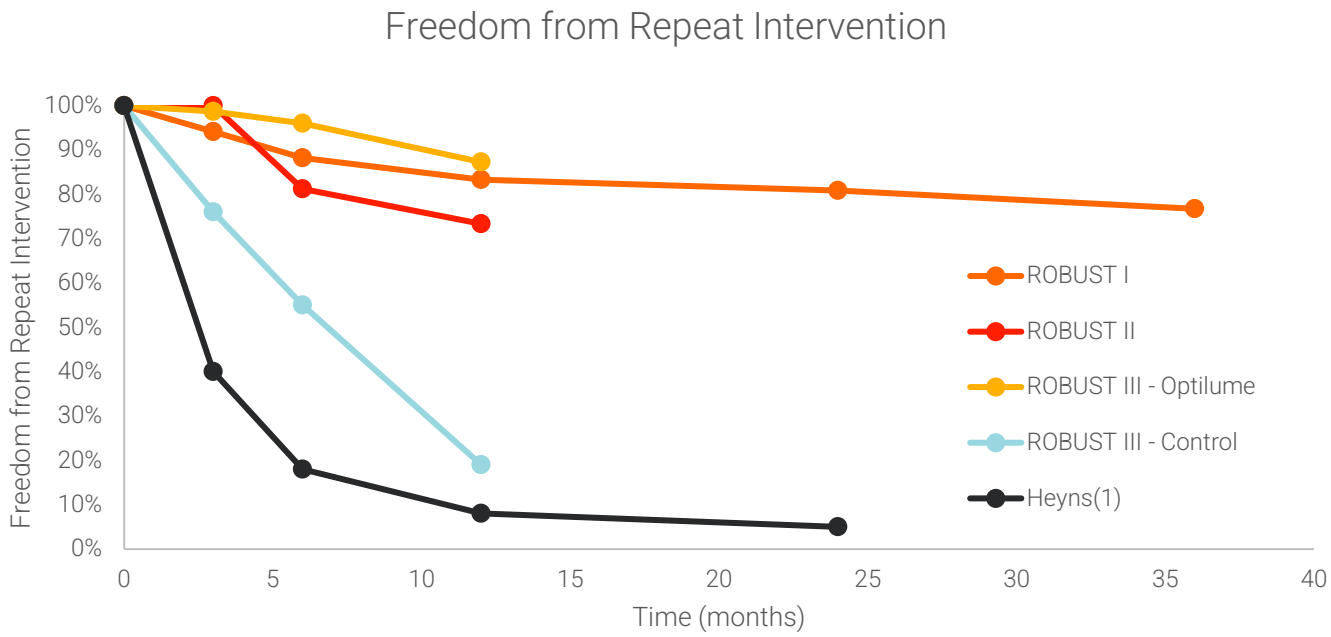
ROBUST Clinical Program – 6 Month Anatomical Success



Anatomical Success – ability to pass a 16F flexible cystoscope through treated area without prior repeat intervention.

Consistent outcomes with the Optilume® DCB in increasingly difficult patient populations. Control outcomes similar among different types of dilation (DVIU, balloon, rigid rods) in ROBUST III.

ROBUST Clinical Program – Freedom From Repeat Intervention



Freedom from Repeat Intervention: Freedom from repeat dilation, urethroplasty, or clean intermittent catheterization through the stated follow up.

[1] Heyns CF et al. *J Urol 1998;160:356-8*

UROTRONIC

ROBUST Clinical Program – Clinical Outcomes

	ROBUST-I	ROBUST-II	ROBUST III*
Follow-up Status	3 Year Complete	1 Year Complete	6 Month Complete, 1 Year ongoing
Optilume Enrollments	53	16	79
Optilume Anatomical Success	6 months: 75% (36/48) 1 year: 76% (35/46)	6 months: 73% (11/15)	6 months: 76% (51/67)
Freedom from Repeat Intervention	3 months: 94% (48/51) 6 months: 88% (45/51) 1 year: 83% (40/48) 2 years: 81% (38/47) 3 years: 77% (33/43)	3 months: 100% (16/16) 6 months: 81% (13/16) 1 year: 73% (11/15)	3 months: 99% (77/78) 6 months: 96% (73/76) 1 year: 87% (48/55)* *FU ongoing
Optilume Average IPSS	Baseline: 25.2 ± 4.5 (n=53) 3 months: 6.1 ± 7.6 (n=51) 6 months: 4.6 ± 5.1 (n=45) 1 year: 4.5 ± 3.9 (n=40) 2 years: 6.9 ± 7.7 (n=38) 3 years: 5.5 ± 6.9 (n=33)	Baseline: 18.4 ± 4.9 (n=16) 3 months: 7.5 ± 6.4 (n=16) 6 months: 7.0 ± 6.7 (n=14) 1 year: 6.5 ± 6.3 (n=8)	Baseline: 21.9 ± 6.9 (n=79) 3 months: 7.0 ± 5.2 (n=72) 6 months: 7.8 ± 5.6 (n=70) 1 year: 8.5 ± 6.3 (n=33)* *FU ongoing
Treatment-related serious complications	90 days: 0% (0/53)	90 days: 0% (0/16)	90 days: 0% (0/79)

Table 11-2: Homogeneity of the Primary Effectiveness Endpoint across Dilation Types
Intent-to-Treat Set

Arm	DVIU	Rigid Rod	Uncoated Balloon	P-value
Stricture Free Rate at 6 Months Post-Treatment n/N (%) / 95% CI				
Optilume Arm	5/6 (83.3%) [35.9%, 99.6%]	-	45/61 (73.8%) [60.9%, 84.2%]	>0.9999

[1] Confidence Intervals (CI) are estimated using the exact approach.
[2] P-value is based on Exact test.

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Title: A Randomized Controlled Trial Evaluating the Optilume Urethral Drug Coated Balloon vs Endoscopic Management for Treatment of Recurrent Anterior Urethral Strictures

Hypothesis/aims of study: Current endoscopic management of anterior urethral strictures includes mechanical dilation or direct visualization internal urethrotomy (DVIU), however long-term success rates are in the range of 35-70% for primary treatment. Multiple endoscopic treatments of the same stricture lead to progressively worse outcomes. The Optilume® Urethral Drug Coated Balloon (DCB) is a urethral dilation balloon with a proprietary paclitaxel coating that combines mechanical dilation of the stricture for immediate symptomatic relief with local drug delivery to maintain urethral patency. ROBUST III is a prospective, multicenter, randomized, controlled single-blind trial to evaluate the safety and efficacy of the Optilume DCB against standard of care endoscopic management of recurrent anterior urethral strictures.

Study design, materials, and methods: Adult men with anterior strictures ≤12F and ≤3cm in length, at least 2 prior endoscopic treatments, International Prostate Symptom Score (IPSS) ≥11, and maximum flow rate (Qmax) <15 mL/sec were randomized 2:1 to receive treatment with the Optilume DCB or standard of care endoscopic management (Control). Subjects with previous urethroplasty or unresolved confounding etiologies (e.g., bladder neck contracture, BPH) were excluded. Subject follow-up post-procedure occurred at 2-5 days (Foley removal), 30 days, 3 months, 6 months, and 1 year. Subjects were blinded to treatment received through 6 months.

The primary endpoint was the proportion of subjects that were stricture free at 6 months as measured by the ability to pass a 16Fr flexible cystoscope or 14Fr catheter through the treated area. Secondary endpoints included freedom from repeat treatment of the study stricture, IPSS, and Qmax. Sexual function was evaluated utilizing the International Index of Erectile Function (IIEF) questionnaire. Subjects who underwent repeat intervention on the study stricture were considered failures for categorical endpoints or assigned the worst observed value for continuous endpoints for timepoints after the intervention. The primary safety endpoint was freedom from a composite of serious device or procedure related complications, including formation of a rectal fistula, unresolved de novo stress urinary incontinence, and urethral rupture or burst.

The statistical hypothesis test for the primary endpoint was based on a two-sample continuity corrected Chi-square test at the two-sided 0.05 (one-sided 0.025) alpha level. A minimum of 126 subjects provided at least 90% power to show superiority of Optilume DCB to standard of care.

Results: The study enrolled and randomized 127 subjects at 23 clinical sites in the United States and Canada (Optilume DCB=79, Control=48). Baseline characteristics were similar between groups, with subjects having an average of 3.6 prior endoscopic treatments and stricture length of 1.7 cm. The majority of strictures were located in the bulbar urethra (92.1%) and were idiopathic in origin (51.2%). Primary 6-month follow-up is complete and 1-year follow-up is ongoing. The proportion of subjects remaining stricture-free at 6 months was 74.6% (50/67) in the Optilume DCB group compared to 26.8% (11/41) in the Control group ($p<0.001$). Outcomes were consistent among subgroups with ≥5 vs <5 dilations and for lengths <2cm vs ≥2cm. The Kaplan Meier estimate for the rate of freedom from repeat intervention through 1-year follow-up was significantly higher for the Optilume DCB as compared to Control. Immediate symptomatic improvement was seen in both groups, however the Control group exhibited symptom scores approaching baseline levels by one year while the improvement in the Optilume group was sustained. A similar trend was seen in Qmax. There was no significant change in IIEF scores in either group. No subjects experienced a serious device related complication. The most frequently reported adverse events included common post-procedural events such as urinary tract infection, post-procedural hematuria, and dysuria.

Interpretation of results: This randomized controlled trial showed that a significantly higher proportion of subjects remained stricture free 6 months after treatment with the Optilume DCB compared to standard endoscopic management. At 1 year, freedom from repeat intervention was significantly higher in the Optilume DCB group. While both groups showed immediate improvements in symptom severity and

voiding function, the benefits were more durable in the Optilume DCB group. Neither group showed a significant change in sexual function through 1 year. The Optilume DCB procedure was safe and well-tolerated. Although published data suggests that stricture recurrence typically occurs within 6-12 months after endoscopic treatment, longer follow-up is needed to capture patients with delayed recurrence.

Concluding message: The Optilume DCB exhibited a significant improvement in both objective and subjective outcomes through 1-year post treatment compared to standard of care and represents a potential breakthrough in the endoscopic management of recurrent anterior urethral strictures. Follow-up through 5 years is planned to further define the durability of the treatment.

Separately submitted (not part of abstract text):

Ethical approval: Institutional Review Board or Ethics Committee approval was obtained for all study sites prior to study commencement. All subjects provided written informed consent.

Funding: ROBUST III was sponsored and funded by Urotronic Inc.

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BENIGN PROSTATIC HYPERPLASIA SPECIFIC HEALTH STATUS MEASURES IN CLINICAL RESEARCH: HOW MUCH CHANGE IN THE AMERICAN UROLOGICAL ASSOCIATION SYMPTOM INDEX AND THE BENIGN PROSTATIC HYPERPLASIA IMPACT INDEX IS PERCEPTIBLE TO PATIENTS?

MICHAEL J. BARRY, WILLIAM O. WILLIFORD, YUCHIAO CHANG, MADELINE MACHI, KAREN M. JONES, ELIZABETH WALKER-CORKERY AND HERBERT LEPOR

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ABSTRACT

Purpose: We assessed the relationship between changes in scores for the American Urological Association (AUA) symptom index and benign prostatic hyperplasia (BPH) impact index with patient global ratings of improvement in a large Veterans Affairs trial comparing different pharmacological therapies for BPH.

Materials and Methods: The primary analyses compared absolute score changes from baseline with global ratings of improvement at 13 weeks for 1,218 men.

Results: Subjects who rated themselves as being slightly improved had a mean decrease in AUA symptom index and BPH impact index scores of 3.1 and 0.4 points, respectively. However, the baseline scores strongly influenced this relationship.

Conclusions: These data provide guidance for investigators using the AUA symptom index and BPH impact index as outcome measures.

KEY WORDS: prostatic hypertrophy, questionnaires, outcome assessment (health care)

The Measurement Committee of the American Urological Association (AUA) has proposed 2 self-administered questionnaires to help capture the health status significance of benign prostatic hyperplasia (BPH): the AUA symptom index, which measures symptom frequency, and the BPH impact index, which measures the health impact of symptoms (tables 1 and 2). These indexes have acceptable test-retest and internal consistency reliabilities, as well as construct and discriminant validities. In addition, the scores have been responsive when patients undergo prostatectomy.[1,2] An important question regarding the use of these indexes that has implications for determining the sample sizes of BPH outcome studies is what changes in scores are perceptible to patients. To date these thresholds have not been defined.

We correlate score changes for these indexes with patient global ratings of improvement in a large randomized, double-blind trial of 4 BPH treatment strategies: placebo, finasteride, terazosin or combination therapy (both agents).

METHODS

In the Veterans Affairs cooperative studies program trial No. 359 men were eligible for randomization if they were at least 45 years old with BPH diagnosed clinically by a study urologist, a peak urine flow rate of 4 to 15 ml. per second and a voided volume of 125 to 500 ml., were on no antihypertensive agents other than diuretics or angiotensin-converting enzyme inhibitors and had an average baseline AUA symptom score (on 2 determinations) of at least 8 points. Men were excluded if they were enrolled in another study protocol or had taken a study drug within the last 4 weeks, drugs interfering with bladder function during the previous 2 weeks or hormones during the previous 3 months, or if they had a history of active cardiovascular disease within the last 6 months, or of orthostatic hypotension or a sitting blood pressure less than 90 over 60 mm. Hg. Finally, men were also excluded if they had a history of prostate cancer, urethral stricture, pelvic irradiation, surgery for BPH, clinically significant renal or hepatic impairment, a prostate specific antigen level greater than 12 ng./ml., neurological diseases associated with primary bladder dysfunction, or active or recurrent urinary tract infections.

Eligible men who agreed to participate completed 2 self-administered questionnaires during a 2-week placebo run-in period to assess symptom severity and health status. Subjects then were randomized to 1 of the 4 arms, and completed the same questionnaires at 2, 4 and every 13 weeks during treatment until 52 weeks were completed. Because of the frequent administration of the indexes a 1-week rather than a 1-month recall time frame was used for all of the component questions. Finally, at each visit patients and investigators made a global assessment of patient improvement from baseline on a 5-point scale: marked, moderate, slight or no improvement, or worse.

The test-retest reliabilities of the 1-week version of the indexes were evaluated by calculating intra-class correlation coefficients between the 2 baseline scores.[3] Internal consistencies were assessed using Cronbach's α statistic.[4] Correlations between scores on the 2 instruments were measured using the Pearson correlation coefficient.[5] The responsiveness of the indexes was tested by calculating standardized effect sizes (mean change divided by the standard deviation of the baseline score) and Guyatt's responsiveness statistic (mean change among all patients divided by the standard deviation of the changes among patients rating themselves unimproved).[3,6] We examined the ability of decreases in scores from baseline to discriminate between subjects rating themselves improved or unimproved by calculating areas under receiver operating characteristic curves[7] using soft-

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TABLE 1. *AUA symptom index*

Question	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1. During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	[0]	[1]	[2]	[3]	[4]	[5]
2. During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating?	[0]	[1]	[2]	[3]	[4]	[5]
3. During the last month or so, how often have you found you stopped and started again several times when you urinated?	[0]	[1]	[2]	[3]	[4]	[5]
4. During the last month or so, how often have you found it difficult to postpone urination?	[0]	[1]	[2]	[3]	[4]	[5]
5. During the last month or so, how often have you had a weak urinary stream?	[0]	[1]	[2]	[3]	[4]	[5]
6. During the last month or so, how often have you had to push or strain to begin urination?	[0]	[1]	[2]	[3]	[4]	[5]
7. During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 Time	2 Times	3 Times	4 Times	5 or More times
	[0]	[1]	[2]	[3]	[4]	[5]

AUA symptom score = sum of questions 1 to 7.

TABLE 2. *BPH impact index*

Question	None/Not at All	A Little	Some	A Lot	
1. During the last month, how much physical discomfort did any urinary problems cause you?	[0]	[1]	[2]	[3]	
2. During the last month, how much did you worry about your health because of any urinary problems?	[0]	[1]	[2]	[3]	
3. Overall, how bothersome has any trouble with urination been during the last month?	[0]	[1]	[2]	[3]	
4. During the last month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?	None	A Little	Some of the Time	Most of the Time	All of the Time
	[0]	[1]	[2]	[3]	[4]

BPH impact score = sum of questions 1 to 4.

ware for continuous, correlated data. Finally, we explored the relationship among patient score changes from baseline with the baseline scores and global ratings of change in linear regression models.

RESULTS

The psychometric properties of the 2 indexes were investigated using baseline data on the first 1,229 men enrolled (mean age 65 ± 6.9 years, standard deviation, range 45 to 80). The median AUA symptom score was 16 points (interquartile range 12 to 21), median peak urine flow rate 10.5 ml. per second (interquartile range 8.1 to 12.9) and median postvoid residual volume 58 ml. (interquartile range 28 to 111). Of the men 79% were white, 10% were black, 9% were Hispanic and 2% were of other ethnic races. Changes in scores were correlated with global ratings using data from 1,165 patients with followup to 13 weeks and at least some data available from that visit (numbers in tables may be slightly less due to item nonresponse).

The intra-class correlation coefficients were 0.74 and 0.71 for the AUA symptom index and BPH impact index, respectively, although the 2 measures were obtained at the beginning and end of the placebo run-in period, during which both indexes demonstrated small but statistically significant decreases (probably due to placebo effect and regression to the mean). Internal consistencies for the AUA symptom index and BPH impact index were 0.67 and 0.74, respectively. The correlation between patient average baseline AUA symptom index and BPH impact index scores was 0.54 ($p < 0.0001$). This moderate correlation provides evidence of the construct validity of both indexes but does not suggest that these question sets measure the same thing.

Table 3 presents the standardized effect sizes for each index as well as Guyatt's responsiveness statistic. For men treated with placebo or medical therapy, the AUA index appeared more responsive than the BPH impact index. These results are different from those obtained from men undergoing prostatectomy in whom the responsiveness of the 2 indexes was equivalent.[1,2]

As an initial step toward determining the impact of different levels of symptoms on patients, we correlated the second baseline AUA symptom index scores with the responses to question 3 on the BPH impact index (table 4), that is a global question about the bother of the condition. AUA symptom scores were originally divided into mild (0 to 7 points), moderate (8 to 19) and severe (20 to 35) ranges based on this question.[1] Estimates of the mean AUA score increased 2 points between "not at all" and "a little," 4.8 between "a little" and "some," and 4.4 between "some" and "a lot" of bother.

In the next analysis, mean absolute and percentage changes in AUA symptom index and BPH impact index scores were calculated for patients rating the condition at 13 weeks as markedly, moderately or slightly improved, unchanged or worse (table 5). In this and all subsequent analyses dealing with change, the average of the 2 baseline scores was used as the best estimate of the true baseline. Because the distributions of percentage changes in scores were considerably skewed (fig. 1), we focused on absolute changes. On average, patients who believed the condition was unchanged had minimal, if any, changes in AUA symptom index and BPH impact index scores. In contrast, those who rated the condition as slightly improved had mean improvements (decreases) in the 2 scores of 3.0 and 0.5 points, respectively, with differences of 2.3 and 0.4 points, respectively, compared to unimproved patients. Men who considered themselves to be moderately improved had AUA symptom index and BPH impact index improvements of 5.1 and 1.1 points, respectively, compared to the corresponding score differences of 4.4 and 1.0 points, respectively, in unimproved men. Patients who rated the condition as markedly improved had even greater mean improvements in scores. Since only 24 patients rated themselves worse, no conclusions can be made for this subset. The pattern of results was similar when the investigator global ratings of patient improvement were correlated

TABLE 3. *Responsiveness statistics for the 2 indexes (1,145 patients)*

	Standard Effect Size*	Guyatt's Responsiveness Statistic†
AUA symptom index	−0.74	−0.82
BPH impact index	−0.33	−0.41

* Mean raw change divided by the standard deviation of the baseline score.
† Mean raw change of all subjects divided by the standard deviation of the change scores of subjects rating the condition unimproved.

TABLE 4. *Mean AUA scores (and 95% confidence intervals) for patients with different responses on a global question about the bother of the urinary condition at baseline*

Overall, How Bothersome has any Trouble With Urination Been in the Last Wk.?	No. Pts.	Mean AUA Score	95% Confidence Interval
Not at all	264	12.4	11.8–13.0
A little	565	14.4	14.0–14.9
Some	343	19.2	18.6–19.7
A lot	57	23.6	22.2–25.1

TABLE 5. *Mean absolute and percent changes in subject AUA symptom index (range 0 to 35) and BPH impact index (range 0 to 13) scores depending on subject 13-week global assessments of degree of change*

Pt. Assessment of Improvement	No. Pts.	Mean Change Scores ± SEM (%)	
		AUA Symptom Index	BPH Impact Index
Marked	223	−8.8 ± 0.34 (−57 ± 2)	−2.2 ± 0.15 (−68 ± 4)
Moderate	298	−5.1 ± 0.29 (−32 ± 2)	−1.1 ± 0.12 (−23 ± 7)
Slight	347	−3.0 ± 0.27 (−16 ± 2)	−0.5 ± 0.12 (+7 ± 8)
None	253	−0.7 ± 0.31 (−2 ± 2)	−0.1 ± 0.13 (+25 ± 7)
Worse	24	+2.7 ± 0.93 (+19 ± 6)	+1.9 ± 0.43 (+66 ± 21)

with changes in AUA symptom index and BPH impact index scores, although investigators appeared to require a somewhat greater AUA symptom index or BPH impact index score decrease to award a higher rating of improvement.

What threshold improvements in scores for these 2 indexes would be reliably perceptible to patients and might be considered clinically significant for outcomes research studies? Any such thresholds are arbitrary and would be accompanied by misclassifications. To explore this issue, we constructed receiver operating characteristic curves and examined the ability of the change scores of each index to predict whether patients showed improvement (slight, moderate or marked) or not (unchanged or worse). Areas under the receiver operating characteristic curves for the AUA symptom index and BPH impact index were 0.74 and 0.67, respectively. The area under the receiver operating characteristic curve, which represents the probability that a randomly selected improved patient would have a greater score decrease than a randomly selected unimproved patient, was significantly greater for the AUA symptom index than for the BPH impact index score ($p < 0.0001$). The sensitivity and specificity pairs for different cutoff points on the receiver operating characteristic curves are presented in table 6. In this context, sensitivity refers to the proportion of improved patients with a decrease in score equal to or more extreme than the cutoff point, while specificity refers to the proportion of unimproved subjects with a less extreme decrease.

To explore whether patient global ratings of improvement depend on the baseline scores as well as the score improvements, we compared mean changes on the AUA symptom index and BPH impact index for each level of self-rated global improvement between subgroups of subjects with higher and lower average baseline AUA symptom indexes (more than or less than 20 points) and BPH impact indexes (more than or less than 5 points, table 7). Both thresholds represent the 75th percentile of the respective distributions, and the former also represents the cutoff point between moderate and severe symptomatology on the AUA symptom index. Again, too few patients rated the condition as worse to draw conclusions for this subgroup. However, for each of the other global rating subgroups a much greater decrease in AUA symptom index or BPH impact index score was necessary to elicit the same self-rating of improvement among patients who started with a higher baseline level (the small standard errors, combined with the large differences between group means, obviate the need for statistical testing). For example, the mean decrease in AUA symptom index scores among men rating the condition as slightly improved was approximately 2 points when the baseline scores were less than 20 points, compared to approximately 6 points if the baseline values were 20 points or greater. Thus, the minimum perceptible differences in both scores were powerfully influenced by patient baseline scores.

Finally, to explore the relationship among baseline scores, global ratings of improvement and change scores, we constructed separate linear regression models with the absolute AUA symptom index and BPH impact index change scores as dependent variables (the 24 patients rating the condition as worse were excluded). Patient baseline scores were included as a continuous independent variable, along with the categories of slight, moderate and marked improvement as indicator variables (no improvement being the reference category), and interaction terms between baseline scores and each of the global improvement categories. The models explained 39% and 33% of the variance in AUA symptom index and BPH impact index change scores, respectively ($p < 0.0001$ for both models). Residual plots suggested that the assumption of a linear relationship between change and baseline scores was reasonable. Figure 2 presents the fitted regression lines in terms of the change scores reflecting no, slight, moderate or marked improvement over the range of baseline scores. The different slopes of the regression lines reflect the interactions between baseline score and each global improvement category. When percentage changes were used as dependent variables, less variation was explained by the same independent variables (29% and 14%, respectively).

DISCUSSION

A decision about what magnitude of improvement in a health status index is clinically significant can be arbitrary. The correlations between changes on the 2 indexes and patient global ratings of improvement provide some framework for making such decisions. However, using global ratings as a gold standard for true perceptible improvement may seem circular. Why not simply use them as primary outcome measures?

In fact, while these 2 types of outcome measures are complementary, indexes such as the AUA symptom index and BPH impact index offer superior measurement reliability over single questions about degree of improvement. In addition, they do not rely on patients recalling a prior health state to compare to the current health state, a task that has been shown to be susceptible to bias.[8,9] Finally, these measures tend to isolate the effect of treatment on a given domain of outcome (such as symptoms), while global ratings represent a synthesis of impacts on multiple domains.

Given the desirability of using indexes, such as the AUA symptom index and BPH impact index, in clinical research, what changes in these indexes should investigators power the studies to detect? Theoretically, the decision should depend on the expected differences in adverse effects between the treatments being compared. When comparing an invasive treatment strategy with considerable side effects to a noninvasive treatment strategy with fewer side effects, only a fairly impressive difference in efficacy would merit adopting the more invasive strategy. In this circumstance, inves-

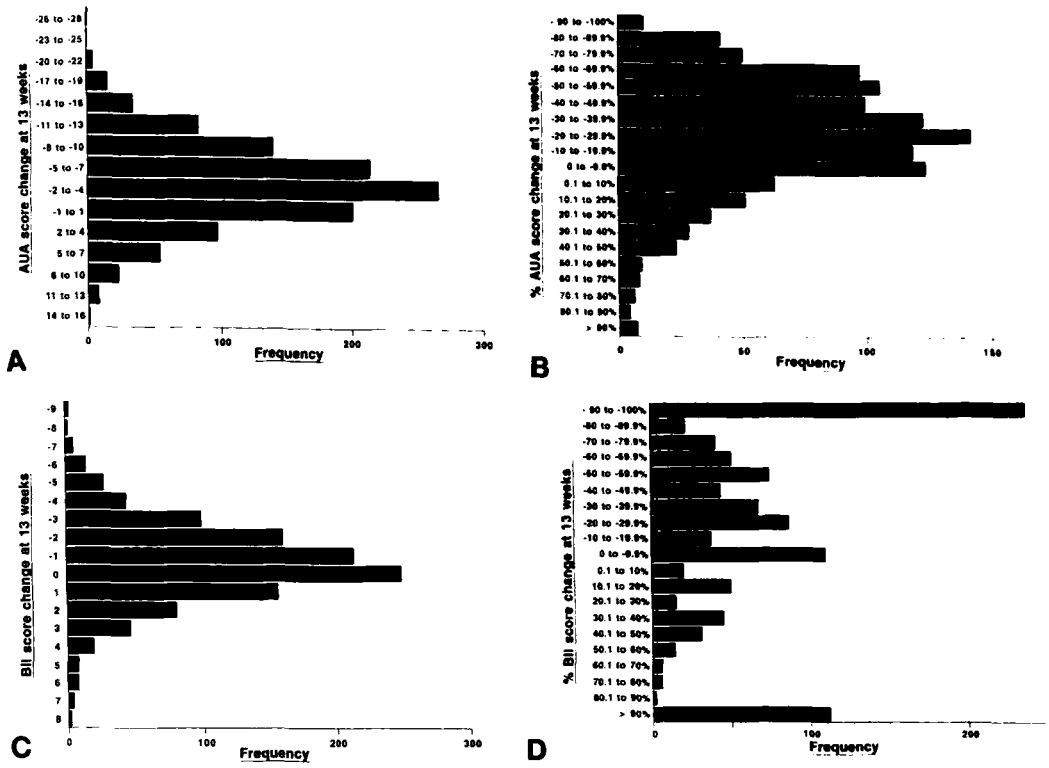

FIG. 1. Distribution of changes at 13 weeks among subjects in cooperative studies program No. 359. *A*, absolute changes in AUA symptom index. *B*, percentage changes in AUA symptom index. *C*, absolute changes in BPH impact index. *D*, percentage changes in BPH impact index.

TABLE 6. *Sensitivity and specificity of different cutoff points on the AUA symptom and BPH impact indexes for discriminating 867 improved from 277 unimproved patients*

Cutoff Points	Sensitivity	Specificity
	AUA symptom index	
−2.0	0.75	0.61
−2.5	0.72	0.65
−3.0	0.68	0.70
−3.5	0.64	0.73
−4.0	0.60	0.77
	BPH impact index	
0.0	0.79	0.51
−0.5	0.67	0.62
−1.0	0.56	0.70
−1.5	0.45	0.77
−2.0	0.35	0.82

In this context, sensitivity is the proportion of subjects rating the condition at least slightly improved with score decreases at or more extreme than the cutoff point, while specificity is the proportion of unimproved subjects with score decreases less extreme than the cutoff point. For example, 68% of improved patients had AUA score decreases of 3 or more points, while 70% of unimproved patients had AUA score decreases of less than 3 points.

TABLE 7. *Mean absolute changes in AUA symptom and BPH impact index scores for each level of self-rated global improvement for subjects with lower versus higher baseline scores*

Pt. Assessment of Improvement	Mean Absolute Change Scores ± SEM (No. Pts.)	
	Lower Baseline Scores	Higher Baseline Scores
	*AUA symptom index**	
Marked	−7.4 ± 0.29 (183)	−15.3 ± 0.76 (40)
Moderate	−4.0 ± 0.29 (227)	−8.7 ± 0.62 (70)
Slight	−1.9 ± 0.29 (252)	−6.1 ± 0.54 (95)
None	−0.2 ± 0.35 (184)	−2.0 ± 0.62 (69)
Worse	+3.3 ± 1.09 (17)	+1.2 ± 1.79 (7)
	BPH impact index†	
Marked	−1.4 ± 0.12 (170)	−4.6 ± 0.36 (52)
Moderate	−0.7 ± 0.12 (218)	−2.4 ± 0.25 (80)
Slight	+0.1 ± 0.13 (224)	−1.6 ± 0.19 (123)
None	+0.4 ± 0.14 (181)	−0.7 ± 0.26 (71)
Worse	+1.8 ± 0.56 (16)	+2.2 ± 0.71 (8)

* Lower baseline score 8 to 19 points, higher baseline score 20 to 35 points.
† Lower baseline score less than 5 points, higher baseline score 5 or more points.

tigators might wish to detect differences in mean AUA symptom index and BPH impact index scores between the study arms consistent with moderate self-rated improvements. BPH studies incapable of detecting differences of at least these magnitudes are probably under-powered.

On the other hand, when 2 strategies with relatively similar levels of invasiveness and expected side effects are compared (such as 2 pharmacological or 2 surgical treatments), investigators may wish to detect smaller differences in mean scores. True net differences corresponding to self-ratings of slight improvement might be reasonable targets. In general, studies with enough patients to detect smaller differences are probably overpowered and run the risk of detecting clinically insignificant differences in group mean scores.

However, to complicate matters, the range of patient baseline scores must be considered when attaching a point value to a slight or moderate improvement rating (table 7 and fig. 2). For example, cooperative studies program No. 359, a trial comparing different strategies of pharmacological treatment and placebo, was designed with a sample size to provide 90% power to detect an approximately 1.5 point difference in group mean AUA symptom index scores among treatment arms. Given that approximately three-quarters of the patients have a baseline score in the moderate range, table 7 suggests that the study is adequately powered to detect dif-

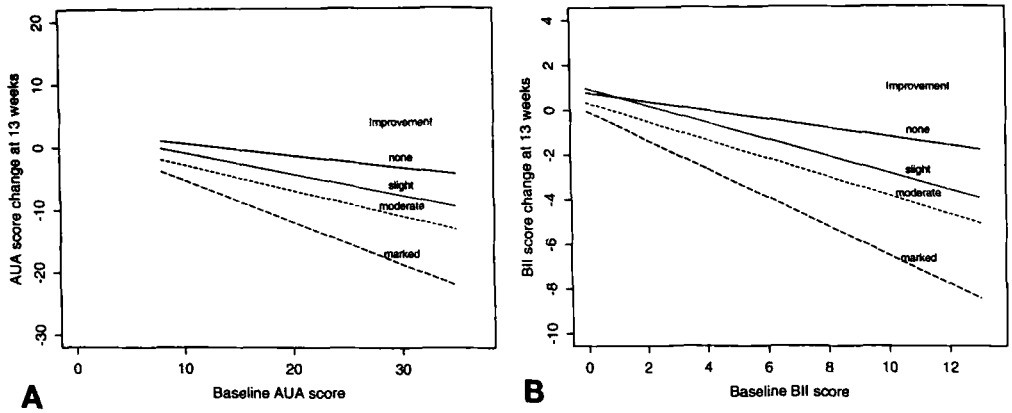

FIG. 2. Relationship between baseline and absolute change scores for subjects rating global improvement at 13 weeks as none, slight, moderate or marked. *A*, AUA symptom index, 1,120 patients. *B*, BPH impact index, 1,117 patients.

ferences between groups that subjects would, on average, consider slight (based on patient perception of change from baseline in this analysis). That these data suggest an eventual finding of no significant difference between the mean AUA symptom index scores of any 2 study arms should be convincing and should also help readers determine the clinical significance of larger differences in group mean scores.

Why use patient rather than investigator global ratings of improvement in determining these thresholds? We believed that the patient's views of improvement were most relevant, since they should be the best judges of how treatment has affected them. However, using physician global ratings would yield only slightly greater estimates of the changes in scores that correspond to any given level of improvement.

Because of the lower apparent responsiveness of the BPH impact index compared to the AUA symptom index, at least among patients receiving pharmacological therapy or placebo, the sample sizes for studies that use both outcome measures will generally be dictated by the specified difference in BPH impact index scores that investigators wish to detect. We previously showed similar levels of responsiveness for these 2 measures among patients who undergo prostatectomy, and tend to have major improvements in symptoms and health status.[2] There are 2 possible interpretations of the evidence of lower responsiveness for the BPH impact index in this study: 1) the BPH impact index may simply be less responsive to smaller degrees of clinically significant change than the AUA symptom index and 2) a slight improvement rating by patients means that the improvement, while perceptible, may not be enough to lessen discomfort and worry, diminish bother and improve functioning (the treatment effects that the BPH impact index is designed to detect).

We do not wish to imply by the preceding discussion that investigators need only present group mean scores when describing the outcomes of BPH treatments. Investigators must describe patient baseline scores, which clearly influence how they perceive the subsequent score changes. Then, some presentation of the distribution of change scores will be helpful to readers when determining what percentages of patients achieve changes of different magnitudes. When comparing outcomes of 2 or more treatment strategies, we favor presentation of confidence intervals around differences in point estimates of outcome measures to provide readers with more information than the p values associated with these differences alone. We also prefer presentation of absolute differences in scores when examining change in these indexes with time and do not find that percentage differences in scores are more closely related to patient global ratings of improvement.

CONCLUSIONS

We examined the relationship between changes in scores on the AUA symptom index and BPH impact index, and patient global ratings of improvement in a large clinical trial to make recommendations to investigators about the clinical significance of changes in these measures. We attempted to present enough data so that individual investigators can select the thresholds in these measures that they wish to detect in their own studies.

Dr. Charles E. Metz developed the receiver operating characteristic software used in the analysis.

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Contains Nonbinding Recommendations

Draft – Not for Implementation

Select Updates for Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 14, 2020.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact OHT3: Office of Reproductive, Gastro-Renal, Urological, General Hospital Device, & Human Factors/DHT3B: Division of Reproductive and Urology Devices at (301)-796-7030.

When final, this guidance will update and supersede the applicable sections of "Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)," issued on August 17, 2010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 1724 and complete title of the guidance in the request.

Table of Contents

Select Updates for Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA has developed this draft guidance to propose select updates to the FDA guidance document "Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)."[1] The existing guidance on devices used for the treatment of BPH remains in effect, in its current form, until this draft guidance is finalized. FDA intends to incorporate this draft guidance into one final guidance document after obtaining and considering public comment on these select updates. The proposed sections referenced below are intended to replace applicable sections of the existing BPH guidance after FDA considers public comment on this draft guidance. The sections of the existing BPH guidance that are not affected by this select update will not be substantively changed and will remain in effect.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[2] For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-non-clinical-and-clinical-investigation-devices-used-treatment-benign-prostatic-hyperplasia.

[2] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

"Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices."[3]

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. Scope

In addition to the devices currently within the scope of the existing BPH guidance, FDA is proposing to add the following devices into the scope of the future final guidance document (Section II) when updated:

Product Code	Product Code Name	Regulation Number
KNS	Endoscopic Electrosurgical Unit (With Or Without Accessories)	21 CFR 876.4300
PEW	Implantable transprostatic tissue retractor system	21 CFR 876.5530
PZP	Fluid jet removal system	21 CFR 876.4350
NOY	Embolic agents for treatment of benign prostatic hyperplasia	21 CFR 876.5550

III. Non-Clinical Testing Recommendations

FDA is proposing to update only a subset of the recommendations included in Section III.K of the existing BPH guidance document.

K. Animal Study

Animal studies[4] provide a valuable assessment of the device's functional design characteristics to evaluate the device for its intended use. The limitations of bench models can make adequate assessment of some safety and effectiveness concerns difficult with bench testing alone. For example, bench testing does not assess tissue necrosis and healing for thermal field-producing

[3] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

[4] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

devices. For most new BPH devices, animal studies provide data to evaluate such safety and effectiveness concerns prior to use in humans.

We recommend that you assess whether animal studies are warranted in your comprehensive non-clinical testing plan. Conducting animal studies for a new device intended to treat BPH depends on factors that include:

- device design;
- material construction;
- mechanism of action;
- duration of clinical use;
- history of clinical use; and
- data from prior animal studies, human clinical investigations (foreign and domestic), or other appropriate studies.

Animal studies intended to evaluate device safety should be conducted pursuant to 21 CFR part 58. To facilitate our evaluation of your study methods and results, we recommend that you provide complete descriptions and justifications for the following:

- choice of animal model and the number of animals tested;[5]
- the test protocol, including objectives and procedures;
- the study results, including the investigator's comments;
- the study conclusions;
- the treatment site;
- all complications;
- all device malfunctions; and
- the study results relating to the human anatomy and the intended use of the device.

In addition, animal study(ies) should include gross and histological examination of the treatment areas by a blinded, independent pathologist that includes the following:

- serial sectioning and staining with hematoxylin and eosin stain and/or a functional stain to evaluate thermal injury, as appropriate;
- representative photomicrographs of histopathological sections; and
- pathologist review and histological description of tissue changes, and extent of changes in three dimensions, in the prostate, rectal wall, bladder neck, external sphincter, neurovascular bundle, and prostatic capsule.

Prior to initiating an animal study, the Agency encourages manufacturers to submit a Q-Submission to obtain detailed feedback on any animal studies for devices intended to treat BPH. For more information, see the FDA guidance document "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[6]

[5] We recommend that you conduct the study using an analytically meaningful number of animals for each experimental condition (i.e., each observation time point, each device operational setting).

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

We recommend that the following specific animal studies be conducted for new thermal field-producing devices and stents.

(1) Thermotherapy

Thermal field-producing (i.e., thermotherapy) devices for the treatment of BPH by design generate tissue damaging temperatures. Bench testing, such as *in vitro* thermal mapping, provides partial evidence that a thermal field-producing device can raise the target tissue to therapeutic temperatures without clinically significant heating of the surrounding non-target tissues (e.g., rectum, bladder). However, these models do not capture important characteristics of the human urological system that impact device performance and safety, such as blood flow, tissue heterogeneity, and active tissue processes such as healing.

We believe animal studies examining the temperature distributions, histological changes, and safety of the non-target tissues are important in assessing the tissue effects of the treatment prior to clinical use in humans. Animal studies are important for devices in which the heating is not localized, and the entire prostate is exposed to prolonged heating (e.g., transurethral microwave thermotherapy (TUMT) devices), or for devices using new ways to generate the thermal field.

We recommend you conduct an *in vivo* animal study to provide complete thermal mapping of the prostate and non-target tissues (i.e., transperineal interstitial thermal mapping including the urethral, intraprostatic, periprostatic, and anterior rectal wall tissues) using intact male dogs of sufficient age and size to mimic the human prostate anatomy. Tissue temperatures should be recorded following treatment until they return to baseline to ensure capture of maximum temperature and time-temperature history. Due to the differences in human and animal anatomy, we recommend image verification of the location of the device components (e.g., treatment applicator, temperature probes) and the temperature sensors.

We recommend you select device operating parameters for the animal study that mimic clinical use in humans to evaluate the safety and functional characteristics of the device design, and to validate the performance of the device for its intended use. You should evaluate the complete range of achievable power levels and temperatures, including the maximum power and time settings. If your device includes multiple applicator designs or variable operational settings (e.g., treatment time, power), we recommend you conduct complete testing for each design and setting. For example, if your device includes both a cooled applicator and a non-cooled applicator, we recommend you evaluate each applicator using minimum, mid-range, and maximum settings in your animal study. If your device includes multiple treatments, the number of treatments used in the animal study should equal or exceed your intended maximum number of treatments.

Because these devices rely on acute tissue injury, followed by necrosis and subsequent healing to achieve their intended use, we recommend you evaluate both the early tissue effects and subsequent early healing (e.g., 24 hours, three weeks after treatment).

As described above, we recommend you provide histological assessment of tissue changes and a discussion of the extent of thermal effects as they relate to human anatomy. Specifically, we

recommend you compare the observed area of histological thermal effects with the relevant anatomy, including:

- in-target compared with non-target tissue; and
- the target tissue in relation to that of surrounding critical tissues, including rectal wall, urethra, neurovascular bundles.

(2) Stents

Whether we recommend conducting animal studies for prostatic stents intended to treat or relieve BPH depends on the device design, material construction, mechanism of action, duration of use, and any novel aspect. For example, we recommend animal data to evaluate the safety of a permanent prostatic stent prior to clinical use in humans.

We recommend the animal study protocol closely approximate the intended clinical methods to evaluate the safety of the procedure, functional design characteristics, and to validate the performance of the device for its intended use. In addition, we recommend you select follow-up periods and sacrifice periods that provide clinically meaningful assessment of the device effects.

We recommend the animal study include:

- placement of a single stent as per clinical protocol;
- placement of the maximum number of stents proposed for use in the clinical study;
- repositioning the device; and
- removal using the manufacturer's recommended techniques.

We recommend this animal study assess the following adverse events using imaging, gross, and histologic evaluation as indicated based on a clinical risk assessment:

- stent migration;
- encrustation;
- erosion;
- pressure necrosis;
- urothelial hyperplasia/tissue ingrowth;
- stone formation;
- urethral edema;
- cellular atypia; and
- device failure or breakage.

We recommend you conduct a macroscopic and microscopic evaluation of the stent including calcification, erosion, and epithelization.

If your stent can be explanted or removed, we recommend you conduct mechanical testing similar to the non-clinical testing on the explanted stents in order to evaluate any changes to the structural integrity of the device that may have occurred due to stent implantation.

If your stent is designed to resorb or degrade *in situ*, we recommend you evaluate the degree of absorption or degradation at multiple time points over the course of its degradation to ensure that tissue response to starting, intermediate, and final degradation products are fully assessed. We also recommend the timing of your evaluations be sufficient to determine the rate of degradation and to demonstrate that complete healing and total elimination of the stent occurs. The selection of time points for the study may depend on the nature of the material and should relate to its estimated degradation time.

IV. Pilot Study Recommendations

FDA does not currently intend to significantly change the content in Section IV of the existing BPH guidance document. FDA is proposing the following changes:

- FDA is proposing to change the name of this section to "Pilot Clinical Study Recommendations;"
- In the fifth paragraph, FDA is proposing to revise the recommendation that if sponsors intend to pool pilot and pivotal study results, that this pooling is planned prospectively and keep the recommendation that sponsors provide a rationale showing that it is statistically and clinically valid to pool the data from the pilot and the pivotal studies; and
- In the seventh and final paragraph, FDA is proposing to include a recommendation that the methods used to characterize the temperature distribution in the prostatic and periprostatic tissues include both the rectal wall and urethra. The current recommendation includes only the rectal wall.

V. Pivotal Study Recommendations

FDA is proposing to change the title of the Section V of the existing BPH guidance to "Pivotal Clinical Study Recommendations" and recommend the use of the FDA guidance "Design Considerations for Pivotal Clinical Investigations for Medical Devices"[7] for FDA's current thinking on the principles for the design of clinical studies on medical devices. FDA only intends to significantly change the following subsections of Section V of the existing BPH guidance document.

C. Randomization and Controls

FDA is proposing to replace Section V.C of the existing BPH guidance document with these recommendations:

Clinical investigations of devices for the treatment of BPH pose unique challenges such as a placebo effect, spontaneous remissions, subjectivity of lower urinary tract symptoms (LUTS) and their impact on quality of life, difficulty in securing reliable measurement of LUTS and quality of life, and wide availability of effective treatments for BPH.

[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.

We believe these challenges are most efficiently overcome by using a randomized, controlled trial design. The benefit of a randomized, controlled trial is its tendency to balance confounding factors, measurable and unmeasurable, between study groups and minimize the potential for bias.

The potential advantages of a randomized, controlled trial design extend not only to the evaluation of device effectiveness, but also to the evaluation of safety. Adverse event rates may be affected by factors such as subject characteristics, device design, evolving procedural methods, and operator experience, and may be much more difficult to evaluate when using historical control data.

Randomizing subjects between study groups is a standard method to minimize selection bias and control for confounding factors. Selection bias occurs when subjects possessing one or more important prognostic factor appear more frequently in one study group than the other. The randomization process assigns subjects to an intervention or control group with a known probability and each subject has an equal chance of being selected for a group. Randomization also protects the trial from conscious or subconscious actions on the part of study investigators that could lead to study groups that are not comparable, e.g., selecting the most symptomatic patients for the therapy thought by the study investigator to be the more aggressive treatment.

We recommend you:

- pre-specify the randomization method in the study protocol;
- balance the assignment of subjects within each site, e.g., stratification by site, block randomization;
- preclude investigators and other study personnel from predicting or influencing the assignment of subjects; and
- prevent natural patterns of patient behavior from influencing study assignment.

When designing a randomized, controlled study, we recommend you select an appropriate control therapy. There are a variety of scientific and ethical issues that may influence the choice of control.[8] Typically, the current standard of care for the targeted patient population represents the most clinically meaningful control. However, other factors may also influence this decision. We recommend you address each of the following specific factors when choosing a control:

- standard of care;
- indications for use of the investigational device;
- any desired representations of device performance in future labeling;
- risks versus benefits, i.e., to permit a clinically meaningful comparison, it is desirable for the risk-to-benefit ratio of the control treatment to be comparable to that of the investigational device;
- ability to effectively mask the investigator, subject, and evaluator;
- time to treatment effect; and
- device design characteristics.

[8] Temple R, Ellenberg SS, Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: Ethical and scientific issues. *Ann Intern Med*, 2000, 133(6):455-461.

Potential control therapies for clinical investigations for the treatment of BPH include:

- an accepted surgical procedure, e.g., transurethral resection of the prostate (TURP);
- a medical device cleared or approved for the treatment of BPH; and
- sham treatment.

TURP is considered the gold standard surgical treatment for BPH and there are many successful clinical trials using TURP as a control.

A control that consists of a treatment with a legally marketed device, similar in design to the investigational device, is often a desirable option because study design, patient enrollment, and data analysis may be straightforward. For example, it might be both simple and appropriate to use a randomized study to compare the safety and effectiveness of a new implantable transprostatic tissue retractor system to a legally marketed system with similar design and operational characteristics.

Sham effect during BPH procedures has been shown to be significant, on the order of change seen with commonly used medications.[9] Sham controlled studies represent one study design and choice of control group which may allow for discrimination of patient outcomes caused by the test treatment from outcomes caused by other factors such as patient or observer expectations. This type of study design may be most appropriate for studies with subjective endpoints, such as reduction in patient-reported symptoms. Sham surgical procedures/treatments typically involve more risk than the placebo control arm in drug trials and these risks should be considered when designing a clinical trial. This study design should be considered when it is methodologically warranted, i.e., when designs that are unblinded are methodologically unacceptable (e.g., because endpoints are subjective) and when a "no treatment" control is methodologically warranted. Furthermore, the withholding of treatment should not lead to serious injury, such as irreversible morbidity, or death. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that investigators, institutional review boards, and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully considered and planned.

While potentially useful to certain stakeholders, the use of an approved drug therapy as a control is complicated because devices used to treat BPH generally have significantly dissimilar expected risks and different mechanisms of action compared to approved drug therapies.[10] Additionally, devices intended to treat BPH achieve full effectiveness quickly, while drug therapies often take many months to reach full effectiveness. Consequently, the results of drug-controlled studies can be difficult to interpret when assessing the safety and effectiveness of a device.

[9] Welliver C, Kottwitz M, Feustel P, McVary K, Clinically and Statistically Significant Changes Seen in Sham Surgery Arms of Randomized, Controlled Benign Prostatic Hyperplasia Surgery Trials. *J Urol*, 2015, 194:1682-7.
[10] AUA Guideline "Surgical Management of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms (2018, amended 2019)" (https://www.auanet.org/guidelines/benign-prostatic-hyperplasia/lower-urinary-tract-symptoms).

It is often difficult to obtain adequate, dependable, and directly applicable historical information from published literature or a prospective chart review due to variations in patient demographics, selection criteria, and evaluation methodologies. Consequently, we believe using an historical control complicates the demonstration of safety and effectiveness in most investigations.

You can employ several strategies to facilitate subject recruitment and retention. For example, 2:1 (or other) randomization schemes increase the likelihood that a given subject will receive the investigational treatment. Study designs may allow sham subjects, for example, to receive treatment with the investigational device after a pre-specified time or significant disease progression.

We generally recommend a randomized, controlled trial to address the challenges described in this guidance document; if you use an alternative study design, we recommend you discuss how it is scientifically sound and will address relevant safety and effectiveness questions. While we recognize that there is no unique "best design" for investigations of BPH treatments, we consider the elements discussed in this document as core features of well-designed studies. As noted, we will consider alternative study designs, but we recommend that you clearly explain the scientific reasoning supporting your alternative design (e.g., How will bias be minimized? How does the study address placebo effects? How does the control compare with current patient characteristics and standards of clinical care?). Prior to initiating a clinical study with an alternative design, FDA encourages manufacturers to submit a Q-Submission to obtain detailed feedback on such studies. For details on Q-Submissions, refer to the guidance "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[11]

For all study designs, we recommend you collect detailed baseline and demographic information on all study subjects so that the study groups can be assessed for imbalances in prognostic factors.

E. Study Endpoints

(2) Primary Effectiveness Endpoint

FDA is proposing to replace Section V.E(2) of the existing BPH guidance document with these recommendations:

The primary effectiveness endpoint should be one that is clinically meaningful and should fully characterize the effect of treatment. Due to the subjective nature of BPH symptoms, it is difficult to find an effectiveness measure that is objective and repeatable (i.e., has low test-retest variability), yet is also meaningful to patients and relevant to their reasons for seeking treatment.

Since its development, the most widely used primary outcome measure used in studies of therapies for BPH has been the American Urological Association Symptom Index (AUA-SI) and the equivalent International Prostate Symptom Score (IPSS). These measures consist of seven

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

questions assessing LUTS associated with BPH (i.e., incomplete emptying, frequency, hesitancy, urgency, weak stream, straining, and nocturia). Each question is scored on a 0-5 scale and summed to form a final score from 0-35, where higher scores reflect more severe symptoms.[12] An additional disease-specific quality of life question scored separately on a 0-6 scale is included in the IPSS. These instruments are considered reliable measures of LUTS due to BPH and have been validated in multiple languages.[13]

Bothersome LUTS is usually the primary reason a patient seeks treatment for his BPH, and most devices used to treat BPH are designed to provide symptomatic relief. In most clinical trials, the primary effectiveness endpoint should demonstrate improvements in symptom severity. Specifically, we recommend you base the primary effectiveness endpoint upon the improvement in AUA-SI (or IPSS) compared to baseline.

Generally, patients are unable to discern an AUA-SI (or IPSS) score difference of less than 3 points.[14] However, the minimal clinically significant difference following treatment depends on the baseline symptom score. Investigations evaluating the minimal clinically significant difference in AUA-SI used drug therapy for BPH. FDA is unaware of studies that identified the minimal clinically significant difference in AUA-SI following device treatment. Furthermore, many trials enroll subjects across more than one symptom severity classification. Therefore, identifying an appropriate minimal clinically significant difference for the AUA-SI following device therapy can be challenging.

One study of men with moderate to severe LUTS used a balanced Likert score to investigate the extent to which patient satisfaction is influenced by a change in BPH symptoms.[15] This study identified a range of improvement in AUA-SI across symptom severity classifications needed to achieve certain satisfaction levels. An improvement of at least 30% in the AUA-SI was used for a "Satisfied" or "Very Satisfied" response. This is an appropriate level of response given the difference in risk profiles between drug and device therapies. Based on this literature, we recommend an improvement of ≥ 30% over baseline as the minimum clinical improvement in AUA-SI following device therapy. Higher risk devices may warrant a more significant benefit. We recommend a 12-month analysis of the primary effectiveness endpoint(s) for an active control trial. For a study design that does not include an active control, we recommend incorporating a sham control. Given the challenge in maintaining a sham control for 12 months,

[12] Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al., The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*, 1992, 148:1549.

[13] Barry MJ, Adolfsson J, Batista JE, et al., Measuring symptoms and health impact of benign prostatic hyperplasia and its treatments. In: Denis L, Griffiths K, Khoury S et al. (eds). Fourth international consultation on BPH. Plymouth: Plymbridge Distributors: 1998: 265-321.

[14] Barry MJ, Willlifred WO, Chang Y, et al., Benign prostatic hyperplasia specific health status measures in clinical research: How much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients. *J Urol,* 1995, 154:1770-1774.

[15] Roehrborn CG, Wilson TH, Black LK, Quantifying the Contribution of Symptom Improvement to Satisfaction of Men with Moderate to Severe Benign Prostatic Hyperplasia: 4-Year Data from the CombAT Trial. *J Urol*, 2012, 187:1732-1738.

we recommend a shorter timepoint for head-to-head comparison between the treatment and sham arms. However, stability of effectiveness should still be demonstrated at 12 months for the *treatment arm* in a sham-controlled trial.

Separation of the irritative and obstructive symptom questions in the AUA-SI (or IPSS) is psychometrically valid, but at this time it is not clear that such sub-score analyses are clinically meaningful.[16]

We recognize that other outcome measures may be appropriate as well due to specific device design characteristics or desired marketing claims. For example, claims for reduction of obstruction could be based on documented improvement in flow rate, results of "pressure/flow" studies (cystometry), and post-void residual urine volume. If you choose an alternative outcome measure, it is important that you provide a scientifically valid rationale that explains its appropriateness for your device.

(3) Primary Safety Endpoint

FDA is proposing to replace Section V.E(3) of the existing BPH guidance document with these recommendations:

We recommend you base the primary safety endpoint on the incidence and severity of adverse events. However, if the device is associated with, or intended to mitigate, a specific safety concern, then it may be appropriate to base the primary safety endpoint on the specific adverse event(s) of interest associated with that concern, while still recording all adverse events.

To collect safety information reliably, we recommend your protocol instruct the investigators to record all adverse events, regardless of whether you believe they are device-related or anticipated. Regardless of study design, we recommend you follow subjects during the premarket follow-up period for one year following treatment to monitor adverse events. We recommend you routinely record the following events:

- genitourinary events, i.e., events associated with the urinary tract and/or the surrounding genital region;
- damage to the bladder floor, trigone, sphincters, and rectum;
- infections;
- worsening sexual dysfunction;
- secondary surgical interventions;
- all transient post-procedure events; and
- deaths.

[16] Barry M.J., et al., Filling and voiding symptoms in the American Urological Association symptom index: the value of their distinction in a Veterans Affairs randomized trial of medical therapy in men with a clinical diagnosis of benign prostatic hyperplasia. *J Urol*, 164:1559-1564, 2000.

Adverse events should be categorized according to their respective relatedness to the device or procedure, and their severity (e.g., using the latest version of the Common Terminology Criteria for Adverse Events[17]). This categorization should be based on pre-defined criteria and can be accomplished by study investigators or an independent, third-party Clinical Events Committee (CEC). Because of the difficulty of determining the root cause of genitourinary events, we recommend you categorize events conservatively as either device- or procedure-related unless there is clear evidence of other causation. Additionally, we recommend that investigators document the onset and resolution times of each adverse event, noting the method of resolution.

We recommend the safety analysis include a descriptive assessment of the types and frequency of adverse events observed in the study, with comparison to the control therapy, as appropriate.

(4) Secondary Endpoints

FDA is proposing to replace Section V.E(4) of the existing BPH guidance document with these recommendations:

FDA believes secondary endpoints, by themselves, are not sufficient to fully characterize treatment benefit. However, these measures may provide additional characterization of the treatment effect. Specifically, secondary endpoints can:

- supply background and understanding of the primary endpoints;
- be the individual components of a composite primary endpoint, if used;
- aid in the understanding of the treatment's mechanism of action;
- be associated with relevant sub-hypotheses (separate from the major objective of the treatment); or
- be used to perform exploratory analyses.

Assuming that the primary safety and effectiveness endpoints of the study are successfully met, we recommend you analyze the secondary endpoints to provide supportive evidence concerning the safety and effectiveness of the device, and to support device performance if you plan to make such representations in your labeling.

Although there are many possible secondary endpoints to consider for clinical investigations of devices intended to treat BPH, we recommend your protocol include the endpoints discussed below:

- Prostate volume: Many devices intended to treat BPH, such as transurethral microwave thermotherapy (TUMT), can reduce prostatic volume. Increases in prostatic volume can also indicate the progression of BPH. Therefore, we recommend that you evaluate prostatic volume throughout the study.
- Uroflowmetry: Decreased peak urine flow rates are common in men with BPH. We recommend you conduct uroflowmetry including peak and average flow rates, total void time, and total void volume at each follow-up visit.

[17] For more information, see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- Post void residual (PVR) urine volume: PVR has generally been considered to reflect the severity of bladder outlet obstruction. We recommend you measure PVR at each follow-up visit to monitor impairment or improvement of bladder emptying due to the treatment or disease progression.
- Quality of life: BPH is associated with impairment of quality of life. Therefore, we recommend you incorporate a validated quality of life measure specific to BPH into the study. The measure most commonly used is the disease-specific quality of life question included with the AUA-SI (or IPSS) questionnaire.
- Return to "Normal" symptom severity: There is value in knowing the percentage of subjects whose symptoms improve to what is considered "normal" (i.e., AUA-SI < 8) after therapy. Conversely, the proportion of subjects whose symptoms worsen after therapy is also important to know. Therefore, we recommend you collect pre- and post-treatment AUA-SI scores.
- Sexual function and dysfunction: Both BPH and many of its therapies adversely affect sexual function. Therefore, we recommend you incorporate a validated, gender-specific measure of sexual function assessed at each follow-up visit.
    - The recommended instrument to assess sexual function is the International Index of Erectile Function, specifically the Erectile Function domain (IIEF-5).[18] The Minimal Clinically Important Difference (MCID) has been shown to be 4 points.[19] However, the MCID is a function of baseline erectile function. For example, the MCID is 2, 5, or 7 for men with mild, moderate, or severe erectile dysfunction, respectively. If your study population is limited to men in only one subgroup of erectile dysfunction (mild, moderate, or severe), it is appropriate to use the specific MCID for your study group. However, if you choose to include men across two or more ranges of erectile dysfunction (e.g., mild and moderate, moderate and severe, or mild, moderate, and severe), then a responder analysis using the appropriate MCID considering baseline values is more appropriate.

Recommendations regarding the statistical analysis of secondary endpoints are discussed in Section IV.N of the existing BPH guidance document.

G. Statistical Hypothesis

FDA is proposing to replace Section V.G of the existing BPH guidance document with these recommendations:

The statistical hypothesis follows directly from the primary objective of the study and establishes the framework for the design of your study. The statistical hypothesis is also used to calculate the sample size and helps determine the statistical methodology that will be used to analyze the

[18] Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology*, 1997,49:822–30.

[19] Rosen RC, Allen KR, Ni X, Araujo AB. Minimal Clinically Important Differences in the Erectile Function Domain of the International Index of Erectile Function Scale. *Eur Urol*, 2011, 60:1010-1016.

primary study endpoint. For these reasons, you should formulate a clear statistical hypothesis that is consistent with the primary objective of your study when you design your pivotal clinical trial and include it in your protocol. All other elements of your clinical study design should be consistent with your statistical hypothesis.

For non-inferiority studies, we recommend the hypothesis incorporate a non-inferiority margin that reflects a maximum tolerable difference that is "clinically insignificant" (i.e., "not clinically meaningful") in the analysis of the primary effectiveness endpoint. Larger values of the non-inferiority margin may be selected by demonstrating significant benefits in the safety of the investigational device.

I. Patient Selection Criteria

FDA is proposing to replace Section V.I of the existing BPH guidance document with these recommendations:

Although BPH is predominantly confined to older men, age and other baseline characteristics of the patient population can impact the effectiveness and safety of different device therapies for BPH. Therefore, we recommend you develop inclusion and exclusion criteria for your clinical trial that select a cohort representative of the population that will be treated clinically, while limiting characteristics that could confound the interpretation of the data.

We recommend your protocol define inclusion criteria that identify an appropriate target population. Specifically, your study should enroll men clinically diagnosed with BPH for which treatment is recommended. The patient characteristics we recommend you consider in developing the inclusion criteria for your study include the following.

- Age: The protocol should state the age range eligible for enrollment. Because BPH is generally confined to older men, we recommend you include men over 50.
- Diagnosis: Investigators should diagnose subjects as having symptomatic BPH. We recommend the diagnosis criteria specified in the protocol be consistent with the current standard of care.
- Prostate size: Frequently, devices intended to treat BPH are specifically designed to treat prostates of a specific size in terms of volume and length. We recommend your inclusion criteria prospectively define intended prostate size within lower and upper limits based on the parameters of the particular therapy.
- Symptom severity: Generally, patients seek treatment for BPH due to bothersome symptoms. We recommend your protocol prospectively define a range of AUA-SI (or IPSS) scores consistent with the severity of symptoms your device is intended to treat. For example, an AUA-SI > 20 is consistent with the current clinical definition of severe BPH.[2012]

[20] Barry MJ, Fowler FJ Jr., O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, et al., The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol, 1992, 148:1549.

- Peak urine flow rate: Reduced urinary flow rates are indicative of bladder outlet obstruction and are suggestive of BPH. We recommend you include subjects with peak urine flow rates that are indicative of obstruction (e.g., < 12 ml/sec).[21]
- Subject compliance and suitability: We recommend enrolling subjects who are able to understand all study requirements and have life expectancies greater than the study period. Further, we recommend enrolling subjects who are able to tolerate the procedure (e.g., good surgical candidates) and agree to baseline and follow-up evaluations specified in the protocol.

Investigational devices present some unknown risk to study subjects. For this reason, patients with substantial comorbidities are more vulnerable and should be protected from this unknown risk by appropriately devising exclusion criteria for a clinical trial. However, FDA recognizes that a device intended to treat BPH could potentially offer an advantage, especially suitable for those subjects with substantial comorbidities (e.g., shorter procedure time, local anesthesia instead of general anesthesia, minimal bleeding risk). We recommend justifying inclusion of such subjects with a clear explanation of the expected benefits and risks if these patients are intended to be included in the study.

We recommend your study protocol define exclusion criteria that prevent enrollment of subjects with characteristics that could confound the interpretation of the data or that suggest that your device poses undue risk. The patient characteristics we recommend you consider in developing the exclusion criteria for your study include the following.

- Confounding conditions: We recommend your protocol exclude men with a history of any illness that might confound the results of the study, produces symptoms that might be confused with those of BPH, or poses additional risk to the patient based on device design. Examples include:
  - cardiac arrhythmias, cardiac disease including congestive heart failure, uncontrolled diabetes mellitus, significant respiratory disease, known immunosuppression, or bleeding disorders;
  - neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes;
  - a post void residual (PVR) volume > 250 ml measured by ultrasound or acute urinary retention;[22]
  - compromised renal function (i.e., serum creatinine level > 1.8 mg/dl, or upper-tract disease);
  - confirmed or suspected bladder cancer;
  - recent (within three months) cystolithiasis or hematuria;

[21] Using current techniques, an adequate minimum voided volume (i.e., 125 ml) is needed to obtain accurate measurement of flow rates. Also, we recommend that you base the baseline flow rates on two separate measurements.

[22] Subjects with acute urinary retention should be excluded or treated as a separate cohort due to confounding problems in this group.

- urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology;
- a history of prostatitis within the last two years; or
- an active urinary tract infection.

- Prostate cancer: We recommend your protocol exclude men with confirmed or suspected malignancy of the prostate based on the digital rectal exam (DRE), prostate biopsy, transrectal ultrasound (TRUS), or prostate specific antigen (PSA) level. We recommend your protocol include testing the PSA level of all subjects. Currently clinical guidelines indicate that a PSA level > 10 ng/ml is indicative of prostate cancer. We recommend your protocol include a prostate biopsy prior to enrollment, if indicated, based on DRE, or if the subject's PSA level is > 2.5 ng/ml and ≤ 10 ng/ml and his free PSA is < 25% of total PSA.[23] Finally, we recommend you follow the aforementioned American Urological Association (AUA) guidelines to help determine in which subjects prostate cancer screening is appropriate based upon age, ethnicity, family history.
- Surgical history: We recommend your protocol exclude men with a history of any surgery that might confound the results of the study, or that poses additional risk to the patient based on device design. Examples include:
  - previous rectal surgery (other than hemorrhoidectomy) or history of rectal disease if the therapy may potentially cause injury to sites of previous rectal surgery, e.g., if a transrectal probe is used;
  - previous pelvic irradiation or radical pelvic surgery;
  - previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate; or
  - cardiac pacemaker or metallic implants in the pelvic/femoral area, if warranted, based on device design (unless electromagnetic compatibility and safety with these implants are prospectively demonstrated).
- Future fertility: We recommend your protocol exclude men interested in future fertility, if your device has the potential to impact fertility.
- Concomitant medications: We recommend your protocol exclude men on medications that affect BPH symptoms as these medications can confound the study results. However, we recognize that requesting men discontinue their BPH medications to participate in the study could put them at risk for adverse events including worsening LUTS, hematuria, infection, or urinary retention. Furthermore, excluding men who cannot or will not discontinue these medications eliminates men who might benefit the most from the device from the study. Therefore, it is reasonable to include men on BPH medications if their dose has been stable after an appropriate period and the dose is not changed throughout the study unless medically warranted.

[23] We recognize that current thinking on best clinical practices on the use of PSA in screening for prostate cancer and the minimum normal value for PSA is under debate in the clinical community (see Barry MJ, Prostate-specific-antigen testing for early diagnosis of prostate cancer, *N Engl J Med*, 2001, 344:1373-1377; and "Early Detection of Prostate Cancer (2018)," AUA Guideline, https://www.auanet.org/guidelines/prostate-cancer-early-detection-guideline). We believe that it is important to exclude subjects with prostate cancer from clinical studies of devices used to treat BPH and, therefore, recommend that you adopt the more conservative limits for PSA as described.

BPH medications include prescription and over-the-counter drugs, and dietary supplements. If potentially confounding medications are clinically appropriate to be taken concurrent with the study, we recommend your protocol indicate that the dosage should not change during the study period unless medically warranted. If you intend to include such medications in your study, subjects should be on them for at least a minimal amount of time prior to the study ("wash-in"), and the recommended wash-in period should be specified. The recommended wash-in and wash-out periods are the same and are described below. If you intend to exclude specific medications from your study, we recommend your protocol specify wash-out periods after which subjects can be enrolled or treated.

For example, we recommend excluding men using:

- Antihistamines, anticonvulsants, and antispasmodics within one week of treatment unless there is documented evidence that the patient was on the same drug dose for at least six months with a stable voiding pattern (the drug dose should not be altered or discontinued for entrance into or throughout the study);
- α blockers within four weeks of treatment;
- Anticholinergics within two months of treatment;
- Androgens, and gonadotropin-releasing hormonal analogs within two months of treatment; and
- 5-alpha reductase inhibitors within six months of treatment.

Your clinical study protocol should justify wash-in or wash-out periods for medications not listed above (e.g., PDE-5 inhibitors, β3 agonists, tricyclic antidepressants).

Subjects who receive new BPH medications or an increased dose of a current BPH medication during the course of a trial should be considered treatment failures.

M. Post-Treatment Evaluations

FDA is proposing to replace Section V.M of the existing BPH guidance document with these recommendations:

We recommend the post-treatment evaluation schedule include multiple follow-up visits spanning the entire study duration, e.g., one, three, six, and 12 months post-treatment. For thermotherapy devices, we recommend a follow-up visit shortly after treatment, (e.g., 8-10 days after removal of a post-treatment catheter), consistent with the standard of care. For devices in which a post-market study is possible or anticipated, we recommend the post-treatment evaluation schedule include periodic follow-up visits, e.g., yearly for all subjects until marketing approval.

Your protocol should clearly describe the follow-up schedule, and identify all tests, measurements, and examinations you plan to conduct at each post-treatment evaluation. To ensure consistency with the investigators and investigational sites, we recommend all tests and measurements be performed using well-recognized methods clearly defined within the protocol.

To allow comparisons to the baseline data, we recommend you perform all applicable post-treatment tests using the same methodology as the pre-treatment evaluation. Additionally, we recommend the control population undergo evaluation identical to the investigational group.

We recommend that post-treatment evaluations include the following tests and assessments:

- Physical examination;
- Updated medical and surgical history, including medications;
- AUA-SI (or IPSS);
- Quality of life assessment;
- Sexual function assessment;
- Adverse events;
- Uroflowmetry including voided volume with a prospectively defined minimum to ensure meaningful analysis (e.g., 125 mL), total time of voiding, peak flow rate, average flow rate, and post void residual volume;
- Cystometry on all patients at later visits, e.g., 6 and 12 months post-treatment, with simultaneous assessment of intravesical and intra-abdominal pressure for determination of detrusor pressure;[24]
- Blood and urine chemistry, e.g., urinalysis, urine cultures, CBC, PSA, BUN, creatinine, and electrolytes;
- Biopsy, if clinically indicated;
- DRE at each follow-up, if appropriate;
- TRUS at 6 and 12 months post-treatment (to include measurement of prostate volume and other relevant dimensions);
- Cystoscopic examination as medically or technically warranted;[25] and
- Proctoscopy, if medically or technically warranted, to monitor any observed rectal injury.

Unless you plan to contraindicate patients interested in future fertility from treatment, we recommend you assess the effects of your device on future fertility by evaluating semen quality and quantity.

N. Statistical Analysis Recommendations

(2) Primary Endpoint Analyses

FDA is proposing to replace Section V.N(2) of the existing BPH guidance document with these recommendations:

The primary statistical analysis of the study generally uses the primary endpoint to assess the study's overall success or failure. Therefore, we recommend you describe and document the details of this analysis in your protocol. To reduce bias, we recommend performing this primary analysis using the intention-to-treat (ITT) population. The ITT population includes all subjects

[24] Detrusor pressure-flow studies should be conducted in the subgroup of patients evaluated pre-treatment.

[25] For some devices, it may be acceptable to conduct the cystoscopic follow-up examination in a subgroup. This subgroup should be randomly selected to minimize bias and consist of at least 30% of the study patients.

randomized into the study regardless of whether the subjects received the treatment to which they were randomized. Using the ITT population preserves the comparability of patients with respect to (observed and unobserved) baseline characteristics. The ITT population is generally regarded as the preferred method for evaluating a new therapy.[26]

In addition to the ITT analysis, we recommend your protocol specify other analyses of the primary endpoint to assess the robustness of the study results. We recommend you conduct these additional analyses to assess whether the results are consistent with the conclusion of the primary ITT analysis and, therefore, are supportive of your study conclusions. You should assess the plausibility of the underlying assumptions for each sensitivity analysis. We recommend these additional analyses include at least the following:

- Analysis of the "per protocol" population (e.g., subjects treated and followed per the protocol);
- Sensitivity analyses using a pre-specified variety of methods for imputing missing data;
- Longitudinal or repeated measures analysis to assess impact of "time post-treatment" upon the results; and
- Assessment of the number of subjects who are "significantly improved," "not significantly improved," and "worse" at each follow-up period relative to baseline.

To investigate the potential impact of subject-related and treatment-related factors upon the primary safety and effectiveness endpoints and to uncover any important prognostic factors, we recommend that you consider subgroup analyses. To minimize bias associated with these analyses, we recommend your protocol prospectively define all important factors. Important factors may include, but are not limited to:

- Investigational site;
- Age;
- Weight or body mass index;
- Ethnicity;
- Duration of BPH symptoms;
- All baseline measures of BPH (e.g., prostate size/volume, peak and mean flow rates, PVR, AUA-SI (or IPSS), and a BPH-specific quality of life score);
- Retreatments;
- Medication usage; and
- Important device-related covariates (e.g., device settings, size).[27]

(3) Secondary Endpoint Analyses

FDA is proposing to replace Section V.N(3) of the existing BPH guidance document with these recommendations:

[26] Ellenberg JH, Intent-to-treat analysis versus as-treated analysis. Drug Inf J, 1996, 30:535-44.

[27] All characteristics of the treatment mode (e.g., size, power level, treatment time) should be analyzed. The data should support the complete range of device sizes and treatment parameters that will be available.

We recommend your protocol prospectively define the statistical analysis plan for important secondary endpoints if you intend to include secondary endpoints in your labeling. If any of the secondary endpoint analyses are intended to support the indications for use or to describe device performance in the labeling (e.g., comparing treatment and control groups using p-values or confidence intervals), we recommend you pre-specify this intention in your study protocol and provide a detailed description of the statistical methods you plan to follow. We recommend that you ensure that the overall Type I error rate is controlled when you plan such analyses. If the secondary endpoint analyses are intended as exploratory analyses or are not intended to support the indication for use or representations of device performance, we recommend you submit simple descriptions of the analyses.

One of the statistical challenges in supporting the indications for use or device performance through multiple statistical tests is the control of the overall type 1 error rate at 0.05 or below. There are many valid multiplicity adjustment strategies available for use to maintain the type 1 error at or below p=0.05, including:

- Bonferroni procedure;
- Hierarchical closed test procedure; and
- Holm's step-down procedure.

Because each of these multiplicity adjustment strategies involves balancing different potential advantages and disadvantages, we recommend you carefully consider each of the adjustment strategies when you design your clinical study and prospectively define the strategy that you intend to use. We recommend your protocol prospectively state a statistical hypothesis for each secondary endpoint for which you intend to make representations about device performance in your labeling.

(4) Missing Data

FDA is proposing to replace Section V.N(4) of the existing BPH guidance document with these recommendations:

Missing data can represent a significant source of potential bias. Although many statistical methods exist for imputing missing data, excessive missing data can introduce an unacceptable level of uncertainty in the results and invalidate the study conclusions. Therefore, we recommend every effort be made to minimize the incidence of missing data through trial design and conduct.[28] We recommend your protocol incorporate the elements listed below.

Efforts to minimize missed visits and drop-outs: We recommend that you design the study to reduce missing data. Strategies to consider include providing incentive for patients to remain in the study, such as randomization (e.g., 2:1) schemes or options for control patients to switch to the investigational device after completion of follow-up or the assessment of the primary

[28] National Research Council. (2010). *The Prevention and Treatment of Missing Data in Clinical Trials.* Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington DC: The National Academies Press.

effectiveness endpoint. We recommend you describe in the protocol the efforts to be used during the course of the study to monitor and minimize the incidence of patient drop-outs, such as monitoring activities, special incentives to subjects for study compliance, methods to remind subjects of scheduled visits, and specific efforts to contact subjects who miss their visit (e.g., telephone calls, postcards, contact next-of-kin); and

Efforts to document the reasons for missing data: We recommend you identify the steps to document:

- The reason for each missed visit, e.g., complications, difficulty getting transportation to the site;
- The reason for each drop-out, e.g., seeking alternate therapy, complications or intolerance to the device, dissatisfaction with the device, moved away; and
- The cause of any death, e.g., autopsy report or death certificate.

To facilitate a complete and detailed accounting of all study subjects, we recommend you collect complete information on each subject's follow-up status during the study. Because loss to follow-up jeopardizes the conclusions that can be made about the long-term safety and effectiveness of a device, we recommend you limit the overall rate of loss to follow-up to less than 20% over the course of the study.

The protocol should specify how you plan to handle missing primary effectiveness endpoint data for the primary analysis. To conduct the ITT analysis in the presence of missing primary endpoint data, we recommend that you use existing statistical methods for missing data, such as multiple imputation.[29] Since these methods usually involve assumptions about the missing data mechanism, the plausibility of the assumptions should be assessed. As discussed in Section V.N(2), sensitivity analyses that compare results obtained under various assumptions about the missing data mechanism should be conducted.

[29] National Research Council. (2010). *The Prevention and Treatment of Missing Data in Clinical Trials.* Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington DC: The National Academies Press.

Appendix 1

FDA is proposing to replace the table in Appendix 1 of the existing BPH guidance document with the following table:

Sources of Bias	Common Bias Mitigation Methods
Selection Bias occurs when patients possessing one or more important prognostic factors appear more frequently in one of the comparison groups than in the others.	• Randomization • Objective diagnostic and outcome measures • Homogeneous study population • Pre-specified protocol, endpoints, and statistical plan
Investigator Bias occurs when an investigator consciously or subconsciously favors one study group at the expense of the others.	• Blinding • Pre-specified protocol, endpoints, and statistical plan
Evaluator Bias is a type of investigator bias in which the person measuring the outcome variable intentionally or unintentionally records the measurements in favor of one intervention over another intervention. Studies that have subjective endpoints (e.g., quality of life) are particularly susceptible to this form of bias.	• Blinding • Objective diagnostic and outcome measures
Placebo or Sham Effect is a bias that occurs when a patient exposed to an inactive therapy believes that he (or she) is being treated with an intervention and subsequently shows or reports improvement.	• Inclusion of a sham arm • Randomization • Blinding • Objective diagnostic and outcome measures
Missing Data can introduce bias when subjects who do not report for follow-up experience a different outcome from those who do.	• Option for active device for sham arm patients after completion of follow-up • Documentation and enhanced compliance • Plan to conduct sensitivity analyses

Quantifying the Contribution of Symptom Improvement to Satisfaction of Men With Moderate to Severe Benign Prostatic Hyperplasia: 4-Year Data From the CombAT Trial

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Abbreviations and Acronyms

BII = BPH Impact Index

BPH = benign prostatic hyperplasia

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

PPSM = Patient Perception of Study Medication

Q11 = question 11

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Purpose: We quantified the magnitude of symptom improvement required to achieve different levels of patient reported satisfaction, as assessed by the Patient Perception of Study Medication questionnaire.

Materials and Methods: This multicenter, international, double-blind, randomized study included men 50 years old or older with International Prostate Symptom Score 12 or greater, prostate volume 30 cc or greater, total prostate specific antigen 1.5 to 10.0 ng/ml, maximum urinary flow greater than 5 and less than or equal to 15 ml per second and minimum voided volume 125 ml or greater. Patients were randomized to dutasteride (0.5 mg) and/or tamsulosin (0.4 mg) but results are reported without respect to treatment. International Prostate Symptom Score and Patient Perception of Study Medication responses were assessed at baseline and at 3-month intervals for 48 months. Using pooled data Patient Perception of Study Medication responses were correlated with changes in International Prostate Symptom Score from baseline for 2 Patient Perception of Study Medication measures, including 1) total score and 2) overall satisfaction on question 11, "Overall how satisfied are you with the study medication and its effect on your urinary problems?"

Results: Patient Perception of Study Medication total score and question 11 correlated significantly with the mean change in International Prostate Symptom Score from baseline ($p < 0.0001$). A response of very satisfied to question 11 was associated with an International Prostate Symptom Score improvement of −9.4 points while a response of very dissatisfied was associated with 1.3-point worsening. There was only moderate correlation between Patient Perception of Study Medication question 11 and changes in symptoms ($r = 0.38$). Thus, factors other than lower urinary tract symptoms also contribute to satisfaction and they could not be formally analyzed in this report.

Conclusions: We noted correlations between patient satisfaction and the magnitude of the International Prostate Symptom Score change from baseline, which allowed us to determine treatment outcomes in terms of true clinical instead of only statistical significance.

Key Words: prostate; prostatic hyperplasia; urination disorders; questionnaires; biomarkers, pharmacological

Patient perceptions and preferences are of increasing importance when making treatment decisions for BPH.[1–3] Treatment satisfaction has important implications for compliance[1] and overall treatment success. Patients may accept

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certain therapy related side effects in return for a greater decrease in symptoms or disease progression. However, it remains unclear how to accurately measure patient perceptions and satisfaction, and the extent to which satisfaction and symptoms are influenced by changes in symptom scores.[4]

The PPSM questionnaire quantifies patient expectations, perceptions and satisfaction with treatment across a range of domains, including effect on urinary problems, daily activity and overall satisfaction. PPSM demonstrated validity and reliability in the CombAT (Combination of Avodart and Tamsulosin) BPH population alone and in relation to standard questionnaires, eg I-PSS and BII.[5]

In this post hoc analysis of CombAT trial 4-year data we investigated the extent to which a change in BPH symptoms influenced patient satisfaction, as measured by total PPSM score and the response to PPSM Q11 ("Overall how satisfied are you with the study medication and its effect on your urinary problems?").

MATERIALS AND METHODS

CombAT Study Design

CombAT was a 4-year, double-blind, randomized study of the effects of dutasteride and tamsulosin alone and in combination on symptoms and clinical outcomes in men with moderate to severe BPH (Clinicaltrials.gov NCT00090103).[6] The design and primary results were reported previously.[6,7] Eligible men were 50 years old or older (median age 66) with clinically diagnosed BPH, I-PSS 12 or greater, prostate volume 30 cc or greater on transrectal ultrasound, total serum prostate specific antigen 1.5 to 10.0 ng/ml, maximum urinary flow rate greater than 5 and less than or equal to 15 ml per second and minimum voided volume 125 ml or greater.

The 4,844 subjects were randomized in a 1:1:1 ratio to receive dutasteride (0.5 mg) plus tamsulosin (0.4 mg), dutasteride (0.5 mg) or tamsulosin (0.4 mg) daily for 4 years. The primary end point at 4 years was time to first event of acute urinary retention or BPH related surgery. Secondary end points were changes in I-PSS, maximum urinary flow rate, and prostate volume and tolerability.

PPSM Questionnaire

The PPSM is a 12-item questionnaire assessing patient satisfaction with treatment. PPSM evaluates urinary problem control, urinary stream strength, pain before and during urination, urinary problems interfering with activity, satisfaction with study medication and its effects on urinary problems, and whether patients would ask their physician for the medication received in the study. PPSM has been validated, supporting its use to assess treatment satisfaction in men with BPH.[5] PPSM was translated for each country using a validated translation process.[8] Additional analysis of PPSM results from CombAT revealed that the PPSM response did not differ significantly across countries.

Subjects completed the self-administered PPSM at baseline and at each 3-month visit during treatment. PPSM total score is calculated as the sum of responses to questions 1 to 4 and 9 to 11. Each question has a response range of 1—very satisfied, 2—satisfied, 3—somewhat satisfied, 4—neutral, 5—somewhat dissatisfied, 6—dissatisfied and 7—very dissatisfied for a total score of 7—highest to 49—lowest satisfaction. PPSM included pain items on an exploratory basis due to the potential for overlapping signs and symptoms of prostatitis among patients with BPH. However, most did not report pain before or during urination at baseline and these questions were subsequently excluded from the total score. This exclusion did not affect questionnaire validity or reliability.[5] Question 12 with the responses yes, no and not sure, which was not used in the total score calculation, was excluded from this analysis. Responses to I-PSS Q11 were also evaluated in isolation since this question asks about overall satisfaction.

Statistical Analysis

Analysis used at visit or actual observed results pooled across all scheduled visits, which occurred each 3 months and across all treatment groups with multiple observations per subject (table 1). This ensured that no data were excluded. Correlation analysis at each visit showed that correlations were consistent across visits, supporting the validity of this approach.

Using pooled data and without regard to treatment the Pearson correlation was performed between total PPSM score and the mean change in total I-PSS from baseline. Although CombAT screening criteria specified an I-PSS of 12 or less, during the 4-week placebo run in period scores tended to decrease, leading to a large range of scores at baseline. Before statistical analysis the PPSM total score was grouped into 6 categories. The Pearson correlation was also performed between the arithmetic mean change in I-PSS from baseline and the response to PPSM Q11. The Spearman rank correlation was also calculated (data

Table 1. *Data points of patients with available PPSM and I-PSS scores*

Visit (mo)	PPSM Total Score		PPSM Q11 Score	
	No. Subjects	% Nonrespondents	No. Subjects	% Nonrespondents
3	4,567	5.7	4,632	4.4
6	4,431	8.5	4,459	7.9
9	4,316	10.9	4,336	10.5
12	4,207	13.2	4,223	12.8
15	4,059	16.2	4,080	15.8
18	3,953	18.4	3,967	18.1
21	3,847	20.6	3,861	20.3
24	3,752	22.5	3,768	22.2
27	3,663	24.4	3,672	24.2
30	3,567	26.4	3,576	26.2
33	3,492	27.9	3,499	27.8
36	3,422	29.4	3,432	29.1
39	3,318	31.5	3,331	31.2
42	3,278	32.3	3,285	32.2
45	3,213	33.7	3,225	33.4
48	3,159	34.8	3,165	34.7
Totals	60,244		60,511	

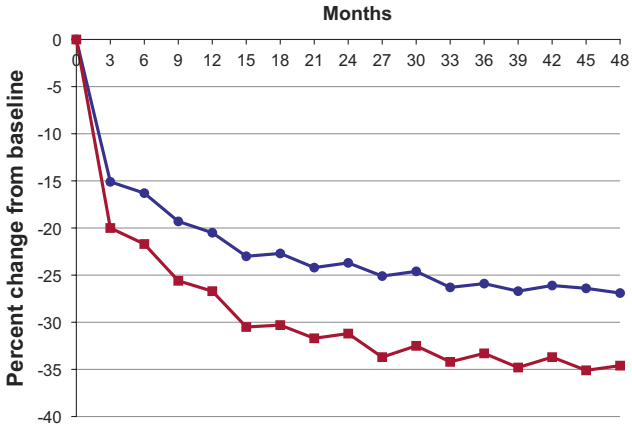

Figure 1. Mean percent change in I-PSS (red curve) and PPSM total score (blue curve) during 4-year study. Data points represent mean values without regard to treatment at visit.

not shown). These estimates were almost identical to the Pearson correlations.

Regression lines were generated for changes from baseline I-PSS by baseline I-PSS in each PPSM Q11 response category. A general linear model was used for pairwise comparisons between each PPSM Q11 response. Generalized estimating equations using PROC GENMOD in SAS® with an independent correlation structure were used to estimate changes in I-PSS for each PPSM response level for 4 baseline I-PSS scores (12, 16, 20 and 30), considering effects for multiple observations per subject.

RESULTS

PPSM and Symptom Improvement

Total score. Using pooled data without regard to treatment mean I-PSS and mean PPSM total score across treatment groups showed similar trends during the study (fig. 1). PPSM total score correlated moderately and statistically significantly with the arithmetic mean change in I-PSS from baseline (Pearson correlation 0.42, $p < 0.0001$). This demonstrated that I-PSS explained approximately 18% of the variation in total PPSM (r^2).

On questions 1 to 4 and 9 to 11 with a total score of 7—best to 49—worst, for subjects with the lowest PPSM total score of 7 to 13 the mean change in I-PSS was −9.2 while for those with the highest total score of 42 to 49 the mean change in I-PSS was 5.3 (table 2).

Question 11. The response to PPSM Q11 correlated significantly with the arithmetic mean change in I-PSS from baseline (Pearson correlation 0.38, $p < 0.0001$). Thus, I-PSS explained approximately 14% of the variation in PPSM Q11 (r^2). As the magnitude of symptom improvement increased from baseline, overall satisfaction increased (fig. 2). For subjects who responded very satisfied to PPSM Q11 the mean change in I-PSS was −9.4 (median −9.0) and for those who responded very dissatisfied the mean change in I-PSS was 1.3 (median 0) (fig. 2).

For each PPSM Q11 response subjects with higher baseline I-PSS scores reported greater I-PSS changes than those with lower baseline scores (fig. 3). The mean change in I-PSS from baseline by baseline I-PSS was significantly different between each PPSM Q11 response category, ie very satisfied vs satisfied and satisfied vs somewhat satisfied ($p < 0.0001$), except for the comparison of dissatisfied vs very dissatisfied (PPSM responses 6 and 7, respectively).

Symptom Improvement and Treatment Satisfaction by Baseline Symptom Severity

Generalized estimation equations were used to estimate changes in I-PSS for each PPSM satisfaction level, accounting for baseline I-PSS. Table 3 shows predicted I-PSS changes for subjects with baseline I-PSS threshold values of 12—CombAT screening entry criterion, 16—moderate BPH symptoms, 20—lowest I-PSS for severe symptoms and 30—severe BPH symptoms.

Using actual baseline I-PSS and predicted I-PSS changes we calculated the range of actual I-PSS values stratified by baseline severity (I-PSS 12 to 30), which were required as an end point to achieve the various satisfaction responses. Figure 4 shows these ranges, which we called therapeutic target zones. For example, to achieve a very satisfied response a man with an I-PSS of 12 at baseline would

Table 2. *Overall month 3 through 48 arithmetic change in I-PSS score from baseline by PPSM total score*

PPSM Total Score	No. Data Points/ No. Subjects	Mean ± SD I-PSS Score		
		Baseline (range)	Arithmetic	Arithmetic Change From Baseline
7–13	12,977/2,126	15.4 ± 6.37 (1–35)	6.3 ± 4.20	−9.2 ± 6.71
14–20	24,178/3,654	16.0 ± 5.83 (1–35)	9.4 ± 4.76	−6.6 ± 6.12
21–27	15,018/3,225	16.7 ± 5.85 (1–35)	12.8 ± 5.60	−4.0 ± 5.87
28–34	6,713/1,851	16.8 ± 6.21 (1–35)	15.2 ± 6.63	−1.6 ± 6.26
35–41	1,166/551	18.9 ± 6.15 (4–35)	20.9 ± 6.10	2.0 ± 6.07
42–49	192/131	19.8 ± 6.43 (4–33)	25.1 ± 6.15	5.3 ± 7.20

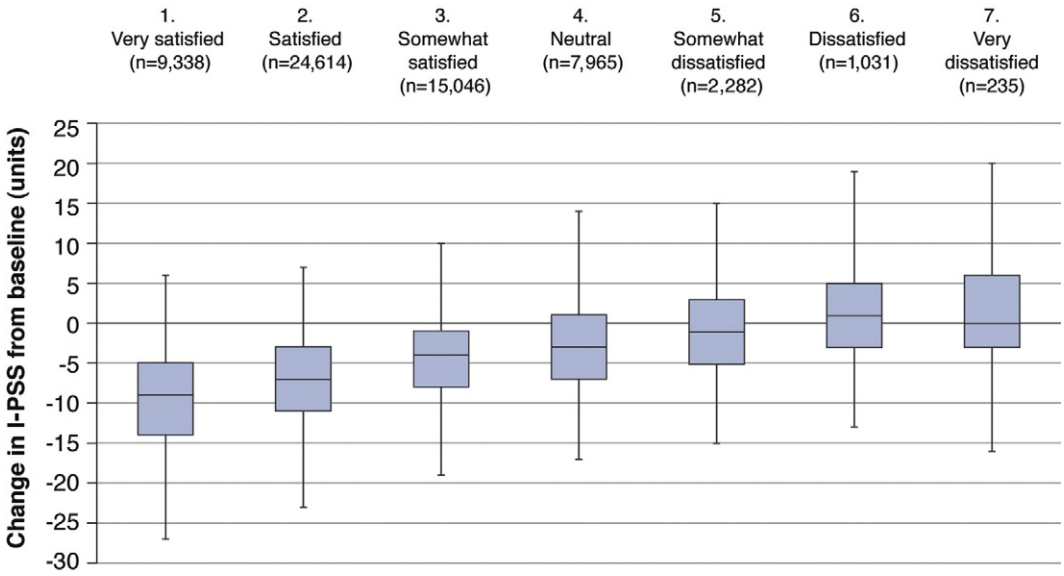

Figure 2. Median I-PSS change from baseline for each response to PPSM Q11. Upper and lower borders of boxes represent 75th and 25th percentiles, respectively. Whiskers indicate 99th and 1st percentiles.

need to achieve an I-PSS of 5.4 after treatment while a man with an I-PSS of 30 at baseline would need to achieve an I-PSS of 8.4 after treatment.

DISCUSSION

The importance of assessing patient reported health outcomes, in addition to objective measures, is recognized by the Food and Drug Administration[9] and in clinical practice guidelines for BPH management.[1,2] Subjective outcome measures such as BII are now widely used to assess the efficacy of interventions for LUTS and BPH. However, the relationship between the magnitude of change in these scores, and patient perception and satisfaction with change is less well studied.

We noted that the degree of patient satisfaction with treatment correlated positively with the magnitude of symptom improvement. Each PPSM Q11 response was associated with significantly different changes in I-PSS across the range of baseline I-PSS assessments except for the responses of dissatisfied and very dissatisfied. Greater changes in I-PSS were associated with higher baseline scores in each PPSM Q11 response category. While the regression lines of the relationship between baseline I-PSS and change from baseline I-PSS for each PPSM Q11 response did not appear parallel, importantly a subject with higher baseline I-PSS had greater range for potential improvement (fig. 3).

These data can be used to predict the symptom improvement needed for overall satisfaction (PPSM Q11). To achieve a response of satisfied or very satisfied a man with very severe symptoms (baseline I-PSS 30) would require an improvement of almost 18 points while a man with moderate symptoms (baseline I-PSS 12) would require an improvement of 4 points. These estimates were based on the model but for each PPSM Q11 response there were subjects with a baseline I-PSS of 32 or greater. These results suggest therapeutic target zones to aim for to achieve patient satisfaction with treatment. A target zone of 8 to 12 for men with moderate to severe symptoms seems required for treatment satisfaction (fig. 4).

The seminal study by Barry et al is the only other published report of the relevance to patients of changes in I-PSS scores.[10] They evaluated change in the American Urological Association symptom index score by patient global assessments of the degree of change. Patient assessment of marked, moderate, slight and no improvement was associated with an American Urological Association symptom index change of −8.8, −5.1, −3.0 and −0.7 points, respectively, while worse was associated with a 2.7 increase in score.

Since the global scale used by Barry et al[10] was not a balanced Likert scale, such as PPSM, direct comparisons are not appropriate. However, the magnitude of improvement they found was required for any degree of perceived change was similar to that required for a response of somewhat satisfied in our analysis (–3.0 and –4.4 points, respectively). Also, the magnitude of improvement required for a marked change was remarkably similar to what we found was required for a very satisfied response (–8.8 and –9.4 points, respectively). While Barry et

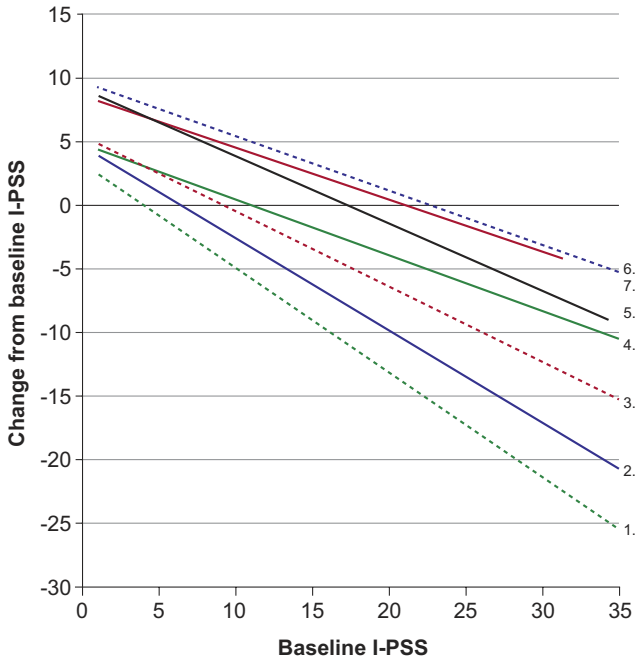

Figure 3. Regression lines show arithmetic mean change in I-PSS from baseline by baseline I-PSS based on general linear models using all I-PSS and PPSM results from month 3 through 48. Lines indicate each PPSM Q11 response category from 1—very satisfied to 7—very dissatisfied, including range of baseline I-PSS values per category. I-PSS mean change from baseline was significantly different between each PPSM Q11 response category, ie very satisfied vs satisfied and satisfied vs somewhat satisfied ($p < 0.0001$) except for dissatisfied vs very dissatisfied.

al asked patients to assess the degree of change in symptoms, we analyzed patient reported satisfaction with change. As did we, Barry et al found that men with more severe symptoms at baseline required a greater magnitude of symptom reduction to perceive improvement.[10]

Applying our identified thresholds to CombAT study treatment results revealed that for a man with moderate LUTS at baseline (I-PSS 16), corresponding to the average baseline I-PSS of CombAT participants,[7] an average improvement of −6.3 points in I-PSS score with combination treatment at 4 years would result in a satisfied rating.

The CombAT trial did not include a placebo arm, mainly for ethical reasons.[11] This is a limitation since there is no referent for the relative changes in patients who did not receive treatment. However, since our investigation focused on the relationship between I-PSS and PPSM score, any effect would apply equally to all 3 treatment arms. A number of other large-scale clinical studies provide an indication of the placebo response for BPH. For example, the average −4.9-point improvement in I-PSS in the placebo arm of MTOPS (Medical Therapy of Prostate Symptoms)[12] would result in a somewhat satisfied overall rating.

The CombAT trial included men 50 years old or older with I-PSS 12 or greater and prostate specific antigen 1.5 to 10 ng/ml or less at baseline. Thus, our study is most applicable to an equivalent population. Approximately two-thirds of subjects in this study completed the visit at 48 months, as expected in a long-term clinical trial. However, the number lost to followup may have affected responses at 48 months compared with those at 3 months.

Data were pooled across all visits for all patients. While pooled data are not a true replication of these results in an equivalent number of individuals, this approach ensured that each subject had the opportunity to be included in analysis and no data were excluded. In this setting using a single response per patient also presented challenges. Averaging measurements across the study would likely have diluted any findings that I-PSS varied during the 4-year study. Alternatively using only 1 response per patient would raise questions of which time point to use.

Also, to estimate changes in I-PSS for each PPSM response level we used generalized estimation equations, which account for individuals and

Table 3. *Predicted I-PSS change per PPSM Q11 response category for baseline I-PSS scores using all PPSM Q11 and I-PSS results from month 3 through 48*

PPSM Q11 Response Category	Mean ± SE Predicted I-PSS Change*			
	Baseline I-PSS 12	Baseline I-PSS 16	Baseline I-PSS 20	Baseline I-PSS 30
1	−6.56 ± 0.11	−9.9 ± 0.12	−13.2 ± 0.17	−21.6 ± 0.35
2	−4.18 ± 0.07	−7.19 ± 0.07	−10.20 ± 0.09	−17.7 ± 0.20
3	−1.50 ± 0.11	−3.88 ± 0.09	−6.25 ± 0.11	−12.17 ± 0.24
4	−0.64 ± 0.16	−2.52 ± 0.14	−4.40 ± 0.17	−9.10 ± 0.35
5	2.61 ± 0.29	0.64 ± 0.22	−1.33 ± 0.21	−6.24 ± 0.45
6	4.59 ± 0.53	2.84 ± 0.37	1.09 ± 0.28	−3.28 ± 0.54
7	4.12 ± 0.90	2.43 ± 0.66	0.74 ± 0.57	−3.49 ± 1.14

* Threshold values based on I-PSS values of 12 (screening every criteria for CombAT), 16 (moderate BPH symptoms), 20 (lowest I-PSS level for severe symptoms) and 30 (severe BPH symptoms).

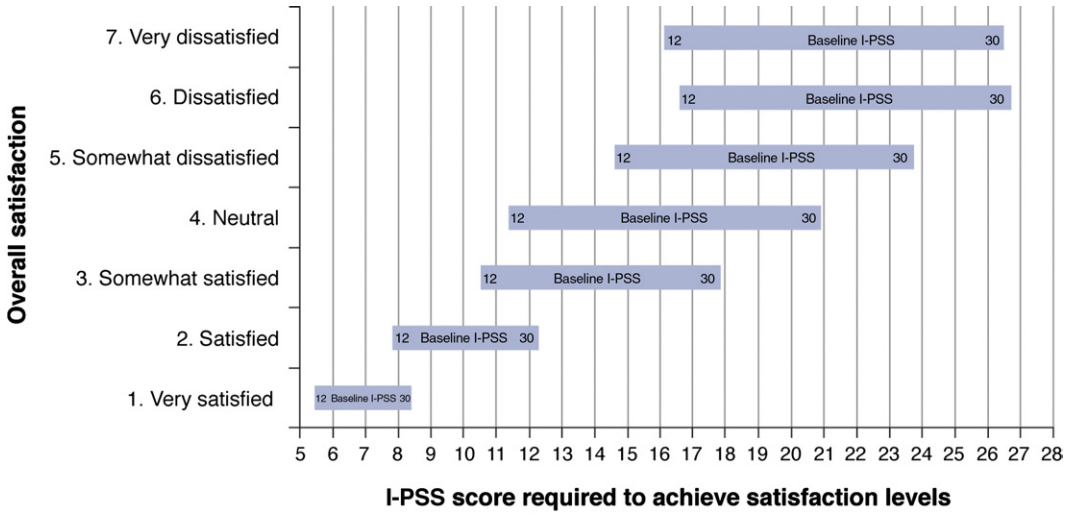

Figure 4. Bars indicate therapeutic target zone to achieve overall treatment satisfaction based on generalized estimation equations with individual effects using all I-PSS and PPSM results from month 3 through 48. Zones were stratified by baseline I-PSS (range 12 to 30). For man with baseline I-PSS 12 to be satisfied with study medication effects on urinary problems, treatment should decrease I-PSS to approximately 8 while man with baseline I-PSS 30 would require symptom score decrease of at least 12 being satisfied with treatment.

multiple observations per subject. Since we used at visit data, outlier responses were possible. However, they were likely to have occurred in each direction, not overly influencing our results, with the advantage of increasing the overall number of observations.

Although our analysis shows that the change in I-PSS explains approximately 18% of the variation in total PPSM and 14% of the variation in Q11, notably factors other than symptom severity influence the variation in patient satisfaction captured by the PPSM questionnaire. As shown by the stronger correlation between actual I-PSS score and satisfaction, a factor may be that patients focus on how they feel at the time of questioning rather than on symptom improvement from baseline. Also, as probed in PPSM Q11, satisfaction is likely to be a broader issue than a response of LUTS. It might include the quality of physician interaction, treatment expectations, partner involvement, side effects and many other variables. These factors were not formally assessed in our report and they are a matter for future research.

PPSM has shown significant moderate correlations with I-PSS and BII,[5] indicating the potential to use these tools in combination to provide enhanced understanding of patient needs and the capacity for improving health outcomes in men with moderate to severe BPH. Patient satisfaction with treatment may also influence patient compliance. Additional PPSM data analysis could be done, including assessments of the perception of treatment satisfaction during years 2 to 4 of the study, when symptom control has stabilized.

CONCLUSIONS

Patient satisfaction is crucial to the long-term success of medical treatment. We noted a significant relationship between patient satisfaction and symptom improvement, although factors other than LUTS may influence satisfaction. Based on our results we recommend a therapeutic target of 5.4 (a 6.6-point improvement) for a man with moderate symptoms at baseline (12 points) to achieve an overall satisfaction rating on PPSM Q11 of very satisfied. To achieve a satisfied or somewhat satisfied rating a target of 7.8 and 10.5 (4.2- and 1.5-point improvement, respectively) would be needed. These changes in symptom thresholds are of the same order of magnitude as those reported by Barry et al.[10] Our results allow for an assessment of LUTS/BPH interventions beyond statistical significance, namely whether the intervention is clinically meaningful.

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Platinum Priority – Reconstructive Urology

Editorial by Guido Barbagli and Massimo Lazzeri on pp. 69–71 of this issue

Defining a Patient-Reported Outcome Measure for Urethral Stricture Surgery

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Abstract

Background: A systematic literature review did not identify a formally validated patient-reported outcome measure (PROM) for urethral stricture surgery.
Objective: Devise a PROM for urethral stricture surgery and evaluate its psychometric properties in a pilot study to determine suitability for wider implementation.
Design, setting, and participants: Constructs were identified from existing condition-specific and health-related quality of life (HRQoL) instruments. Men scheduled for urethroplasty were prospectively enrolled at five centres.
Intervention: Participants self-completed the draft PROM before and 6 mo after surgery.
Measurements: Question sets underwent psychometric assessment targeting criterion and content validity, test-retest reliability, internal consistency, acceptability, and responsiveness.
Results and limitations: A total of 85 men completed the preoperative PROM, with 49 also completing the postoperative PROM at a median of 146 d; and 31 the preoperative PROM twice at a median interval of 22 d for test-retest analysis. Expert opinion and patient feedback supported content validity. Excellent correlation between voiding symptom scores and maximum flow rate ($r = -0.75$), supported by parallel improvements in EQ-5D visual analogue and time trade-off scores, established criterion validity. Test-retest intraclass correlation coefficients ranged from 0.83 to 0.91 for the total voiding score and 0.93 for the construct overall; Cronbach's α was 0.80, ranging from 0.76 to 0.80 with any one item deleted. Item-total correlations ranged from 0.44 to 0.63. These values surpassed our predefined thresholds for item inclusion. Significant improvements in condition-specific and HRQoL components following urethroplasty demonstrated responsiveness to change ($p < 0.0001$). Wider implementation and review of the PROM will be required to establish generalisability across different disease states and for more complex interventions.
Conclusions: This pilot study has defined a succinct, practical, and psychometrically robust PROM designed specifically to quantify changes in voiding symptoms and HRQoL following urethral stricture surgery.

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1. Introduction

Patient-reported outcome measures (PROMs) are health questionnaires that patients complete before and after an intervention to determine whether their symptoms or health-related quality of life (HRQoL) have changed [1,2]. PROMs indicate patient-perceived benefit from surgery and are necessary for preoperative patient counselling, performance benchmarking, and resource allocation [3], as emphasised in health care policy statements by the UK and US governments [4,5].

Urethral stricture disease is a common and recurring condition that affects approximately 300 per 100 000 men [6]. Surgical interventions, including urethral dilatation, endoscopic urethrotomy, and urethroplasty, aim to return patients to a state of normal voiding. A recent Cochrane review [7] identified only two direct comparative studies of these options, both of which employed clinician-driven outcome measures such as time to recurrence or change in maximum flow rate (Q_{max}) to gauge success. A robust PROM will allow urologic surgeons to measure directly the benefit that patients derive from their interventions and facilitate comparative studies of effectiveness.

A systematic literature review failed to identify a condition-specific PROM sufficiently robust for use in urethral stricture surgery [8]. Therefore we set out to define a pragmatic instrument and pilot it in a group of men undergoing urethroplasty. Aims of this study were to identify transferable question sets from existing validated instruments, to reevaluate their psychometric properties against an established checklist [9,10], and to refine the content of the draft PROM in a stepwise fashion to produce a final version ready for widespread implementation and further review.

2. Patients and methods

2.1. Selection of constructs

A group of UK urethral surgeons convened to identify symptoms reported by men with anterior urethral stricture disease which are expected to improve following surgery. We identified relevant validated English-language question sets, symptom and bother scores, and HRQoL measures from two online resources [11,12]. We began with a set of constructs that encompassed voiding, postmicturition, and storage lower urinary tract symptoms (LUTS); sexual and ejaculatory function; and symptom-specific and generic HRQoL measures. We went on to refine this long list in consensus-building meetings of the clinician group according to patients' views elicited in semistructured interviews. Patients and clinicians agreed that questions targeting storage LUTS were not of specific importance in describing the expected benefits of urethral stricture treatment. Similarly, questions relating to sexual function were insensitive to change owing to a low baseline incidence and lack of deterioration following urethroplasty. Following this elimination process we defined an item-reduced PROM comprising voiding and postmicturition LUTS, together with condition-specific and generic HRQoL measures, which was interrogated according to well-described psychometric techniques [9,10,13,14].

The final urethral surgery PROM (Appendix A) comprises a LUTS construct consisting of six summative questions (Appendix A, Q1–6) derived from the International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms (ICIQ MLUTS) module [15,16] to generate a total score between 0 (asymptomatic) and 24 (most symptomatic); a separate LUTS-specific quality-of-life (QoL) question from the ICIQ MLUTS (Appendix A, Q7); and Peeling's voiding picture [17] (Appendix A, Q8). The EQ-5D [18] was included to assess overall HRQoL. The postoperative PROM is supplemented with two further questions addressing overall patient satisfaction (Appendix A, Q9 and 10).

2.2. Patients

Men scheduled for bulbar or one- or two-stage penile urethroplasty were identified from five specialist urology centres. We asked them to self-complete the draft PROM preoperatively and 4–6 mo following one-stage or the second stage of a two-stage urethroplasty. Patients completed the paper questionnaire unaided, and anonymised responses were collated in an online database.

We estimated that 40 participants were required to complete both the pre- and postoperative PROM at 6 mo to establish responsiveness [19] and that 30 patients were required to test-retest the questionnaire to establish reliability. To ensure these numbers were achieved allowing for a 6-mo follow-up lead time, we recruited 85 men, all of whom completed the preoperative PROM for assessment of internal consistency.

2.3. Psychometric criteria for evaluation of patient-reported outcome measures

Validity is the degree to which the content of a questionnaire covers the conceptual domain it intends to measure. Content validity was assessed in rounds of expert consensus meetings, document circulation, patient interviews, and by identifying areas of missing response data and criterion validity by correlating LUTS construct scores with Q_{max} and overall satisfaction.

Test-retest reliability is a questionnaire's ability to be stable or reproducible with time. Thirty-one men agreed to complete the draft PROM twice preoperatively for test-retest analysis. Agreement was assessed using Bland-Altman plots [20] and intraclass correlation coefficients (ICCs); an ICC >0.70 was the predefined threshold for inclusion [21,22].

Internal consistency is the extent to which question items within the same construct measure the same conceptual domain and thus whether it is valid to sum those item scores. Cronbach's α statistics and item-total correlations were employed to assess the interrelationship between question items within the LUTS construct (Appendix A, Q1–6). We predefined values >0.70 and 0.20, respectively, as thresholds for acceptability [13,19,21,22].

Responsiveness was addressed by examining LUTS and HRQoL construct scores before and after urethroplasty for statistically significant changes using the paired Student *t* test [22].

3. Results

A total of 85 men (median age: 42.5 yr; range: 16–72 yr) enrolled in this study: 68 (80%) underwent a one-stage bulbar procedure and 17 (20%) a one- or two-stage penile urethroplasty. Forty-nine men completed both the pre- and postoperative PROM at a median interval of 146 d following completion of their urethroplasty. Thirty-six men completed the preoperative PROM but were awaiting surgery when interim psychometric analysis confirmed that preset significance levels had been achieved, and thus they were not asked to complete the postoperative PROM.

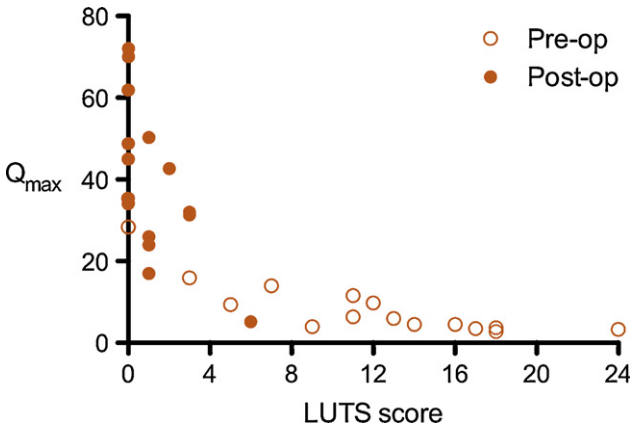

Fig. 1 – Scatter plot of lower urinary tract symptoms (LUTS) score versus maximum flow rate (Q_{max}).

3.1. *Psychometric evaluation*

3.1.1. *Content validity and acceptability*

Contemporary expert opinion, consensus-building meetings of the research group, patient interviews, and literature review strongly supported the content validity of the PROM. For every question item we encountered a nonresponse rate of ≤1%, and nonresponses were distributed across the question items such that no one item could be identified as weak, indicating acceptability to patients.

3.1.2. *Criterion validity*

Uroflowmetry with a purposively sampled heterogeneous subgroup of 15 patients established strong negative correlation between Q_{max} and total voiding LUTS scores both pre- and postoperatively (Fig. 1 and Table 1). We encountered a ceiling effect in the postoperative data; 7 of 15 men (47%) were asymptomatic (score zero) following urethroplasty. Forty-seven of 49 men (96%) who completed the postoperative questionnaire reported being *satisfied* or *very satisfied* with the outcome of their operation, 38 of whom (81%) felt their residual voiding symptoms interfered with their HRQoL *a little* or *not at all*.

3.1.3. *Internal consistency*

For the summative LUTS voiding construct (Appendix A, Q1–6), Cronbach's α was 0.80 and ranged from 0.76 to 0.80 with any one item deleted. Item-total correlations were similarly high: Pearson correlation coefficients between any one item and the total score of the remaining items ranged from 0.44 to 0.61 (Table 2).

Table 1 – Correlation statistics for lower urinary tract symptoms score versus maximum flow rate

	Pearson *r*	Two-tailed *p*	95% CI
Preoperative LUTS vs Q_{max}	−0.82	0.0002	−0.94 to −0.52
Postoperative LUTS vs Q_{max}	−0.65	0.0091	−0.87 to 0.20
All LUTS vs Q_{max}	−0.75	<0.0001	−0.88 to −0.54

CI = confidence interval; LUTS = lower urinary tract symptoms; Q_{max} = maximum flow rate.

Table 2 – Reliability statistics for six-question summative lower urinary tract symptoms construct

	ICC	Item-total correlation	Cronbach's α with item deleted
Q1	0.85	0.52	0.78
Q2	0.91	0.54	0.78
Q3	0.87	0.61	0.76
Q4	0.88	0.63	0.76
Q5	0.83	0.61	0.76
Q6	0.89	0.44	0.80

ICC = intraclass correlation coefficient.

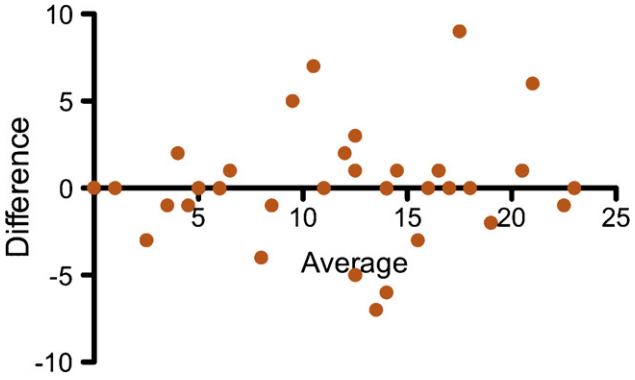

Fig. 2 – Bland-Altman plot of test-retest lower urinary tract symptoms (LUTS) scores. The difference between test and retest scores is plotted against the test-retest average (mean) for each patient. Plots are interpreted qualitatively. In this case variability remains consistent as average LUTS scores increase, and the average difference between test and retest scores (bias) is small (0.11). For future measurements the difference between test and retest scores should lie between the limits of agreement (+6 to −6) 95% of the time.

3.1.4. *Test-retest reliability*

The median test-retest interval was 22 d, which was expected to be too short a period for individual patients' disease to progress appreciably. For the summative LUTS voiding construct (scored 0–24), 95% limits of agreement were between +6 and −6 with a bias of 0.11 (standard deviation of bias: 3.2) (Fig. 2). ICCs ranged from 0.83 to 0.91 for each of the LUTS question items (Table 2) and 0.93 (95% confidence interval [CI], 0.87–0.96) for the total scores, all of which exceeded our predefined threshold of 0.70.

3.1.5. *Responsiveness*

Total LUTS scores decreased from a median (mean) of 12 (11.8) preoperatively to 1 (3.0) postoperatively ($p < 0.0001$; 95% CI, 6.8–11.5; Table 3 and Fig. 3). Peeling's stream picture scores followed a similar pattern: median (mean) scores fell from 4 (3.7) preoperatively to 2 (1.8) postoperatively ($p < 0.0001$, 95% CI, 1.3–2.1; Fig. 4). These figures corroborate a ≥1 scale point improvement in the Likert-type condition-specific QoL question in 37 of 49 men (76%);

Table 3 – Responsiveness statistics for constructs generating a numerical score

Construct	Item	Preoperative mean	Postoperative mean	*p*	Mean of differences	95% CI of mean of differences
6-Q LUTS	Q1	1.60	0.58	<0.0001	1.09	0.60–1.59
	Q2	2.91	0.42	<0.0001	2.61	2.11–3.12
	Q3	2.00	0.39	<0.0001	1.61	1.10–2.11
	Q4	2.02	0.47	<0.0001	1.61	1.13–2.08
	Q5	2.07	0.43	<0.0001	1.61	1.11–2.20
	Q6	1.31	0.82	0.07	0.48	−0.05–1.00
Peeling	Q8	3.57	1.81	<0.0001	1.69	1.33–2.05
EQ-5D	EQVAS	71	81	0.0006	10	4–15
	TTO	0.77	0.87	0.003	0.10	0.17–0.03

CI = confidence interval; LUTS = lower urinary tract symptoms.

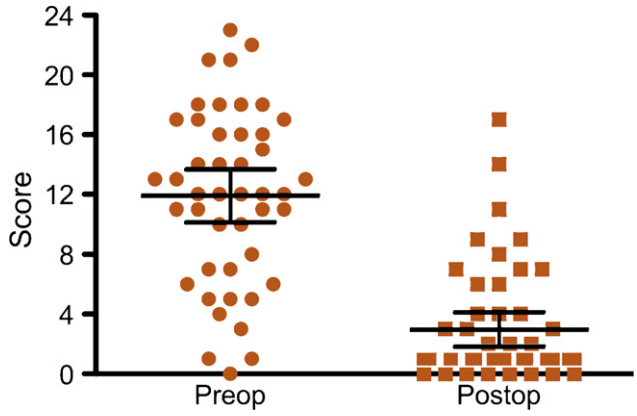

Fig. 3 – Pre- versus postoperative lower urinary tract symptoms scores (mean and 95% confidence interval).

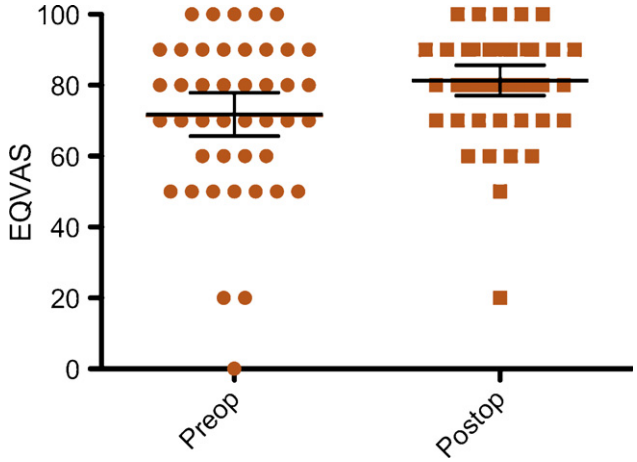

Fig. 5 – Pre- versus postoperative EQ-5D visual analogue scores (EQVAS) scores (mean and 95% confidence interval).

≥2 scale point improvement in 20 men (41%), and a 3 scale point improvement in 9 men (18%).

EQ-5D visual analogue scores improved from a preoperative median (mean) of 80 (71) to 90 (81) postoperatively (p = 0.0006; 95% CI of the mean of difference, 4–14; Table 3 and Fig. 5). EQ-5D time trade-off (TTO) scores were calculated from UK-weighted value sets corresponding to one of 243 possible five-digit health states generated by EQ-5D. Following urethroplasty, TTO scores improved from a mean of 0.77 preoperatively to 0.87 postoperatively (p = 0.003; 95% CI of the mean of the difference, 0.04–0.18).

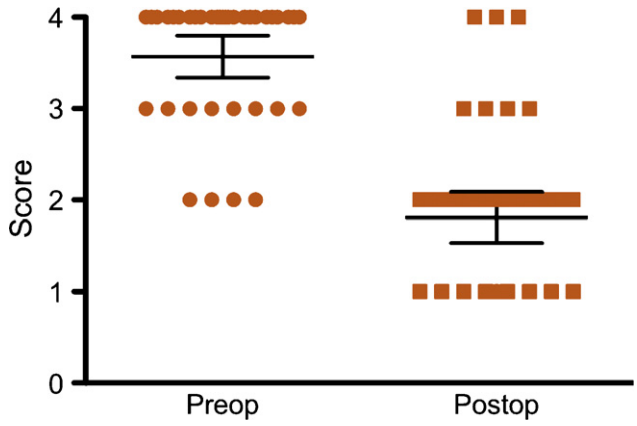

Fig. 4 – Pre- versus postoperative picture scores (mean and 95% confidence interval).

4. Discussion

Interventions targeting urethral strictures aim to improve symptoms and reduce risk of recurrence. Their success should be measured in transparent and transferable terms that testify to the benefit conferred to an individual patient and allow comparisons of clinical and cost effectiveness between surgeons, competing surgical procedures, and health care providers [2]. Recurrence rate, Q_{max}, and urethrography are the established clinician-orientated measures, but a validated tool designed to measure patient-reported benefit from urethral stricture surgery was lacking.

In this study we defined a fit-for-purpose PROM for urethral stricture surgery by mapping constructs from existing instruments designed for symptomatically related conditions. We have demonstrated in a pilot study involving men undergoing urethroplasty for anterior urethral strictures that the resultant tool is valid and reliable according to established psychometric criteria.

The development process followed in our study adheres to the key phases of: identification of relevant content from expert opinion, literature review, and patient feedback;

piloting in an appropriate patient cohort before and after surgery; and abbreviated psychometric testing. We also predefined statistical thresholds for the psychometric properties of responsiveness to change, acceptability to patients, content and criterion validity, test-retest reliability, and internal consistency [21,22].

For routine clinical use, PROM questionnaires should remain concise and focused to encourage uptake and clear-cut analysis, and only items pertaining to patient-centred benefit should be included. In this study clinician and patient opinion substantiated baseline psychometric analysis, indicating that items tackling storage LUTS, sexual function, and cosmesis were not of prime importance, and on this basis they were not included in the final PROM. Broader implementation and appraisal may ultimately testify to their importance in specific disease states such as men requiring complex reconstruction of the distal penile urethra. And although the generic HRQoL measure should have captured severe deleterious effects, bolt-on constructs addressing sexual function and cosmesis may be required.

The identification of relevant existing validated instruments meant that extensive field testing of novel items generated through work with focus groups of men with urethral strictures was not needed. Our more restricted approach, comprising semistructured interviews with patients and clinicians together with quantification of changes following urethroplasty, rapidly established that the chosen question sets fulfilled criteria for suitability as a PROM for this group of patients. A potential drawback is neglecting other causes of voiding symptoms, such as benign prostatic enlargement (BPE), when they coexist with a urethral stricture. Men in this study did not have evidence of symptomatic BPE before surgery and gained a high degree of benefit from urethroplasty, making concurrent occult BPE unlikely.

We elected to pilot the prototype PROM in a group of men with the most common disease location (anterior urethra) who were undergoing an intervention (urethroplasty) with a high likelihood of benefit at the preset postoperative measurement time point of 6 mo. This standardisation was necessary to establish psychometric validity and reliability. The size of the patient sample was governed partly by estimates based on previous studies [23] and partly by statistical thresholds that established when each desired psychometric property had been achieved. Once these conditions had been met it was not necessary to continue data collection, and for this reason the sample size varies according to the property being tested.

Wide-scale deployment of this PROM will allow stratification of outcomes according to a spectrum of factors including but not limited to patient age, comorbidity, and body mass index; stricture length and location; and surgical competence. The performance of this PROM in the context of various interventions such as urethrotomy and other types of urethroplasty deserves further assessment.

Systematic literature review did not identify any previous studies defining a validated PROM for urethral stricture disease. Morey et al used the American Urological Association (AUA)-7 questionnaire in 1998 to compare symptomatic and clinical outcomes in men undergoing urethroplasty. They found that AUA-7 scores fell markedly after surgery, which correlated with Q_{max} and urethrographic appearance indicating criterion validity and sensitivity to change [23]. A subsequent study reported good correlation between total AUA-7 scores and Q_{max} as preoperative measures of disease severity [24]. We elected to use the ICIQ MLUTS voiding construct because it incorporates hesitancy and postmicturition dribble as additional domains, both of which patients identified as important and both of which performed well in psychometric testing. Kessler et al provided further evidence of the need for a urethral stricture surgery PROM in 2002 by reporting clear discordance between clinician- and patient-reported success in 20% of 267 men following urethroplasty [25]. This study lacks preoperative data, however, and men were surveyed at varying intervals from 2 to 8 yr after surgery. In our study all patients completed the postoperative questionnaire at the same predefined and clinically relevant time interval [1].

5. Conclusions

This study demonstrates that it is feasible to construct a robust PROM within a short time frame by identifying and reevaluating constructs from existing patient-completed instruments. The next step will involve broader deployment and review to establish generalisability across interventions and health care systems.

Author contributions: Matthew J. Jackson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mundy, Pickard, Andrich, Chapple, Watkin, Jackson, Sciberras, N'Dow.
Acquisition of data: Sciberras, Jackson, Mangera, Brett.
Analysis and interpretation of data: Jackson, Sciberras, Pickard, Mundy.
Drafting of the manuscript: Jackson, Sciberras, Pickard, Mundy, Andrich.
Critical revision of the manuscript for important intellectual content: Jackson, Sciberras, Mangera, Watkin, N'Dow, Chapple, Andrich, Pickard, Mundy.
Statistical analysis: Jackson, Sciberras.
Obtaining funding: None.
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Appendix A

Thank you for completing this questionnaire. The following questions are designed to measure the effect that urethral strictures have on patients' lives.

Some questions may look the same but each one is different. Please take time to read and answer each question carefully, and tick the box that best describes your symptoms over the past 4 weeks.

If you currently have a urethral or suprapubic catheter (a catheter through the lower abdomen) please start at page 4.

1 Is there a delay before you start to urinate?

- Never ❑
- Occasionally ❑
- Sometimes ❑
- Most of the time ❑
- All of the time ❑

2 Would you say that the strength of your urinary stream is…

- Normal ❑
- Occasionally reduced ❑
- Sometimes reduced ❑
- Reduced most of the time ❑
- Reduced all of the time ❑

3 Do you have to strain to continue urinating?

- Never ❑
- Occasionally ❑
- Sometimes ❑
- Most of the time ❑
- All of the time ❑

4 Do you stop and start more than once while you urinate?

- Never ❑
- Occasionally ❑
- Sometimes ❑
- Most of the time ❑
- All of the time ❑

5 How often do you feel your bladder has not emptied properly after you have urinated?

- Never ❑
- Occasionally ❑
- Sometimes ❑
- Most of the time ❑
- All of the time ❑

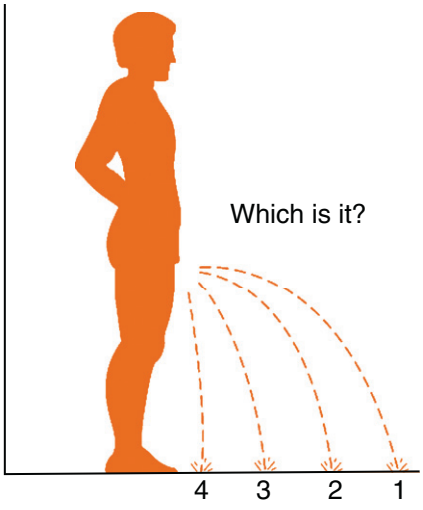
6 How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

- Never ❑
- Occasionally ❑
- Sometimes ❑
- Most of the time ❑
- All of the time ❑

7 Overall, how much do your urinary symptoms interfere with your life?

- Not at all ❑
- A little ❑
- Somewhat ❑
- A lot ❑
- ❑

8 Please ring the number that corresponds with the strength of your urinary stream over the past month.



(From Peeling 1989)

9 Are you satisfied with the outcome of your operation?

- Yes, very satisfied ❑
- Yes, satisfied ❑
- No, unsatisfied ❑
- No, very unsatisfied ❑

10 If you were unsatisfied or very unsatisfied is that because:

- The urinary condition did not improve ❑
- The urinary condition improved but there was some other problem ❑
- The urinary condition did not improve and there was some other problem as well ❑

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ❑
- I have some problems in walking about ❑
- I am confined to bed ❑

Self-Care

- I have no problems with self-care ❑
- I have some problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

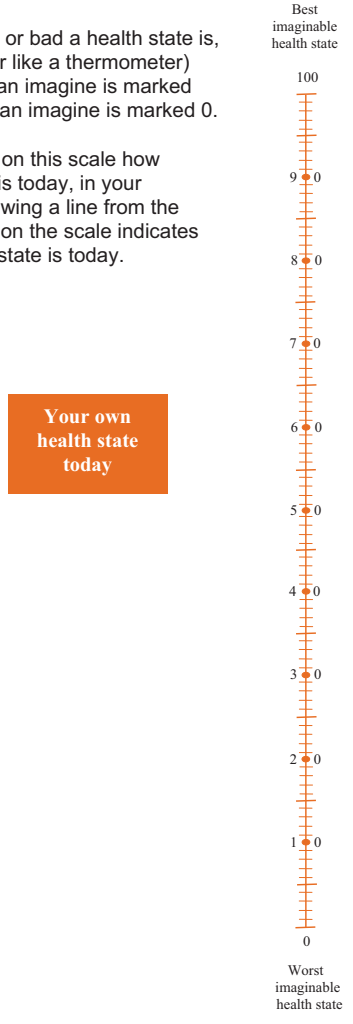
I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



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ORIGINAL ARTICLE

Psychometric validation of a German language version of a PROM for urethral stricture surgery and preliminary testing of supplementary ED and UI constructs

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Abstract
Purpose To validate a German language version of the patient-reported outcome measurement (PROM) following urethral stricture surgery (USS) in a cohort of men undergoing one-stage buccal mucosa graft urethroplasty (BMGU) for urethral stricture. Furthermore, to explore the responsiveness of erectile function (EF) and urinary incontinence (UI) constructs in the context of this intervention.
Methods The USS-PROM captures voiding symptoms (ICIQ-MLUTS) and health-related quality of life (HRQoL) (EQ-5D). To evaluate EF and UI, the IIEF-5 and ICIQ-UI SF were included. Between March 2012 and April 2013, all patients undergoing BMGU at our institution were prospectively enrolled in this study. Psychometric assessment included internal consistency, test–retest reliability, criterion validity and responsiveness.
Results Ninety-three men completed the USS-PROM before and 3 months after surgery, with 40 (43 %) also completing the USS-PROM 6 months after surgery to assess reliability. Internal consistency: for the ICIQ-MLUTS, Cronbach's α was 0.83. The test–retest intraclass correlation coefficient was 0.94. There was a negative correlation between change in ICIQ-MLUTS total score and change in Q_{max} ($r = -0.40$). All values exceeded our predefined thresholds. Significant improvements of voiding symptoms and HRQoL demonstrate responsiveness to change (all p values <0.001). While ICIQ-UI scores did not change ($p > 0.05$), IIEF-5 scores improved significantly ($p = 0.048$).
Conclusions The German language USS-PROM shows similar psychometric properties to the English language version. This instrument can be improved by assessing EF by the use of IIEF-5. Further studies with larger patient cohorts are needed to evaluate the significance of measuring UI in urethroplasty patients.

Keywords Urethral stricture · Urethroplasty · Patient-reported outcome measure (PROM) · Validation · Buccal mucosa graft · Quality of life

Introduction

Urethroplasty is the gold standard therapy in patients with recurrent urethral stricture [1, 2]. However, due to the complexity of the disease, urethroplasty is seldom performed [3]. Moreover, it has been shown that the majority of urologists believe that urethroplasty becomes only a treatment of choice after failed endoscopic attempts [4]. Despite its poor success rate, patients with recurrent strictures are continuously submitted to multiple endoscopic urethrotomies [5].

Similarly to all surgical procedures, outcome measures of urethral stricture surgery (USS) combine objective and subjective end points. Assessing, reporting and comparing these outcome measures clearly aim to improve quality of care and reduce costs [6–8]. If physicians make treatment decisions based on health outcomes, medical errors and unnecessary treatments could be prevented; thus, patients are more likely to receive high-quality care

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[9]. In consequence, subjective, patient-reported outcome measures (PROM) such as voiding symptoms, pain, mobility and health-related quality of life (HRQoL) are equally important as objective outcome measures derived by maximum flow rate, urethrography or urethrocystography after USS [4, 10].

Currently, only one validated PROM exists following male anterior urethroplasty evaluating voiding symptoms and HRQoL [11, 12]. However, there is an urgent need for a German language version of the USS-PROM so it is accessible to people whose first language is not English. In addition, men who undergo urethroplasty for urethral stricture disease are at great concern on erectile function and urinary incontinence. Unfortunately, the current USS-PROM does not address these healthcare outcomes, which is criticized by several authors [7, 8, 12, 13].

Therefore, the aim of this study was to validate a German language version of the USS-PROM in patients undergoing one-stage buccal mucosa graft urethroplasty (BMGU) for urethral stricture. Furthermore, we aimed to explore the responsiveness of erectile function and urinary incontinence constructs in the context of reconstructive surgery for urethral stricture disease.

Patients and methods

Patient population

Institutional review board approval was received prior to the study. Between March 2012 and April 2013, all patients treated with one-stage BMGU for urethral stricture disease at our institution were prospectively enrolled in this study. Patients completed the USS-PROM prior to surgery, 3 and 6 months after surgery.

USS-PROM

The USS-PROM comprises a construct evaluating lower urinary tract symptoms (LUTS) consisting of six questions derived from the International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) module [14, 15] to generate a total score. In addition, it includes a separate LUTS-specific QoL question from the ICIQ-MLUTS (ICIQ-MLUTSqol); and Peeling's voiding picture [16]. To assess overall HRQoL, the USS-PROM includes the EuroQOL five-dimensional questionnaire (EQ-5D) addressing mobility, self-care, usual activities, pain/discomfort and anxiety/depression [17], and the EQ-5D visual analogue scale (EQ-VAS), which is a vertical scale between 100 for "best imaginable health state" and 0 for "worst imaginable health state." The postoperative USS-PROM incorporates two further questions addressing overall patient satisfaction [11].

In order to assess urinary incontinence and erectile function rates of patients undergoing BMGU, the USS-PROM was complemented by the International Consultation on Incontinence Questionnaire-Urinary Incontinence (ICIQ-UI SF) [18] and the International Index of Erectile Function (IIEF-5), respectively [19].

Psychometric criteria for evaluation of USS-PROM

First, following the recommendation by Dawson et al. [20], the USS-PROM was translated into German and retranslated into English.

Second, *internal consistency* was assessed and represents the extent to which question items within the same construct (here LUTS) measure the same conceptual domain and thus whether it is valid to sum those item scores [11]. Cronbach's α statistics and item-total correlations were used for quantifying the interrelationship between question items within the LUTS construct. Threshold values were between >0.70 and 0.20, respectively, as previously reported [11, 21].

Third, the *test–retest reliability* was assessed and represents the ability of a PROM to be stable or reproducible over time. Therefore, patients were asked to complete the USS-PROM at 3 and 6 months after surgery. We estimated that 35 patients are required to additionally complete the USS-PROM at 6 months after surgery [22]. Agreement was assessed using Bland–Altman plots [24]. We followed the method of Terwee et al. [25] and accepted a minimum reliability threshold of 0.70 (intraclass correlation coefficients) to sufficiently test–retest USS-PROMs reliability.

Fourth, c*riterion validity* was assessed by correlating LUTS construct scores with Q_{max} and overall satisfaction [11].

Finally, *responsiveness* was addressed by examining LUTS, HRQoL, urinary incontinence and erectile function construct scores before and after urethroplasty for statistically significant changes using the paired Student *t* test [23]. Due to the explorative study design, power analysis for assessing the responsiveness of urinary incontinence and erectile function was not required.

Results

Baseline characteristics prior to surgery

A total of 93 men were enrolled in this prospective, longitudinal study, completing the complemented USS-PROM before and at 3 months after surgery. The median

Table 1 Baseline parameter of 93 patients treated with buccal mucosa graft urethroplasty for urethral strictures

Baseline parameter	*n*	%
Age at surgery in years (median; mean)	60; 57.1	
Body mass index—BMI (median; mean)	26; 27.4	
Operating time in min (median; mean)	65; 71.2	
Stricture lengths in cm (median; mean)	2; 2.1	
Transplant lengths in cm (median; mean)	5; 5.1	
Stricture location		
Penile	27	30.0
Bulbar	66	70.0
Disease duration		
<1 year	4	4.3
1–5 years	34	36.5
6–10 years	17	18.3
>10 years	30	32.3
Not clinically	8	9.7
Previous interventions		
Urethral trauma	21	22.6
Radiation therapy	4	4.3
Urethritis	12	12.9
Urinary infection	34	41.0
Lichen sclerosus	3	3.2
Hypospadia	2	2.2
Foley preoperative	32	34.5
Intermittent self-catheterization	7	6.7
Dilatation	51	57.3
Urethral stent	5	6.7
Urethrotomy	69	75.6
Urethroplasty (=Redos)	21	22.6
TURB	6	6.5
TURP	15	16.1
HoLEP	2	2.2
Radical prostatectomy	8	8.6

(interquartile range = IQR) age of patients was 60 (48–70) years, and majority (70 %) of strictures were bulbar located (Table 1). In total, 69 (75.6 %) and 21 (22.6 %) patients did experience at least one previous urethrotomy and/or urethroplasty (redos), respectively.

Psychometric evaluation

Internal consistency

For the summative ICIQ-MLUTS, Cronbach' α was 0.83 for the overall score and ranged between 0.76 and 0.89 with any one item deleted, which exceeded out predefined thresholds. Item-total correlations were similar (0.25–0.77).

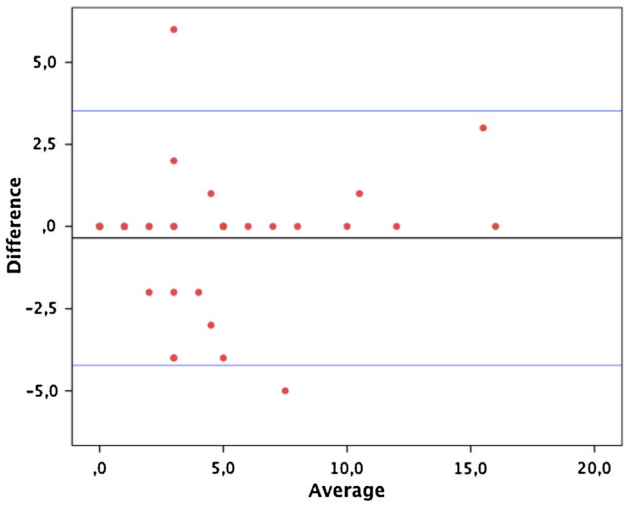

Fig. 1 Bland–Altman plot of test–retest lower urinary tract symptoms (LUTS) scores. The difference between test and retest scores is plotted against the test–retest average (mean) for each patient

Test–retest reliability

Forty (43 %) patients also completed the USS-PROM 6 months after surgery, which was sufficient to assess reliability. The median test–retest interval was 96 days. For the summative ICIQ-MLUTS (scored 0–24), 95 % limits of agreement were between +3.52 and −4.22 (t of mean = 0.64; $p = 0.526$; standard deviation of bias: 1.9) (Fig. 1). For the LUTS construct, intraclass correlation coefficients ranged from 0.83 to 0.91 for each of the ICIQ-MLUTS questions (Table 2), and 0.94 (95 % CI 0.89–0.96) for the total scores, which surpassed the predefined thresholds.

Validity

Q_{max} increased significantly from a median (mean) of 6.6 (7.9) preoperatively to 24.2 (29.6) postoperatively ($p < 0.001$; 95 % CI of mean of differences, 18.3–24.7). There was a negative correlation between change in the LUTS construct total score and change in Q_{max} ($r = -0.40$; $p = 0.001$), which exceeded our predefined thresholds. In total, 85 % of patients reported being *satisfied* or *very satisfied* with the outcome of their USS; 77 % felt their residual voiding symptoms interfered with their HRQoL *a little* or *not at all*.

Responsiveness (Table 3)

Total ICIQ-MLUTS scores decreased significantly from a median (mean) of 13 (12.8) preoperatively to 4 (5.0)

Table 2 Results of reliability analyses and internal consistency for the six questions summative ICIQ-MLUTS

	ICC	Item-total correlation	Cronbach's α with item deleted
Q1	0.88	0.73	0.78
Q2	0.82	0.75	0.77
Q3	0.89	0.77	0.76
Q4	0.86	0.76	0.77
Q5	0.89	0.55	0.82
Q6	0.80	0.25	0.89

ICC intraclass correlation coefficient

postoperatively ($p < 0.001$; 95 % CI of mean of differences, 6.7–9.5). Total score of EQ-5D visual analogue improved significantly from a preoperative median (mean) of 80 (71.5) to 85 (81.0) postoperatively ($p < 0.001$; 95 % CI of the mean the difference 5.5–13.5). While ICIQ-UI scores did not change significantly ($p > 0.05$), IIEF total scores improved significantly from a preoperative median (mean) of 8.0 (12.7) to 16.0 (15.2) postoperatively ($p = 0.048$; 95 % CI of the mean the difference 0.02–4.87).

Discussion

In reconstructive urology, clinicians are often confronted with a heterogeneous cohort of patients with an extensive medical history involving recurrent strictures after multiple interventions with different techniques. Consensual outcome measures in these patients are currently lacking [12], limiting direct comparisons which are key to improve quality of care. To date, the USS-PROM represents the only validated PROM tool [11]. Indeed, such a PROM tool aims at improving quality of care. For example, beyond information on surgical failure rates after USS, patients can be counseled including subjective outcome measures such as voiding symptoms and HRQoL. In fact, this will lead to more realistic preoperative patient expectations and postoperative satisfaction. Indeed, based on its general comparability, the USS-PROM holds the potential to set up global standards for study designs, data collection, surgical treatment type and follow-up visits in patients undergoing surgery for urethral stricture disease. Urologists could use these measured health outcomes to evaluate their performance compared to other surgeons and thereby improve the quality of care. On the other hand, patients, insurance companies and political players can make their decisions based on health outcome guided data. Most recently, an international working group of patients, registry representatives, urologists and radiation oncologists set up outcome measures including PROM for patients with localized prostate cancer [26]. These measures included treatment approaches, clinicopathologic baseline characteristics, acute complications for surgery and radiation patients, survival and disease control and patient-reported health outcomes. This example demonstrates the current scope and need to measure outcomes including subjective PROMs as a quality control tool [9].

In light of this context, for the first time, we validated a German version of the USS-PROM by Jackson et al. in a large one-stage BMGU patient cohort. Our results clearly show that the USS-PROM represents a clinically reliable and effective tool to assess patient-reported outcome following urethral surgery. This strong USS-PROM's reliability in actually measuring what it intends to measure is in line with Barbagli et al. [27] who were the first to validate the USS-PROM in Italian. Similar to our results, they confirmed a significant correlation between change in LUTS voiding symptom score and change in Q_{max}, and a significant improvement in the EQ-5D VAS total score. Unfortunately, like the USS-PROM by Jackson et al., the Italian version neither assessed erectile function nor urinary incontinence. Another recently published study confirmed these findings with significant improvement in AUA symptom score (AUSSS) and AUA QoL in 110 patients through a self-administered standardized non-validated PROM [7]. Of note, this study is limited by the lack of a standardized

Table 3 Responsiveness: preoperative and 3 months postoperative comparison of the patient-reported outcome measurement (PROM) including validated instruments in 93 patients who underwent one-stage buccal mucosa graft urethroplasty for anterior urethral stricture disease

	Preoperative mean	Postoperative mean—at 3 months	*p* value	Mean of differences	95 % CI of mean of differences
ICIQ-MLUTS	12.84	5.01	<0.001	8.07	6.68–9.52
Peeling's voiding picture	3.42	2.03	<0.001	1.39	1.16–2.64
EQ5D-VAS	71.47	80.99	<0.001	9.52	5.51–13.52
ICIQ-UI	3.89	3.35	0.28	0.54	0.45–1.55
IIEF-5	12.73	15.17	0.048	2.45	0.02–4.87

ICIQ-MLUTS International Consultation on Incontinence Questionnaire-Male Lower Urinary Tract Symptoms, *EQ5D-VAS*: EuroQOL five-dimensional questionnaire-visual analogue scale, *ICIQ-UI* International Consultation on Incontinence Questionnaire-Urinary Incontinence (short form), *IIEF-5* International Index of Erectile Function-5 (short form)

postoperative follow-up visit, as patients were seen within 2.5 years after surgery. Additionally, that patient cohort was very heterogenous including 60 BMGU, 32 anastomotic urethroplasties, 11 fasciocutaneous flaps and 7 staged urethroplasties. Nuss et al. evaluated different urethral stricture disease signs and symptoms in 204 patients with anterior urethral stricture before urethroplasty. Interestingly, one-fifth (21 %) of patients presented with LUTS symptoms which are not included in the used AUASS such as dysuria and spraying stream. It demonstrates the importance of addressing the actual disease and the need for a validated PROM measuring these outcomes.

The strength of this study is that with showing that this instrument has similar psychometric properties in a separate cohort of men to the original study, in a different healthcare system, in a different country and with different surgeons doing the operation you can now reasonably draw the conclusion that the instrument "works" and that further evidence of generalizability is not mandatory for people to be confident about the fact that the data it generates reflect a real change in the way men perceive their symptoms after urethral reconstruction. In this way we have shown that the USS-PROM is suitable for wider use. For example, this USS-PROM can now be used to generate data that will help relevant stakeholders in the German healthcare system make informed decisions about interventions for urethral stricture. Equally it will facilitate meaningful direct comparisons with other centers/healthcare systems who use the English language version of the instrument, thereby facilitating multi-institutional and larger datasets. Randomized controlled trials are difficult and expensive in reconstructive urology, to the point where the amount of money it costs to do one might not actually be a cost-effective way to work out whether the interventions themselves are cost effective.

We confirmed that HRQoL improves significantly after urethral surgery. It demonstrates the importance of evaluating HRQoL even in patients undergoing USS and stands in contrast to other studies assessing functional related QoL only [8, 28, 29].

We found in our cohort of patients treated with one-stage BMGU, that erectile function improves significantly after surgery. It underscores the need for its evaluation in patients undergoing urethroplasty by complementing the IIEF-5, thereby improving the USS-PROM. Coursey et al. [30] validated a PROM to evaluate erectile function in 152 patients undergoing anterior urethroplasty. While a non-matched cohort of men undergoing circumcision was used as a control group, the authors did not find any significant difference in the two cohorts. There are four studies which evaluated erectile function by either IIEF [31], or IIEF-5 short form [7, 32, 33]; however, none has shown a significant difference. Using the Brief Male Sexual Function Inventory (BMSFI), Sharma et al. [34] reported on a significant improvement in ejaculation and overall satisfaction in patients after anterior urethroplasty.

We did not find any significant changes in the ICIQ-UI SF in this present study; however, for patients undergoing urethroplasty for urethral stricture disease, urinary incontinence still represents a major concern. Currently, it is not really possible to say whether this is because there was no change in reality or whether the questionnaire is insensitive to eliciting change after this operation unless some other "old standard" measure of incontinence is administered at the same time to triangulate. Further studies with larger patient cohorts are needed to evaluate whether this is a significant and valuable outcome, which should be measured in patients undergoing urethroplasty for urethral stricture disease.

This study has some limitations. The test–retest evaluation was done by comparing the 3 and 6 months postoperative USS-PROM. In an ideal world, the test–retest interval would be probably <3 months, but the scores do not change appreciably for most of the patients irrespective of their mean score (i.e., difference is zero most of the time whether or not they are high or low on the scale to start with) and we would not expect a measurable change in a patients symptoms between months 3 and 6 after one-stage BMGU for anterior urethral stricture, which is why we selected this particular cohort to test the instrument. In fact, we believe this is an ideal population in which to validate a PROM for interventions for urethral stricture because, as far as it is possible to be in the real world of reconstructive urethral surgery, the procedure itself is pretty standardized. We are testing the questionnaire on this occasion not the operation so it is important to try to minimize variability in the intervention as far as possible without making the inclusion criteria to restrictive.

There is clearly attrition between the 3 months ($n = 93$) and 6 months ($n = 40$) postoperative USS-PROM. If this were a case series, this would have introduced a potential bias but in the context of a PROM validation study, where it is the questionnaire not the outcome per se that is under scrutiny, this does not an issue. In this context, no longer follow-up is needed for the purpose of PROM development or to demonstrate its value—if it works now it should work forever.

We believe there is a need for further qualitative work with men with urethral stricture to explore some of the issues and find out whether there are any other quality of life problems that we are not measuring yet, particularly across different ethnic groups and in developing nations where they have very different healthcare systems and needs and that could then be addressed with other symptom scores or completely new questions developed from in depth semi-structured interviews. Complementation of

ejaculatory function, complications and comorbidity, especially in patients with harvested buccal mucosa, needs be evaluated in more detail and should be addressed in further research projects. Clearly, further translation and repeating the process in different healthcare systems is a worthwhile venture so that in the end everyone is using the same metric.

Conclusions

A German language version of USS-PROM that is already in routine use by urethral surgeons in the UK has comparable psychometric properties in an analogous patient population, but in the setting of a different healthcare system, different language, different culture and different surgeons. This indicates that the earlier findings are generalizable outside the United Kingdom National Health Services, thus advocating its further translation in other European languages in order that urethral surgeons can make direct comparisons across geopolitical borders. Mean IIEF score improved after urethroplasty but the change, while bordering statistical significance had a wide confidence interval the lower bound of which nearly touches zero. Urinary incontinence did not appear to change after urethroplasty, but it is not clear whether this is actual or a reflection of the sample size. These findings need to be triangulated against qualitative and further quantitative research.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All persons gave their informed consent prior to their inclusion in the study.

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SIU/ICUD Consultation on Urethral Strictures: The Management of Anterior Urethral Stricture Disease Using Substitution Urethroplasty

Christopher Chapple, Daniela Andrich, Anthony Atala, Guido Barbagli, André Cavalcanti, Sanjay Kulkarni, Altaf Mangera, and Yosuke Nakajima

In this systematic review of the literature, a search of the PubMed database was conducted to identify articles dealing with augmentation/substitution urethral reconstruction of the anterior urethral stricture. The evidence was categorized by stricture site, surgical technique, and the type of tissue used. The committee appointed by the International Consultation on Urological Disease reviewed this data and produced a consensus statement relating to the augmentation and substitution of the anterior urethra. In this review article, the background pathophysiology is discussed. Most cases of urethral stricture disease in the anterior urethra are consequent on an ischemic spongiofibrosis. The choice of technique and the surgical approach are discussed along with the potential pros and cons of the use of a graft vs a flap. There is research potential for tissue engineering. The efficacy of the surgical approach to the urethra is reviewed. Whenever possible, a 1-stage approach is preferable from the patient's perspective. In some cases, with complex penile urethral strictures, a 2-stage procedure might be appropriate, and there is an important potential role for the use of a perineal urethrostomy in cases where there is an extensive anterior urethral stricture or where the patient does not wish to undergo complex surgery, or medical contraindications make this hazardous. It is important to have accurate outcome measures for the follow-up of patients, and in this context, a full account needs to be taken of patients' perspectives by the use of appropriate patient-reported outcome measures. The use of symptoms and a flow rate can be misleading. It is well established that with a normally functioning bladder, the flow rate does not diminish until the caliber of the urethra falls below 10F. The most accurate means of following up patients after stricture surgery are by the use of endoscopy or visualization by urethrography. Careful consideration needs to be made of the outcomes reported in the world literature, bearing in mind these aforementioned points. The article concludes with an overview of the key recommendations provided by the committee. UROLOGY 83: S31–S47, 2014.

There are many management options available for urethral stricture disease commencing with less invasive urethral dilatation, urethral stenting, and urethrotomy, progressing to anastomotic and substitution urethral reconstruction. Each patient must be treated on the basis of their individual circumstances and with due regard for consent. In this article, we present the consensus decision of the committee appointed by the International Consultation on Urological Disease (ICUD) on the management of anterior urethral strictures that are too lengthy for an anastomotic procedure.

METHODS

A committee was appointed by the ICUD. The chair conducted a literature search in September 2010 through PubMed (US National Library of Medicine—National Institutes of Health) for peer-reviewed articles on strictures of the anterior urethra treated by substitution/augmentation urethral reconstruction. Search terms included: substitution urethral reconstruction, augmentation urethral reconstruction, dorsal onlay, ventral onlay, lateral onlay, bulbar urethral reconstruction, penile urethral reconstruction, Asopa, Palminteri, and panurethral urethral reconstruction. Non-English articles and articles dealing with solely pediatric cases were excluded. After removal of duplicates, 80 articles were identified. From these, 11 were further excluded because the outcomes could not be categorized for the mixed populations described, and 3 review articles were excluded because the data were not original. The remaining 66 articles were categorized by technique according to the site of surgery and the graft used.

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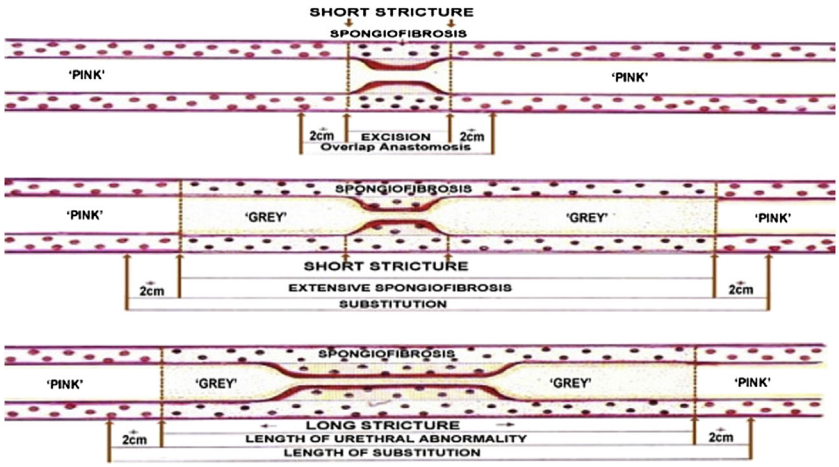

Figure 1. Diagrammatic representation of the length of narrowing caused by the stricture, ischemic spongiofibrosis, and the length of substitution graft required. From Reference 1, with permission. (Color version available online.)

The committee met at the SIU meeting in Marrakech, Morocco in October 2010 to discuss the presented evidence and provide recommendations for the proposed techniques for substitution of the bulbar and penile urethra. The evidence for each graft was also considered. Recommendations were formulated by consensus committee opinion and are based on the ICUD modified system.

PREOPERATIVE ASSESSMENT

It is important to have a clear anatomic assessment of the site and length of the stricture. It is recognized that most men will usually have a tight stricture at the first presentation. Indeed, it was first described in 1968[2] that the effective diameter of the unobstructed male urethra was in the order of 10F, and until the stricture narrowed beyond this point, there would be no significant interference with flow.

The current standard of care is to use a combined ascending and descending urethrogram to image the urethra, supplemented where necessary by urethroscopy. An ischemic urethra looks white or gray, and healthy well-vascularized tissue appears pink. The length of urethral narrowing might not correspond directly to the length of ischemic spongiofibrosis and thus to the length of graft required (Fig. 1). It has been suggested that intracorporeal injection of contrast[3,4] or ultrasonography[5,6] might be useful.

PREOPERATIVE COUNSELING

Preoperatively, the patient must be warned about the risks of the procedure and of possible complications, the failure rate, the need for additional procedures, the need for follow-up, and the rate of recurrence.

Three retrospective studies have reported that anterior urethral reconstruction has an insignificant long-term effect on erectile dysfunction.[7-9] Alterations in penile appearance and sexual performance might occur after anterior urethral reconstruction, but these are usually transient and more likely with longer strictures, advancing age, and preceding history of erectile dysfunction. A prospective study has recently reported that there is a risk of erectile dysfunction within the first few months after surgery,[10] but with time this improves, and most men will have full recovery by 7 months. The authors did note the persistence of erectile dysfunction in some men, but long-term follow-up would be necessary before they could categorically provide advice on the basis of this information.

CHOICE OF URETHRAL RECONSTRUCTION TECHNIQUE

In determining the type of urethral reconstruction that is appropriate, one must consider the length of the stricture, its cause (in particular lichen sclerosus), and any previous surgery. The etiology of a stricture has an influence on any decision, because inflammatory strictures and those associated with lichen sclerosus have a tendency to be longer and also have a tendency to recur because of recrudescence of the underlying disease process.

The bulbar urethra is surrounded by the thickest portion of the corpus spongiosum and is eccentrically placed toward the dorsum. Thus, the dorsal aspect of the surrounding tissues of the corpus spongiosum is thin, whereas ventrally they are thick. Distally, the urethra becomes more centrally placed, and through the glans it is relatively ventrally placed (Fig. 2).

Anastomotic urethral reconstruction involves stricture excision and primary anastomosis of the urethral ends. Surgeons cannot simply excise a stricture and restore continuity because of the potential for causing chordee. It is a useful rule that the bulbar urethra should not be mobilized distal to the penoscrotal junction, and therefore for longer strictures, a substitution procedure might be necessary. Similarly, it is very uncommon to be able to perform an anastomotic urethral reconstruction in the penile urethra, except in the context of a very limited traumatic injury.

Traditionally, only bulbar strictures <3 cm were considered suitable for an anastomotic procedure.

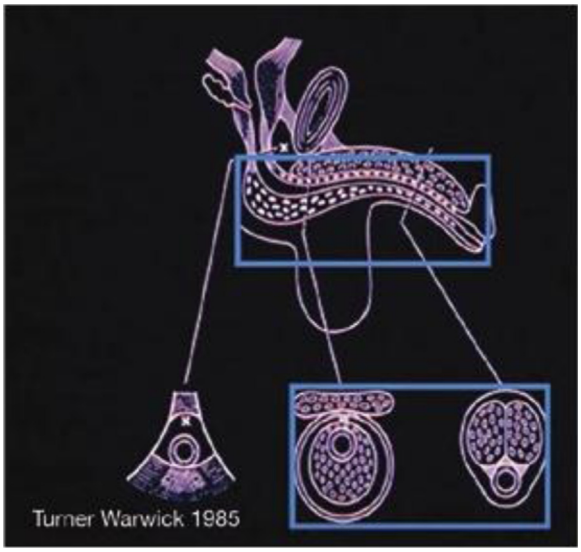

Figure 2. Diagrammatic representation of corporal thickness in the bulbar and penile urethra. From Reference 1, with permission. (Color version available online.)

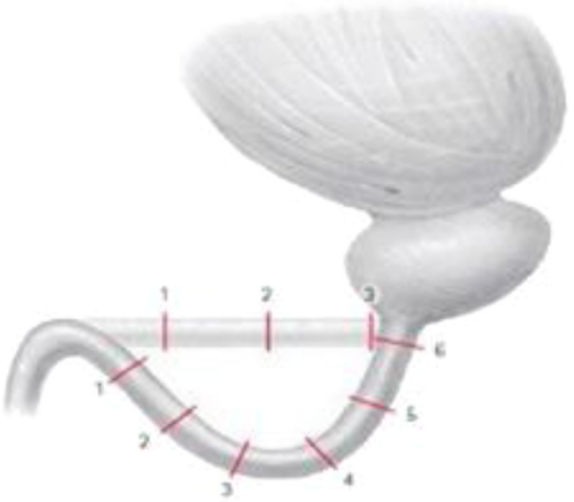

Figure 3. Diagrammatic representation of the additional length (in centimeters) gained by separation of the corpora cavernosa. Numbers represent length in centimeters. From Reference 42, with permission. (Color version available online.)

However, using techniques (covered elsewhere) such as freeing up the urethra and separating the corpora and straightening the natural curve of the urethra (Fig. 3) another few centimeters might be gained when dealing with bulbar strictures.

Morey and Kizer[11] compared anastomotic procedures carried out for a stricture length ranging from 2.6 to 5.0 cm and reported success rates of 91%, as compared with a control group with stricture lengths <2.5 cm. However, the series had only 11 patients in each group, and the mean follow-up period was 22 months.

Three large series looking at the success rates of anastomotic urethral reconstruction have recently been reported, with Santucci et al,[12] Barbagli et al,[13] and Eltahawy et al[14] reporting success rates between 91% and 98%.

Clearly, the amount of length that can be gained will depend on the anatomy of the individual male patient, including the length and elasticity of the distal urethral segment, and more particularly, the size of the penis and urethra. It is now clearly established that anastomotic urethral reconstruction in the bulbar urethra, when performed by an experienced surgeon, is associated with a success rate of up to 95%.[12-14] The remainder of this analysis gives an overview of the various techniques for augmentation urethral reconstruction and reviews the evidence relating to their use.

AUGMENTATION URETHRAL RECONSTRUCTION

Augmentation urethral reconstruction can be a 1-stage or a 2-stage procedure. There are 3 potential options with a 1-stage procedure:

1. Augmented anastomosis—excise stricture and restore a roof strip of native urethra augmented by a patch,
2. Onlay augmentation—excise stricture and carry out patch augmentation,
3. Tube augmentation—excise stricture and insert a circumferential patch. This method has a high failure rate of up to 30%.[15]

A 2-stage procedure involves excision of the stricture and the abnormal urethra and reconstruction of a roof strip, which is allowed to heal before second-stage tubularization.

GRAFTS vs FLAPS

Controversy previously existed regarding whether one should use a graft or flap, but it is now clearly established from a review of the literature that the stricture recurrence rate is 14.5%-15.7% using a flap or a graft.[16] It can therefore be concluded that in most instances, there is no advantage of a flap over a graft in terms of stricture recurrence rate. A randomized controlled trial confirmed that the efficacy of grafts and flaps was identical, but there was a much higher morbidity with penile skin flaps, which were also technically more complex and were thus less likely to be preferred by patients.[17]

In carrying out an augmentation procedure, one must also consider whether full-thickness tissue or partial-thickness tissue should be used; partial-thickness tissue has a greater propensity to contract.

Alternative options that have been suggested in the past include scrotal skin,[18] extragenital skin,[19] bladder epithelium,[20] and colonic mucosa.[21] In contemporary practice, genital skin and oral mucosa are most commonly used, although there is interest in the potential for tissue engineering in the future.[22] Genital skin flaps are particularly useful when dealing with strictures in the penile urethra, where an onlay flap of penile skin can be especially helpful.

Jenkins et al[23] found the scrotal pull-through procedure to have a high incidence of complications, and Blandy reported on the significant long-term morbidity associated with the use of scrotal skin, which should not be used except in unusual circumstances.

A number of flap designs have been described, varying in terms of the orientation of the skin island and the dissection of the fascial pedicle. When considering a penile flap, identify an area of hairless penile skin of adequate length for use in the reconstruction of the urethral defect. Ensure that the patient is not shaved so that the position of hair can be identified perioperatively. Next, on the basis of the anatomy of the penis, decide the configuration of the flap, that is, transverse, longitudinal, or oblique. Thereafter, determine the elevation technique of the fascial pedicle. Remember that the skin is a "passenger" on the subcutaneous tissues/fascial tissues. Ventral onlay skin flaps are particularly useful in the management of penile strictures with etiologies other than lichen sclerosus.

In the bulbar urethra, the current standard of care is to use a graft in most cases, because the efficacy of grafts and flaps appears to be virtually identical. Indeed, it is well recognized that a number of complications can occur after flap reconstruction, including penile hematoma, skin necrosis, fistula formation, and if one is using a distal flap derived from the prepuce, penile, and glans torsion. In the longer term, flaps are associated with a higher risk of sacculation (diverticulum formation).

Barbagli et al[24] have reviewed their experience using dorsal onlay skin graft urethral reconstruction and reported a series of 38 patients, of which 65.8% of cases were considered successful at a mean follow-up of 111 months. It is of interest that most recurrences in this series occurred within the first year. A similar experience has been reported in patients with no underlying progressive condition, such as lichen sclerosus, who underwent augmentation urethral reconstruction objectively assessed using urethrography or endoscopy.[25]

Andrich et al[26] reported that in the longer term, the recurrence rate after an augmentation procedure is far worse than would be expected according to the existing literature, with a recurrence rate of 42% at 15 years for augmentation and 14% for anastomotic procedures. However, this study reported on a mixed population of cases at a tertiary center and probably represents a worst-case scenario.

The results of the different configurations of augmentation urethral reconstruction are summarized in Table 1. The complete data set is included in Tables 2-9.

Table 1. Average data for the different configurations of augmentation urethroplasty

Technique	Total Patients Reported (N)	Average Follow-up (mo)	Average Success Rate (%)
Dorsal onlay bulbar	934	42.2	88.3
Ventral onlay bulbar	563	34.4	88.8
Lateral onlay bulbar	6	77	83
Asopa	89	28.9	86.7
Palminteri	53	21.9	90.6
One-stage penile	432	32.8	75.6
Two-stage penile	129	22.2	90.5
Panurethral	240	30.1	88.2

ORAL MUCOSAL GRAFTS

Most patients undergoing augmentation urethral reconstruction, and particularly patients with lichen sclerosus, are optimally managed by an oral mucosa patch augmentation. Oral mucosa is simple to harvest, tough, resilient, and easy to handle. It is taken as a full-thickness unit, and for most patients, the donor areas are adequate. It takes very effectively and has a thick epithelium with a thin lamina propria and a dense panlaminar vascular plexus, which allows early inosculation. This mucosa is used to being wet and appears to be resilient to skin diseases such as lichen sclerosus. Conversely, preputial grafts are semiwet, and scrotal and penile grafts are used to a dry environment. Skin has a higher rate of lichen sclerosis recurrence. Oral mucosa also has a privileged immunology, and preclinical work suggests that it shows fibroblast behavior that results in less fibrosis, offering quite a different profile than that of skin.

In harvesting buccal mucosa, the parotid duct is identified opposite the upper second molar tooth. Infiltration with 1 in 200,000 adrenaline is helpful, and the buccal mucosa is excised in the plane superficial to the underlying muscle. Labial (lip) mucosa can be managed in a similar fashion, but is thinner and more difficult to handle and is associated with greater morbidity. Lingual (tongue) mucosa is harvested from the under surface of the tongue.[27] Lingual mucosa is slightly thinner than buccal mucosa. The landmarks to be identified are the lingual duct and nerve. A comparative study of buccal and lingual mucosa has reported that grafts from these sites are very similar in macroscopic appearance.[28] The initial results using lingual mucosa have been reproduced by others and appear to be equivalent to those of buccal mucosa.[28-30]

Reported complications of oral mucosal grafts include intraoperative hemorrhage, postoperative infection, pain, swelling, and damage to salivary ducts. In some cases, patients note initial limitation of oral opening, although this is usually transient. Occasionally, there can be loss or alteration of sensation within the cheek and even more so on the lower lip.[31,32] A permanent palpable scar because of the formation of a fibrous band might be noticed by the patient. Both numbness and deformity have also been reported, particularly after the harvesting of tissue from the lower lip.

Barbagli et al[33] in a survey of 295 patients reported that 98.4% would undergo the surgery again and concluded that harvesting from a single cheek with closure of the donor site was a safe procedure with high patient satisfaction.

Contemporary evidence suggests that closure of the donor site is not essential.[34] Gentle apposition might be

Table 2. Outcomes and follow-up of ventral onlay bulbar urethroplasty

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Morey et al 1996[55]	13	18	BM	Uroflowmetry/symptom score Urethrography 3 and 12 mo	Any instrumentation	100
Wessells et al 1996[56]	27	23	BM 7 BLM 2 PS 21	Uroflowmetry 3 and 12 mo Urethrography 2/3 wk, 3 and 12 mo	Any instrumentation, radiographic presence of stricture	100 100 90
Pansadoro et al 1999[57]	7	20	BM	Uroflowmetry Urethrography 2 wk, 6, and 12 mo, then annually	Stricture recurrence on urethrography	86
Andrich et al 2001[58,59]	29	48-60	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 6 and 18 mo Urethroscopy in last 45 cases	Development of symptoms leading to urethrogram or urethroscopy	86
Meneghini et al 2001[60]	20	6-28	BM	Uroflowmetry 3, 6, 9, and 12 mo Urethrography 6 and 12 mo	Any objective or subjective modification of uroflowmetry leading to urethral instrumentation	80
Palminteri et al 2002[61]	24	18	BM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk and 12 mo Urethroscopy 12 mo	Any instrumentation	95.8
Lewis et al 2002[62]	22	12-54	BM	Uroflowmetry 3 and 12 mo Urethrography 3 and 12 mo	Any instrumentation	86
Kane et al 2002[63]	53	25	BM	Uroflowmetry 3, 6, and 12 mo, then annually with symptom score Urethrography 3 wk and 3 mo	Recurrence on radiological studies and requiring intervention	94
Heinke et al 2003[64]	38 (30 bulbar)	22.8	BM	Uroflowmetry 6 and 12 mo and PVRU estimation Urethrography 3 wk, repeat if deteriorating Qmax	Failure after repeat intervention (some patients also performing ISD)	81.6
Pansadoro et al 2003[65]	9	41	BM	Uroflowmetry—periodic Urethrography 2 wk, 6 and 12 mo, then annually	Recurrence of symptoms	89
Elliott et al 2003[66]	60	47	BM	Urethrography 3 wk, 3, 6, and 12 mo, then as required	If stream reduced or symptoms recurred	90
Dubey et al 2003[67]	18	45.7	6PS 7 BM 6BLM	Uroflowmetry 6 mo (all patients performed ISD 16F up to 6 mo) Urethrography 6, 12, and 18 mo, then as required	Need for urethral calibration/dilatation with/without DIVU after 18 mo	77.8
Fichtner et al 2004[68]	32 (15 bulbar)	82.8	BM	Uroflowmetry 6 and 12 mo with symptom score and PVRU estimation Urethrography 3 wk	Symptomatic recurrence	87
Kellner et al 2004[69]	18	50	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required	Abnormal voiding Need for intervention	87 (includes 5 penile)

Continued

Table 2. Continued

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Berger et al 2005[70]	7	70.7	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk	If stream or symptoms deteriorate	43
Barbagli et al 2005[43]	17	42	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required Urethroscopy as required (Qmax <14 mL/s)	Any instrumentation	83
McLaughlin et al 2006[71]	58 (48 reported)	29.6	BM	Symptom score at 12 mo No routine urethrography Urethroscopy if deterioration in symptoms	Any recurrence found on urethroscopy if subjective deterioration in symptoms	94
Palminteri et al 2007[72]	1	21	SIS	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk and 12 mo or if Qmax <14 mL/s Urethroscopy 3 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	100
Fiala et al 2007[38]	10	31.2	SIS	Urethrography 3, 6, 9, 12, and 18, then annually If Qmax <15 mL/s or IPSS >7 then urethrography	Stricture on urethrography	90
Levine et al 2007[73]	12	58.1	BM	Urethrography 2 wk	Any instrumentation	83
Dubey et al 2007[17]	8 15 (bulbopenile)	22.6	BM	Uroflowmetry Urethrography 3 wk, then if required Urethral calibration 16F or urethroscopy 1, 3, 7, 10, and 16 mo, then annually	Recurrence of stricture	89.9 (includes bulbar)
Barbagli et al 2008[24]	93	36	OM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 2/3 wk IF Qmax <14 mL/s then urethrography and urethroscopy	Any instrumentation	91.4
Barbagli et al 2008[74]	6	15.25	OM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk, 6 and 12 mo If Qmax <14 mL/s then cystourethrography and urethroscopy	Any instrumentation	100
Dalela et al 2010[75]	13	16.4	BM	Uroflowmetry and PVR estimation Urethrography if Qmax <14 mL/s Urethroscopy if Qmax < 14 mL/s	Qmax <14 mL/s	84.6

BLM, bladder mucosa; BM, buccal mucosa; CM, colonic mucosa; DIVU, direct internal visual urethrotomy; GS, groin skin graft; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; ISD, intermittent self-dilatation; LBM, labial mucosa; LM, lingual mucosa; OM, oral mucosa; PAS, postauricular skin graft; PS, penile skin; PVRU, postvoid residual urine; Qmax, maximum urine flow; SG, full-thickness skin graft; SIS, porcine small intestinal submucosa; SS, scrotal skin; TA, tunica albuginea; TV, tunica vaginalis.

Table 3. Outcomes and follow-up of dorsal onlay bulbar urethroplasty

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Barbagli et al 1996[76]	20	46	SG	Uroflowmetry 4, 8, and 12 mo Urethrography 2/3 wk and once more and if Qmax <14 mL/s	Recurrence on urethrography	95
Barbagli et al 1998[77]	37	21.5 (13.5 BM)	31 PS 6 BM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk, repeat if Qmax <14 mL/s	Any instrumentation	92 (100 BM)
Pansadoro et al 1999[57]	23	20	BM	Uroflowmetry Urethrography 2 wk, 6 and 12 mo, then annually	Stricture recurrence on urethrography	100
Iselin et al 1999[78]	29	19	PS or BM	Urethrography 3 wk, 3, 12, and 18 mo	Radiographic evidence of recurrence	97
Barbagli et al 2001[79]	40	43	PS	Uroflowmetry 4, 8, 12 mo, then annually Urethrography 2/3 wk, 4 mo or if Qmax <14 mL/s	Any instrumentation	85
Andrich et al 2001[59]	42	48-60	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 6 and 18 mo Urethroscopy in last 45 cases	Development of symptoms leading to urethrogram or urethroscopy to confirm recurrence	95
Joseph et al 2002[80]	14	32	BM or PAS	Uroflowmetry 12 and 18 mo Urethrography 3 wk, 12 and 18 mo	Recurrence on urethrography	100
Pansadoro et al 2003[65]	56	41	BM	Uroflowmetry—periodic Urethrography 2 wk, 6 and 12 mo, then annually	Recurrence of symptoms	98
Dubey et al 2003[67]	16	22	BM	Uroflowmetry 6 mo (all patients performed ISD 16F up to 6 mo) Urethrography 6, 12, and 18 mo, then as required	Need for urethral calibration/dilatation with/without DIVU after 18 mo	87
Andrich et al 2003[49]	51	6	BM or SG	Uroflowmetry 6 wk, 3 and 6 mo Urethrography 6 mo	Restricturing on urethrography	98
Barbagli et al 2004[81]	45	71	PS	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required Urethroscopy as required (Qmax <14 mL/s)	Any instrumentation	73
Berger et al 2005[70]	40	70.7	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk	If stream or symptoms deteriorate	95
Raber et al 2005[82]	30	51	17 PS 13 (BM)	Uroflowmetry 6, 12, and 18 mo with IPSS and IIEF scores Urethrography 3 wk, repeated if required Urethroscopy as required	Qmax <20 mL/s Symptoms requiring intervention (DIVU or ISD)	76 (85)
Dubey et al 2005[83]	41	36.2	BM	Uroflowmetry 3, 6, 9 and 12 mo with ongoing	Symptom recurrence or inability to pass 16ch catheter	90

Continued

Table 3. Continued

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
				urethral calibration (16F) Urethrography at 3 mo, then as required		
Barbagli et al 2005[43]	27	42	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required Urethroscopy as required (Qmax <14 mL/s)	Any instrumentation	85
Barbagli et al 2006[84]	6	16	BM	Uroflowmetry 6 and 12 mo, then annually Urethrography 2 wk, 6 and 12 mo, then annually	Any instrumentation	100
Donkov et al 2006[85]	9	18	SIS	Uroflowmetry 6 wk, 18 mo Urethroscopy 3 mo	Decreased flow rate or stricture recurrence	89
Simonato et al 2006[27]	8	18	LM	Uroflowmetry 3 and 12 mo Urethrography 2 wk, 3 and 12 mo Urethroscopy 3 and 12 mo	Qmax <15 mL/s Need for instrumentation	87.5
Xu et al 2007[86]	12	57	BM	Uroflowmetry 14-18 d, 3-6 mo (most patients) Urethrography 14-18 d Urethroscopy in some patients at 12 mo	Any complication	77 (includes tubularized BLM and CM grafts
Palminteri et al 2007[72]	3	21	SIS	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk and 12 mo or if Qmax <14 mL/s Urethroscopy 3 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	100
Radopoulos et al 2007[87]	16	49.9	PS	Uroflowmetry 3/4 and 12 mo Urethrography 3/4 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	81
Foinquinos et al 2007[88]	7	1-5	TV	Uroflowmetry and urethrography	Poor uroflowmetry Poor urethrography	100
Levine et al 2007[73]	21	53	BM	Urethrography 2 wk	Any instrumentation	86
Dubey et al 2007[17]	4	22.6	BM	Uroflowmetry Urethrography 3 wk, then if required Urethral calibration 16F or urethroscopy 1, 3, 7, 10, and 16 mo, then annually	Recurrence of stricture	89.9 (includes penile)
Barbagli et al 2008[24]	22 38	41 111	OM PS	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 2/3 wk If Qmax <14 mL/s then urethrography and urethroscopy	Any instrumentation	77.3 65.8
Barbagli et al 2008[74]	6	15.25	OM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk, 6 and 12 mo If Qmax <14 mL/s then urethrography and urethroscopy	Any instrumentation	100

Continued

Table 3. Continued

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
O'Riordan et al 2008[89]	52	34	BM	Urethrography 3 wk Symptoms interview	Any instrumentation	86
Simonato et al 2008[28]	11	17.7	LM	Uroflowmetry 3 and 12 mo Urethrography 2 wk, 3 and 12 mo Urethroscopy 3 and 12 mo	Inability to void, a postvoid residual Any instrumentation	81.8
Kulkarni et al 2009[90]	88	56	OM	Uroflowmetry every 4, 8, and 12 mo, then annually Urethrography 3 wk, Urethrography if Qmax <12 mL/s	Any instrumentation	91
Das et al 2009[29]	6	9	LM	Uroflowmetry 3 and 6 mo Urethrography 3 wk, 3 and 6 mo	Qmax <15 mL/s, need for instrumentation	83.3 (includes penile)
Kulkarni et al 2009[44]	12	22	OM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk If Qmax <14 mL/s then urethrography and urethroscopy	Any instrumentation	92
Manoj et al 2009[91]	8	21.7	PAS	Uroflowmetry 3 and 6 mo, annually in some patients Urethrography 3 wk, repeat if Qmax <14 mL/s	Any instrumentation	100
Fransis et al 2009[92]	30	23	BM	Uroflowmetry/PVRU 3 and 12 mo, then yearly Urethrography 6 mo Urethroscopy when required	Abnormal voiding, stricture on urethrography and need for instrumentation	94
Schwentner et al 2010[93]	42	57.2	29 PS 13 GS	Uroflowmetry/PVR 3, 6, 9, and 12 mo Urethrography at catheter removal, then if required	Presence of symptoms and low flow rate	90.5
Arlen et al 2010[94]	22	10.5	BM	Urethrography 3/4 wk Urethroscopy if symptoms developed	Any instrumentation	83.3

GS, groin skin graft; IIEF, International Index of Erectile Function; LM, lingual mucosa; PAS, postauricular skin graft; SG, full-thickness skin graft; TV, tunica vaginalis; other abbreviations as in Table 2.

useful in helping to control bleeding; other techniques include the use of fibrin glue, which can be applied locally (but is very expensive), and standard diathermy hemostasis. Overzealous closure of the cheek donor site appears to worsen pain and might result in perioral numbness, difficulty with mouth opening, and alterations in salivary function.[31,34]

ACELLULAR MATRICES AND TISSUE ENGINEERING

There has been interest in the use of acellular bladder matrix, with positive results being reported by El-Kassaby et al.[35] However, this is a viable option only if there is a healthy, well-vascularized urethral bed with limited residual ischemic spongiofibrosis and healthy urethral mucosa at both ends.[36] Regrettably, this is not often the case in which there is a long stricture requiring augmentation. Positive results were reported by Fiala et al[37] using porcine small intestinal submucosa matrix. However, a recent update suggests that with longer-term follow-up, the success rate might deteriorate. Hauser et al[38] reported a poor success rate using small intestinal submucosa.

In the future, bioengineered buccal mucosa might be of use, particularly for complex strictures where lengthy amounts of oral mucosa are necessary, and ongoing preclinical research is being conducted.[22,39] This requires a donation of keratinocytes and fibroblasts obtained from a patient before surgery via a small biopsy carried out under local anesthesia. These cells are cultured and

Table 4. Outcomes and follow-up of lateral onlay bulbar urethroplasty

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Barbagli et al 2005[43]	6	42	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required Urethroscopy as required (Qmax <14 mL/s)	Need for instrumentation	83
Barbagli et al 2008[24]	6 (Same patients as mentioned previously)	77	OM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 2/3 wk, then as required Urethroscopy as required (Qmax <14 mL/s)	Need for instrumentation	83

Abbreviations as in Table 2.

attached to the matrix to create a lengthy piece of tissue. Providing the biopsy is taken from the patient undergoing urethral reconstruction, there is no allergenic response as long as the underlying matrix is immunologically inert. The principal problems with using biologic matrices relate to a marked exudative process and an unpredictable degree of tissue contraction.

GRAFT POSITIONING

Barbagli et al[40] initially reported dorsal graft urethral reconstruction using skin, and subsequently buccal mucosa (a modification of the Monseur technique).[41] Initially, this was applied in the context of an augmented anastomotic repair. Recent debate surrounds the advocacy of transection of the corpus spongiosum because of concern over damage to the urethral blood supply. If there is a severely ischemic area of corpus spongiosum, transection is unlikely to be important, as the residual blood flow through the ischemic area is not likely to be significant.

Concerning onlay augmentation, the options are a ventral, lateral, or dorsal approach. A review of dorsal and ventral onlay grafting has suggested comparable success rates of 88% at 3 years, regardless of which approach is used for the onlay.[45] There is likely to be less bleeding from an incision in this plane and potentially less interference with blood supply as one extends into the proximal and distal "more normal" urethra.

Recently, Kulkarni et al[44] reported a 1-sided anterior dorsal approach, preserving the bulbospongiosus muscle and lateral vascular and nerve supply to the urethra, as having a success rate of 92% in a small series of 24 patients with a short mean follow-up of 22 months. Asopa et al[46] described a ventral sagittal urethrotomy transurethral lumen approach, with placement of a dorsal inlay graft. Fifty-eight men underwent treatment, with a mean follow-up of 42 months and a success rate of 87%. Palminteri et al[48] have suggested that, in addition to placement of a dorsal graft via the Asopa approach, a ventral onlay could be applied as well. A success rate of 89% with a mean follow-up of 22 months in 48 cases was reported.

One-stage tube repairs should not be used routinely, and it is clear from a review of the literature that the revision rate for a 2-stage procedure before formal closure is on the order of 20%-25%, which equates well with the finding of Greenwell et al[15] of a 30% failure rate with a tube urethral reconstruction.

Two-stage reconstruction should be considered whenever there is concern about the success of any reconstructive procedure in the penile urethra, particularly after hypospadias repair or in the presence of lichen sclerosus.

A small literature base reports on staged reconstruction in which a graft is placed during the first stage and later tabularized at the second stage, but it must be emphasized that the literature reports a 22.5% revision rate for a first-stage urethral reconstruction.[49] When the patient is given information about a 2-stage procedure, he must be warned that the second stage can only be completed when the first stage is adequate for closure.

In carrying out penile surgery, the important factor to bear in mind is the tendency for chordee, and use of an artificial erection is advised during the reconstruction. After first-stage urethral reconstruction, 10%-39% of patients show contraction because of scarring of the initial graft and this requires new grafting techniques.[50]

Second-stage closure requires tubularization of the first-stage, and the aim is to achieve a roof of 25-30 mm to provide a satisfactory augmentation of the urethral lumen, allowing for the inevitable contraction that occurs during subsequent healing. It is essential to avoid overlaying suture lines and to provide for tissue to be interposed between urethral closure and skin closure. Thus, if the tissues of the penis are thin, then mobilization of a tunica dartos flap or tunica vaginalis island from the scrotum is appropriate. Complications after second-stage urethral reconstruction (fistula formation, glans dehiscence, and meatal stenosis) have been reported in 30% of patients.[50]

Andrich and Mundy[51] reported that there is a tendency for recurrence in the marsupialized segment of the urethra, particularly in lichen sclerosus patients, and that therefore a perineal urethrostomy might be a more reliable form of management for full-length urethral

Table 5. Outcomes and follow-up of 1-stage penile urethroplasty

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Venn et al 1998[95]	28 (patch) 11 (tube)	36	BM	Regular uroflowmetry Urethrography 6 mo	Recurrence on urethrography	96.4 54.5
Andrich et al 2001[59]	41	24-60+	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 6 and 18 mo Urethroscopy in last 45 cases	Development of symptoms leading to urethrogram or urethroscopy to confirm recurrence	100
Metro et al 2001[96]	14	63.6	BM	Uroflowmetry 6 and 12 mo with symptom score	Need for ISD >6 mo	57.1
Andrich et al 2003[49]	20	6	BM or SG	Uroflowmetry 6 wk, 3 and 6 mo Urethrography 6 mo	Restricturing	95
Fichtner et al 2004[68]	17	82.8	BM	Uroflowmetry 6 and 12 mo with symptom score and PVRU estimation Urethrography 3 wk	Symptomatic recurrence	88.2
Dubey et al 2005[83]	16	36.2	BM	Uroflowmetry 3, 6, 9, and 12 mo with ongoing urethral calibration (16F) Urethrography 3 mo, then as required	Symptom recurrence or inability to pass 16F catheter	85.7
Dubey et al 2005[97]	25	32.5	BM	Uroflowmetry 3, 6, 9, and 12 mo, then every 6 mo with ongoing urethral calibration (16F) Urethrography 3 wk	Symptomatic recurrence	88
Kellner et al 2004[69]	5	50	BM	Uroflowmetry 3, 6, and 12 mo, then annually Urethrography 3 wk, then as required	Abnormal voiding Need for intervention	87 (includes 18 bulbar)
Palminteri et al 2007[72]	1 3 (bulbopenile)	21	SIS	Uroflowmetry 4, 8, 12 mo, then annually Urethrography 3 wk and 12 mo or if Qmax <14 mL/s Urethroscopy 3 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	0 (33 bulbopenile)
Fiala et al 2007[36]	9 31 (bulbopenile)	31.2	SIS	Urethrography 3, 6, 9, 12, and 18 mo, then annually If Qmax <15 mL/s or IPSS >7 then urethrography	Stricture on urethrography	55.5 (84 bulbopenile)
Radopoulos et al 2007[87]	5	49.9	PS	Urethrography and flow rate at 3/4 mo and at 1 y	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	30
Foinquinos et al 2007[88]	4	1-5	TV	Uroflowmetry and urethrography	Poor uroflowmetry Poor urethrography	100
Levine et al 2007[73]	13	45	BM	Urethrography 2 wk	Any instrumentation	70 ventral onlay 66 dorsal onlay
Barbagli et al 2008[84]	45	55	PS 23 (OM 22)	Uroflowmetry every 4 mo until 1 y, then annually Urethrography 2 wk If Qmax <14 mL/s then urethrography, ultrasonography, and urethroscopy	Any instrumentation	78 (82)
Kumar et al 2008[98]	41	18	TA	Urethrography—no description of timing	Poor caliber at urethrogram Poor urethral lumen at urethrosonogram	67

Continued

Table 5. Continued

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
					Patient unsatisfied and dilatation required Qmax <20 mL/s	
Simonato et al 2008[28]	8 penile 5 (bulbopenile)	17.7	LM	Uroflowmetry 3 and 12 mo Urethrography 2 wk, 3 and 12 mo Urethroscopy 3 and 12 mo	Inability to void, a postvoid residual Any instrumentation	100 penile 60 bulbopenile
Kulkarni et al 2009[90]	8	56	OM	Uroflowmetry every 4, 8, 12 mo, then annually Urethrography 3 wk Urethrography if Qmax <12 mL/s	Any instrumentation	100
Das et al 2009[29]	6	9	LM	Uroflowmetry 3 and 6 mo Urethrography 3 wk, 3 and 6 mo	Qmax <15 mL/s Any instrumentation	83.3 (includes bulbar)
Singh et al 2009[99]	8	19	BM	Uroflowmetry, urethrography, urethroscopy—no details on timing	Qmax <15 mL/s, abnormal urethrogram or urethroscopy, need for any intervention	88 (includes 8 panurethral)
Manoj et al 2009[91]	12	21.7	PAS	Uroflowmetry 3 and 6 mo, annually in some patients Urethrography 3 wk, repeat if Qmax <14 mL/s	Any instrumentation	92
Xu et al 2010[100]	56	17.2	LM	Uroflowmetry 2 or 3 mo, then 6 mo Urethrography when Qmax <15 mL/s Urethroscopy when Qmax <15 mL/s	Not described	87 (includes bulbar cases)

TA, tunica albuginea; other abbreviations as in Tables 2 and 3.

Table 6. Outcomes and follow-up of penile urethroplasty via the 2-stage technique

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Venn et al 1998[101]	16	36	BM	Not described	Not described	93.8
Andrich et al 2003[49]	58	6	BM or SG	Uroflowmetry 6 wk, 3 and 6 mo Urethrography 6 mo	Restricturing	98
Dubey et al 2005[83]	15	24.2	BM	Uroflowmetry 3, 6, 9, and 12 mo with ongoing urethral calibration (16F) Urethrography 3 mo, then as required	Symptom recurrence or inability to pass 16F catheter	86.7
Dubey et al 2005[97]	14	32.5	BM	Uroflowmetry 3, 6, 9, and 12 mo, then every 6 mo with ongoing urethral calibration (16F) Urethrography 3 wk	Symptomatic recurrence	78.6
Levine et al 2007[73]	5	36	BM	Urethrography 2/3 wk	Any instrumentation	80
Meeks et al 2008[102]	6	17	SG	Not described	Failure of graft take	100
Kulkarni et al 2009[90]	15	56	OM	Uroflowmetry every 4, 8, and 12 mo, then annually Urethrography 3 wk Urethrography if Qmax <12 mL/s	Any instrumentation	73

Abbreviations as in Tables 2 and 3.

Table 7. Outcomes and follow-up of panurethral urethroplasty

Authors	No. Treated	No. of Stages	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Andrich et al 2003[49]	24	2	6	BM or SG	Uroflowmetry 6 wk, 3 and 6 mo Urethrography 6 mo	Restricturing	91.7
Gupta et al 2004[103]	4 8 (bulbopenile)	1	12	BM	Uroflowmetry every 3 mo Urethrography 3 wk Urethroscopy 3 mo	Qmax <15 mL/s Reduced caliber urethra	92
Dubey et al 2005[83]	12	1	36.2	BM	Uroflowmetry 3, 6, 9, and 12 mo with ongoing urethral calibration (16F) Urethrography 3 mo, then as required	Symptom recurrence or inability to pass 16F catheter	83.3
Singh et al 2009[99]	8	1	19	BM	Uroflowmetry, urethrography, urethroscopy No details on timing	Qmax <15 mL/s, abnormal urethrogram/ urethroscopy, any intervention	88 (includes 8 penile)
Xu et al 2009[21]	36	1	53.6	CM	Uroflowmetry 3 or 4 mo Urethrography at catheter removal Most patients uroflowmetry and urethrography every 3 to 6 mo or if Qmax <15 mL/s	Abnormal voiding, any intervention	85.7
Manoj et al 2009[91]	15	1	21.7	PAS	Uroflowmetry 3 and 6 mo, annually in some patients Urethrography 3 wk, repeat if Qmax <14 mL/s	Any instrumentation	80
Kulkarni et al 2009[44]	12	1	22	OM	Uroflowmetry 4, 8, and 12 mo then annually Urethrography 3 wk If Qmax <14 mL/s then urethrography/ urethroscopy	Any instrumentation	92
XU et al 2009[104]	25	1	26.8	9BM X 2 7 LM X 2 9 LM + BM	Uroflowmetry Urethrography if problems	Any instrumentation	92
Das et al 2009[29]	18	1	9	LM	Uroflowmetry 3 and 6 mo Urethrography 3 wk, 3 and 6 mo	Qmax <15 mL/s Any instrumentation	83.3 (includes bulbar)
Mathur and Sharma 2010[105]	86	1	36	TA	Uroflowmetry and pt satisfaction 6, 12, 24, and 36 mo Urethrography 6, 12, 24, and 36 mo Urethroscopy in 10 patients	Good caliber or partially narrowed urethra (urethrography), Qmax <20 mL/s, requiring >1 dilatation/year	89.5

Abbreviations as in Tables 2, 3, and 5.

strictures, particularly in elderly patients. Peterson et al[52] also support this view.

PATIENT FOLLOW-UP

Follow-up protocols after urethral reconstructive procedures vary among series. The most commonly used method is uroflowmetry.[46] For voiding symptoms to appear and flow rates to diminish, there has to be a significant reduction in the caliber of the urethra to <10F.[2]

Anatomic assessment of the repair site potentially provides the most accurate information with regard to success and the potential for recurrent stricture formation. Although contrast urethrography is most widely used in

Table 8. Outcomes and follow-up of urethroplasty via the Asopa technique

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Asopa et al 2001[46]	12	8-40	10 PS 2 BM	Uroflowmetry at last follow-up Urethrography 7 wk Urethroscopy in 4 cases	Any instrumentation	91.7
Palminteri et al 2007[72]	7	21	SIS	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk and 12 mo or if Qmax <14 mL/s Urethroscopy 3 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	100
Singh et al 2008[106]	25	12	LM	Uroflowmetry 3, 6, and 12 mo Urethrography 3 wk, 3, 6, and 12 mo	Qmax <15 mL/s, abnormal urethrogram or urethroscopy, any intervention	80
Pisipati et al 2009[47]	45	42	BM	Uroflowmetry 3 and 6 mo, every 6 mo thereafter Urethrography 3 wk Urethroscopy 3 mo	Qmax <15 mL/s	87

Abbreviations as in Tables 2 and 3.

Table 9. Outcomes of combined ventral plus dorsal onlay bulbar urethroplasty

Authors	No. Treated	Follow-up (mo)	Type of Graft	Follow-up Method	Definition of Failure	Success Rate (%)
Palminteri et al 2007[72]	5	21	SIS	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk and 12 mo or if Qmax <14 mL/s Urethroscopy 3 and 12 mo	Abnormal voiding Any instrumentation Evidence of stricture on urethrography	100
Palminteri et al 2008[48]	48	22	BM	Uroflowmetry 4, 8, and 12 mo, then annually Urethrography 3 wk IF Qmax <14 mL/s then urethrography and urethroscopy	Abnormal voiding Need for instrumentation	89.6

Abbreviations as in Table 2.

this context, direct visualization is likely to provide the best information relating to the stricture and the urethra in general.[46]

A crucial parameter is patient satisfaction, which can be assessed by a patient-reported outcome measure. Although this will not give an indication of surgical healing or allow for earlier identification of complications, it is designed to give a complete picture of patient improvement and satisfaction. Recently, a urethral surgery patient-reported outcome measure has been validated in English[53] and Italian.[54] However, aspects such as donor site morbidity have not been included in the assessment.

RECOMMENDATIONS

1. The first operation is likely to be the most successful, and preference should be given to the simplest technique that is likely to be most effective, avoiding augmentation urethral reconstruction if possible (level 3; A).
2. If augmentation (substitution) urethral reconstruction is being considered, an onlay flap for strictures in the penile urethra can also be considered (level 3; B).
3. In most cases, grafts are preferred over flaps for augmentation urethral reconstruction, particularly in the bulbar urethra, because there is a greater morbidity with the use of flaps compared with grafts, and they have similar efficacy (level 2; B).
4. One-stage penile augmentation (substitution) urethral reconstruction is less successful than a 2-stage procedure, except in carefully selected groups (level 3; B).
5. There is no significant difference in outcome between a ventral, lateral, dorsal, or combined approach to augmentation (substitution) urethral reconstruction (level 2; A).
6. Tube substitution procedures should be avoided (level 3-4; A).
7. Scrotal skin should be avoided where possible because of the high associated morbidity (level 3; A).
8. Oral mucosa is the most versatile augmentation (substitution) material (level 3; A).
9. Oral mucosa is currently considered the substitution material of choice for reconstruction of stricture secondary to lichen sclerosus (level 3; A).
10. Neither bladder nor colonic mucosa is recommended for use as primary alternatives for lengthy

augmentation in cases of lichen sclerosus, as they require a more invasive harvesting approach (level 3; C).

11. There is no evidence that transection of the corpus spongiosum during a primary augmentation (substitution) procedure leads to a worse outcome (level 3; B).
12. Patient-reported outcome measures for evaluating the results of urethral surgery require further development for the future (level 4; A).
13. Objective assessment with urethrography or endoscopy is recommended to determine the success rate of surgery in terms of stricture recurrence (level 4; A).
14. Any technique that requires the ingrowth of endogenous epithelial and fibroblast cells using acellular matrix is unlikely to be applicable to an extensive stricture with a poorly vascularized graft bed. The direction for tissue engineering remains investigational and should not be used outside an ethics committee—approved research trial. Future research should be focus on the development of cell-seeded matrices that can be used for long strictures with extensive spongiofibrosis or a poorly vascularized graft bed (level 3; B).

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EAU Guidelines on Urethral Strictures

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1. INTRODUCTION

1.1 Aims and scope

The European Association of Urology (EAU) Urethral Strictures Guidelines aim to provide a comprehensive overview of urethral strictures in male, female and transgender patients. The Panel is aware of the geographical variations in healthcare provision.

It must be emphasised that guidelines present the best evidence available to the experts; however, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Urethral Strictures Guidelines panel consists of an international multidisciplinary group of clinicians with particular expertise in this area. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/urethral-strictures/.

1.3 Available publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/urethral-strictures/. A list of supplementary tables supporting this text can also be found online, along with an appendix of abbreviations specific to this text: https://uroweb.org/guideline/urethral-strictures/?type=appendices-publications.

1.4 Publication history

This document is a new Guideline first published in 2021. Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2. METHODOLOGY

2.1 Methods

For the 2021 Urethral Strictures Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2008 and 2019 and restricted to English language publications. The panel defined by consensus inclusion and exclusion criteria for each topic before the scope search. Detailed search strategies are available online: https://uroweb.org/guideline/urethral-strictures/.

Relevant literature prior to the 2008 scope search cut-off was allowed if it was estimated to be of exceptional value by the panel. Relevant literature after the 2019 scope search cut-off was searched for by the panel member dedicated to a specific topic.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternatives.

The Panel wants to highlight that "success" in urethral stricture treatment is poorly defined and subjective. "Success" is usually defined as urethral patency, either subjective by the absence of voiding symptoms or objective by imaging or urethral calibration. Despite urethral patency, the patient themselves might not consider the treatment as successful because of functional consequences (e.g., post-void dribbling, erectile/ejaculatory dysfunction, altered genital appearance). In this Guideline, the Panel agreed to avoid the term "success". Instead, the term "patency rate" or "stricture recurrence rate" will be used to clarify that only stricture recurrence was taken into consideration (as assessed by the authors).

The Panel would like to stress that patency after urethral surgery is dependent on the general principles of wound healing. These principles have stood the test of time and need to be respected at any time [5]. Some examples:

- An anastomosis should be made between healthy urethral ends and without any tension.
- A graft requires a well-vascularised graft bed with a close contact between the graft and graft bed to promote imbibition and inosculation.
- If the full circumference of the urethral mucosa is destroyed, spontaneous regeneration will not take place.
- Contraction and fibrosis in a wound stops only after it is covered by its epithelium.

The Panel conducted two systematic reviews to support guideline recommendations:

- What is the role of one-stage oral mucosa urethroplasty in the management of strictures due to male Lichen Sclerosus (LS)?
- A systematic review of various free graft urethroplasty (FGU) techniques for the management of bulbar urethral strictures.
- The results of these reviews are included in the 2021 Urethral stricture guidelines.

2.2 Review

The Urethral Strictures Guidelines were peer reviewed prior to initial publication in 2021.

2.3 Future goals

The results of the two systematic reviews will be submitted for publication in European Urology (Focus). Summary papers of the guidelines will be drafted and submitted for publication to European Urology (Focus). These papers will include the following topics:

- Diagnosis, peri-operative care and follow-up of urethral strictures
- Treatment of strictures in females and transgender patients
- Treatment of male strictures

An update of the strictures guideline will be conducted when deemed necessary, but at latest after five years. Further systematic reviews will be conducted after approval of the Guidelines Office.

3. DEFINITION, EPIDEMIOLOGY, AETIOLOGY AND PREVENTION

3.1 Definitions

In males, a urethral stricture refers to a narrowed segment of the anterior urethra due to a process of fibrosis and cicatrisation of the urethral mucosa and surrounding spongiosus tissue ("spongiofibrosis") [6, 7]. In the male posterior urethra, there is no spongiosus tissue and at this location the terms stenosis is preferred [6, 7]. The definition of meatal stenosis is generally accepted as a short distal narrowing at the meatus, without involvement of the fossa navicularis [7].

There is no universal definition for what constitutes a female urethral stricture (FUS). Female urethral stricture is defined by most authors as a 'fixed anatomical narrowing' causing reduced urethral calibre [8, 9]. This reduced

urethral calibre is variously defined as between < 10 Fr to < 20 Fr [10, 11] with the majority of series defining < 14 Fr as diagnostic, compared with a 'normal' urethral calibre of 18-30 Fr.

In transgender patients, the term stricture is also used to define a narrowing of the reconstructed urethra despite the absence of surrounding spongious tissue.

3.2 Epidemiology

In males, a sharp increase in incidence is observed after the age of 55 years, with a mean age of 45.1 [12, 13]. Overall, the incidence is estimated to be 229-627 per 100,000 males [12]. The anterior urethra is most frequently affected (92.2%), in particular the bulbar urethra (46.9%) [13].

In females, 2-29% of patients presenting with refractory lower urinary tract symptoms (LUTS) have bladder outflow obstruction (BOO) [14-17] of whom 4-20% will have a urethral stricture [16-18]. True FUS therefore occurs in 0.08-5.4% of women with refractory LUTS. There is a markedly increased incidence in women over 64 years old [19].

In children, most strictures are traumatic: related to iatrogenic causes in 27.8-48% and external trauma in 34-72% [20]. Less frequent congenital (13%), inflammatory (4%), or post-infectious strictures (1%) are seen. The bulbar urethra is the most frequently affected part of the urethra [20].

After hypospadias repair, meatal stenosis and urethral strictures are reported in 1.3-20% of cases, depending on the severity of the hypospadias and the technique used [21]. There is a significantly higher incidence of this type of strictures in well-resourced countries due to a higher surgical repair rate [22].

Up to 18% of all urethral strictures have been reported to involve the meatus or fossa navicularis usually due to failed hypospadias repair (FHR), lichen sclerosus (LS), trauma/instrumentation or idiopathic causes [23-26].

Meatal stenosis post-circumcision has been reported in less than 0.2% of children undergoing circumcision as neonates [12].

In female-to-male (FtM) transgender patients ("trans men"), approximately 51% will suffer a urethral stricture [27]. Strictures almost exclusively arise at the neomeatus in male-to-female (MtF) transgender patients ("trans women") and occur in 14.4% of cases [28].

3.3 Aetiology and prevention

Stricture aetiology differs significantly throughout different regions in the world, due to differences in healthcare quality and environmental and practice patterns [22]. Regardless of geography, urethral stricture disease adversely impacts physical health and quality of life (QoL) [29, 30], notwithstanding costs associated with the treatment of primary and recurrent disease [31, 32]. The rationale for preventing urethral strictures is to avoid morbidity to the individual and costs to society. Prevention of urethral strictures encompasses reducing the causes of stricture (e.g., infection, trauma, iatrogenic injury) and where this is not possible mitigating the risk.

3.3.1 Aetiology and prevention in males

a. Sexually transmitted infection

Urethritis due to sexually transmitted infection (STI), in particular gonorrhoea, was previously a major cause of urethral strictures in well-resourced countries accounting for 40% of all cases [33]. The wide-scale promotion of safe sexual practices and easier access to sexual health services, resulting in timely treatment with antimicrobials, is thought to have led to the considerable reduction in the problem [33]. Infective urethritis now accounts for 0.9% to 3.7% of cases in contemporary series from well-resourced countries [33, 34] but continues to be the major cause of strictures in low-resourced countries comprising 41.6% of all strictures [35].

Summary of evidence	LE
Access to investigation and treatment of STI is associated with a temporal decline in the incidence of infective urethritis related strictures.	3

Recommendation	Strength rating
Advise safe sexual practices, recognise symptoms of sexually transmitted infection and provide access to prompt investigation and treatment for men with urethritis.	Strong

b. Inflammation

Lichen sclerosus involves the urethra in 20% of cases [36] and is the most common cause of panurethral stricture disease (48.6%) [13]. The aetiology of LS has not been fully elucidated but is thought to be have an autoimmune origin [37]. Lichen sclerosus may be associated with environmental factors and non-autoimmune comorbidities. Uncircumcised men are far more likely to suffer LS than circumcised men [age-adjusted odds ratio (OR) of 53.55; (95% confidence interval (CI): 7.24-395.88] [38]. Lichen sclerosus is also associated with higher mean body mass index (BMI), diabetes mellitus, coronary artery disease, tobacco usage, hyperlipidaemia, and hypertension [39-41].

c. External urethral trauma

External trauma to the urethra is the second most common cause of stricture formation in adults [33]. The urethra is vulnerable to trauma during certain activities including sport, driving a vehicle, sexual intercourse and during combat. The bulbar urethra is the site most frequently affected by blunt trauma [7], usually as a result of straddle injuries or kicks to the perineum. Penile fracture is associated with a urethral injury in 15% of cases [42]. Motor vehicle accidents are the main cause of blunt injuries to the posterior urethra associated with pelvic fractures [43]. Penetrating injuries of the urethra are uncommon during non-combat situations [44].

d. Iatrogenic urethral injury

Iatrogenic injury to the urethra is one of the most common causes of strictures in well-resourced countries [13, 33] accounting for 32% to 79% of all strictures [33, 45]. In children, specifically iatrogenic causes were identified in 6.7-25% of cases [46]. Preventing iatrogenic urethral injury represents the main way in which urologists can prevent urethral strictures. Iatrogenic urethral injury most commonly results from urethral instrumentation (e.g., catheterisation, cystoscopy), surgery for benign prostatic obstruction (BPO), surgery for prostate cancer, or radiotherapy [34].

d.1 Urethral catheterisation

Urethral strictures are a recognised complication of urethral catheterisation accounting for 11.2-16.3% of all strictures [13, 33]. In a meta-analysis by Hollingsworth and colleagues the pooled percentage of patients who developed urethral stricture or erosion after short-term catheterisation (< 3 weeks) in higher quality studies was 3.4% (CI: 1.0% to 7.0%) [47]. In studies comprised mainly of men with spinal cord injury with indwelling urethral catheters, the pooled estimate of urethral stricture or erosion was 8.7% (CI: 0.0%-18.7%) [47].

Urethral strictures following catheterisation may arise as a consequence of injury during attempts at insertion or during the period a catheter remains *in situ*. During insertion the urethra may be injured by formation of a false passage by the catheter tip (29.7%) or inflation of the balloon within its lumen (70.3%) [48]. The rate of urethral injuries due to catheterisation was found to be 3.2 per 1,000 inpatients [49]. A six-month prospective multicentre study found that of 37 patients with catheter-related urethral trauma referred to urologists, 24% continued to perform intermittent self-dilatation (ISD) once weekly and 11% required at least one urethral dilation for urethral stricture [50]. In another follow-up study of 37 patients with catheter-related urethral trauma, 78% of patients developed urethral stricture [48]. The most common locations of trauma are the bulbar and posterior urethra [51].

Catheter-related trauma can be prevented through several measures [52]. Studies have indicated around 25% of all indwelling catheterisations in hospitals were unnecessary and inappropriate [53, 54]. Implementation of guidelines [55, 56] and specific criteria [57] have been shown to reduce catheterisation rates. Several studies have identified deficits' in the knowledge of urethral catheterisation amongst resident doctors [58, 59]. This is postulated to be a factor in catheter-related trauma [59]. A targeted training program on urethral catheterisation for nursing staff was shown to be effective in reducing iatrogenic urethral injuries in a prospective single institution study [49].

In addition to guidance and education, another approach to safer catheterisation is modification of the standard Foley catheter. A novel catheter balloon pressure valve safety system was developed to prevent balloon inflation injury though this has not been assessed in comparative studies [60, 61]. Bugeja *et al*. studied the use of urethral catheterisation device (UCD) incorporating a guidewire, in prospective observational cohort study that included 174 patients. The incidence of adverse events was 7% with standard Foley catheterisation vs. 0% with the UCD (no statistical analysis was performed) [62]. A further prospective observational study found that Seldinger technique catheterisation could be used successfully by non-urology trained doctors [63]. These technologies need to be further assessed in prospective randomised studies incorporating cost-benefit analysis.

Catheter diameter is suggested as a possible contributing factor to urethral stricture due to a pressure effect on the urethral wall [64]. Decreasing the catheter size from 22 Fr to 18 Fr significantly decreased the risk of fossa navicularis strictures (6.9% vs. 0.9%, p=0.02) after radical prostatectomy (RP) [65]. Catheter material may also have an influence on the occurrence of stricture. In the 1970s/80s several comparative studies in patients undergoing cardiac surgery demonstrated that non-coated latex catheters were associated with a greater incidence of urethritis and more stricture formation than silicone catheters [66-68]. Other studies showed no difference [69-71]. Modern latex catheters have polymeric coatings [72] due to the concern with regards to stricture alongside the risk of hypersensitivity and the demonstrable *in vitro* toxicity of latex. Prolonged urethral catheterisation has also been implicated in the aetiology of stricture (e.g., poly-trauma, burns patients) [45].

Summary of evidence	**LE**
A significant proportion of catheter insertions in hospitalised patients were considered unnecessary.	2b
Education programs can reduce the incidence of catheter-related urethral injury.	2a
Larger catheter size was associated with a greater risk of navicular fossa strictures.	3
Non-coated latex catheters are associated with a greater degree of urethritis and possibly a greater risk of urethral strictures than non-latex catheters or coated latex catheters.	1a

Recommendations	**Strength rating**
Avoid unnecessary urethral catheterisation.	Strong
Implement training programmes for physicians and nurses performing urinary catheterisation.	Strong
Do not use catheters larger than 18 Fr if urinary drainage only is the purpose.	Weak
Avoid using non-coated latex catheters.	Strong

d.2 Transurethral prostate surgery

Urethral stricture following transurethral prostate surgery occurs in between 4.5% to 13% of patients [73], whereas bladder neck stenosis (BNS) occurs in between 0.3% to 9.7% [74]. Transurethral surgery is the most common cause of iatrogenic urethral stricture accounting for 41% of all causes [45]. The most common location for urethral stricture is the bulbomembranous urethra, followed by the fossa navicularis and penile urethra [75, 76]. Postulated mechanisms include friction at the penoscrotal junction, lack of adequate lubrication, repetitive 'in and out' movement of the resectoscope, breach of mucosal integrity leading to urine extravasation and monopolar current leak due to inadequate resectoscope insulation [77]. Bladder neck stenosis may be related to excessive and/or circumferential resection and the use of relatively large resection loops which may generate excessive heat in small intraurethral adenomas leading to scarring [74, 78]. Stenoses of the posterior urethra may also be due to a prolonged period of post-operative inability to void [79].

d.2.1 Risk factors for development of urethral stricture and bladder neck stenosis

Several risk factors for the development of urethral stricture and BNS following transurethral prostate surgery have been identified. Both prostatic inflammation (OR: 4.31) and operative time > 60 min (OR: 4.27) were found to be independent predictors of stricture after monopolar transurethral resection of prostate (TURP) [80]. In terms of bipolar TURP, slower resection rate (OR: 0.003), intraoperative urethral mucosa rupture (OR: 2.44) and post-operative infection were shown to be independent predictors (OR: 1.49) [81, 82]. A larger-calibre endoscopic sheath (26 Fr vs. 24 Fr) was associated with a greater risk of bulbar urethral stricture following monopolar TURP (11.4% vs. 2.9%, p=0.018) [83]. Room temperature irrigation solution was associated with a greater risk of urethral stricture following combined transurethral resection and vaporisation of the prostate compared to body temperature irrigation (21.3% vs. 6.3%, p=0.002) [84].

Bladder neck stenosis is known to occur more frequently in smaller prostate glands after both monopolar and bipolar TURP [85, 86]. Lee *et al*. found that adenoma weight was an independent risk factor for BNS after monopolar TURP [86]. Meanwhile, Tao *et al*. found total prostate volume (< 46.2 g) (OR: 1.5), but not resected gland weight, to be an independent risk factor [81].

d.2.2 Incidence of urethral stricture and bladder neck stenosis with different energy modalities

A systematic review and meta-analysis by Cornu *et al*. showed no significant differences in urethral stricture and BNS rates by energy modality (monopolar, bipolar, holmium laser enucleation, photoselective vaporisation) [73]. In another meta-analysis assessing outcomes of thulium (Tm:Yag) laser and bipolar TURP, no difference in urethral stricture and BNS rates were found between the two modalities [87]. The presence of potentially confounding factors such as endoscopic sheath diameter, energy setting used, procedural length and length of follow-up make inter-study comparisons between energy modalities problematic. Overall, there is no strong

evidence that any single modality is associated with a clinically significant higher incidence of urethral stricture and BNS than others. Selection of modality should be based on a comprehensive evaluation of clinical safety and efficacy. A summary of incidences of urethral stricture and BNS with different modalities is presented in Table 3.1.

Table 3.1: Incidence of urethral stricture and bladder neck stenosis by transurethral modality (adapted from Chen *et al*. 2016 [74]**)**

Modality	Urethral stricture	Bladder neck stenosis
Transurethral resection of prostate (TURP) - monopolar and bipolar	1.7 to 11.7%	2.4 to 9.7%
Holmium enucleation of the prostate (HoLEP)	1.4 to 4.4%	0 to 5.4%
Photo-selective vaporisation (PVP)	0 to 4.4%	1.4 to 3.6%

d.2.3 Interventions to prevent urethral stricture and bladder neck stenosis

Sciarra and colleagues conducted a single-blind randomised control trial (RCT; n=96) to assess the use of rofecoxib for stricture prevention following TURP. At twelve months follow-up a urethral stricture was found in 17% and 0% of cases in the placebo and rofecoxib groups, respectively (p=0.0039) [88]. Chung *et al*. conducted a single blinded RCT (n=180) evaluating the effect of urethral instillation of hyaluronic acid (HA) and carboxymethylcellulose (CMC). Urethral stricture on urethrography was diagnosed in 1.25% and 8.64% of patients in the treatment and placebo group respectively (p=0.031). Further randomised studies are needed to confirm these findings and the safety of the pharmacological interventions.

Several earlier comparative studies assessed whether routine preliminary urethrotomy with an Otis urethrotome prevented the incidence of stricture following TURP [89-92]. Only one of these reported at least twelve month follow-up, finding no significant difference in stricture rate in patients undergoing TURP alone vs. Otis urethrotomy followed by TURP (21% vs. 14%) [93]. Others have suggested performing internal urethrotomy where there is pre-existent meatal or urethral strictures [94].

Adjunctive transurethral incision of the prostate (TUIP) at the end of TURP to reduce the rates of BNS was studied by Lee and colleagues [86]. A total of 1,135 patients of whom 667 underwent TURP and 468 underwent TURP plus TUIP were retrospectively studied. At median follow-up of 38 months, the incidence of BNS was 12.3% for the TURP group vs. 6.0% for the TURP plus TUIP group ($p < 0.001$). In glands < 30 g, the incidence of BNS in the TURP vs. the TURP plus TUIP group was 19.3% and 7.7%, respectively ($p < 0.05$). The clinical efficacy and safety of additional surgical interventions to prevent urethral stricture and BNS need to be confirmed in larger prospective RCTs before their use can be recommended.

Summary of evidence	LE
An RCT with more than twelve months follow-up failed to demonstrate a significant reduction in stricture rate using routine urethrotomy prior to TURP.	1b

Recommendation	Strength rating
Do not routinely perform urethrotomy when there is no pre-existent urethral stricture.	Strong

d.3 Radical prostatectomy

Radical prostatectomy has been associated with vesico-urethral anastomosis stricture (VUAS) in between 0.5% to 30% of patients [74], though most modern series report it in the range of 1% to 3% [95]. The risk of stricture formation after salvage RP is notably higher (22-40%) [96]. Most VUAS develop within the first two years [96, 97]. A 2012 meta-analysis by Tewari *et al*. showed no significant difference in VUAS between open-, laparoscopic and robotic RP [98]. In contrast, a more recent analysis of a national cohort in the UK found that VUAS rate after robotic RP was 3.3%, which is significantly lower than following laparoscopic (5.7%) or open RP (6.9%) [99]. These findings are consistent with an earlier similar study conducted in the USA [100]. The difference in VUAS rates may be explained by the level of experience and surgical volume of surgeons [101]. The cohort studies represent “real world” data, including all levels of surgical experience and surgical volumes whereas the meta-analysis is based on clinical studies. Thus the better outcomes for robotic RP in the population studies may be related to the shorter learning curve [102].

d.3.1 Risk factors for development of vesicourethral anastomosis strictures

These include higher grade cancer, more advanced stage, higher prostate volume, coronary artery disease, obesity, hypertension, diabetes mellitus, previous bladder outlet surgery and older age [95, 103, 104]. Surgical factors include use of non-nerve-sparing technique, anastomotic urine leak, increased operative time and increased estimated blood loss [95, 103, 104]. In addition, low-volume surgeons (< 40/year) were shown to have higher VUAS rates, 27.7%, compared to high-volume surgeons (> 40/year), 22% [105].

d.3.2 Interventions to prevent vesicourethral anastomosis strictures

Srougi *et al*. studied bladder neck mucosal eversion in a prospective RCT of 95 patients. No significant difference was found in rates of VUAS at twelve months follow-up [106]. A meta-analysis by Kowelewski *et al*. comparing interrupted vs. continuous vesico-urethral anastomosis suturing found no difference in VUAS rates [107]. Another systematic review by Bai *et al*. compared barbed sutures to conventional sutures, although heterogeneity across studies precluded meta-analysis, no patients developed VUAS with either approach [108].

d.4 Prostate radiation and ablative treatments

Urethral strictures occur in 1.5% of patients undergoing external beam radiation therapy (EBRT), 1.9% having brachytherapy (BT) and 4.9% who receive combination EBRT-BT at around four years follow-up [109]. These strictures typically occur in the bulbomembranous urethra [110]. As opposed to RP, stricture incidence after irradiation increases with time [96, 109]. For the ablative treatments, the stricture incidence after cryotherapy and high-internsity focused ultrasound (HIFU) is 1.1-3.3% and 1-31%, respectively [96]. The use of these treatment modalities in the salvage setting is associated with increased risk of stricture formation: 3-10% after salvage EBRT, 5-12% after salvage cryotherapy and 15-30% after salvage HIFU [96]. Due to the increasing utilisation of prostate irradiation (EBRT, BT) and ablative treatments (cryotherapy, HIFU), an increasing number of respectively radiation-induced and ablative treatment-induced strictures are expected [111].

d.4.1 Risk factors for the development of radiation strictures

Awad *et al*., performed a multivariate meta-regression analysis including 46 studies, finding combining ERBT + BT and length of follow-up to be significant predictors of urethral stricture following prostate radiation [109]. Factors not shown to predict urethral stricture included biochemical equivalent dose, age and androgen deprivation therapy [109]. Previous TURP was not included in the analysis, but has been found to be independent predictor of stricture (HR: 2.81) in a previous multivariate analysis from a single institution [112] as has PSA level < 10 ng/ml (HR: 0.47) [113].

d.4.2 Interventions to prevent radiation induced urethral strictures

Delaying adjuvant or salvage EBRT by nine months is associated with lower rates of urethral stricture (HR 0.6) [114]. This has to be balanced with risk of delaying treatment in terms of cancer control [74]. In BT, it has been reported that downward movement of needle applicators occurs between fractions [115]. This may explain why strictures occur below the prostatic apex [113] in the so called “hot spot” [116]. Several measures taken together are thought to have contributed to a reduction in urethral stricture formation with BT including reduction of dose to the “hot spot”, more careful needle placement, avoiding midline insertion and the introduction of plastic needles rather than steel [109].

e. Failed hypospadias repair.

Although urethral strictures after hypospadias repair are sometimes considered as iatrogenic [33], they are a very specific subtype and should be considered as a separate entity. The main reasons for this are the absence of spongiosus tissue at different levels within the penile urethral segment, and the lack of high-quality local tissues for urethral reconstruction [117].

f. Congenital

The diagnosis of a congenital urethral stricture can only be made in the absence of other possible aetiology, such as iatrogenic, inflammatory and traumatic causes [20]. Congenital strictures are thought to be consequent to incomplete or incorrect fusion of the urethra formed from the urogenital sinus with the urethra formed following closure of the urethral folds. They typically have a deep bulbar location and are usually short. In general, congenital strictures are diagnosed at a young age (Moorman’s ring or Cobb’s collar).

g. Idiopathic

Idiopathic strictures are seen in 34% of all penile strictures and in 63% of all bulbar strictures [118]. Unrecognised trauma is thought to be a possible aetiology of idiopathic urethral strictures [22].

*3.3.2 **Aetiology in females***

The cause of FUS was idiopathic in 48.5%, iatrogenic in 24.1%, resulting from prior urethral dilations, difficult/traumatic catheterisation with subsequent fibrosis, urethral surgeries (mainly diverticulum surgery, fistula repair and anti-incontinence procedures) and trauma (mainly following pelvic fracture) in 16.4% [119-131]. Radiation therapy and infections are rare causes of FUS [132]. The commonest segment of urethra affected is the mid- or mid-to-distal (58%). Panurethral strictures are rare (4%) [10, 119, 121, 122, 124-126, 131, 133].

For further information see online supplementary Tables S3.1 and S3.2.

4. CLASSIFICATIONS

4.1 According to stricture location

Classification according to stricture location is important as this will affect further management.

*4.1.1 **In males***

4.1.1.1 Anterior urethra

The anterior urethra runs from the meatus to the urogenital diaphragm and is surrounded in its entire length by the corpus spongiosum [6, 134]. Further subdivision is made in three different areas (from distal to proximal) [7]:

Meatal strictures: these strictures are located at the external urethral meatus and may extend into the fossa navicularis of the glans.

Penile strictures: these are located in the segment between the fossa navicularis and the bulbar urethra. Externally, the penile urethra begins approximately at the balanopreputial sulcus and continues to the penoscrotal junction. The whole penile urethral segment lies in the groove ventral to corpora cavernosa and is surrounded by a thin layer of corpus spongiosum.

Bulbar strictures: the bulbar urethra starts at the penoscrotal junction and is surrounded by the bulbospongious muscle. It ends in the membranous urethra proximally at the level of the urogenital diaphragm. The bulbar urethra can be subdivided into a proximal and distal part. The proximal bulbar urethra is defined as the segment within 5 cm of the membranous urethra; the urethra lies eccentrically in this part with abundant ventral spongious tissue. The distal bulbar urethra is defined as the adjoining segment extending to the penoscrotal junction [135]. Strictures extending towards the membranous urethra are termed bulbomembranous strictures (BMS).

Penobulbar strictures: these extend from the penile urethra into the bulbar segment, compromising long segments of urethra.

The difference between penobulbar strictures and multifocal strictures should be noted. The latter are defined by two or more narrowed segments, either in the same or different subdivision of the urethra but preserving healthy lengths of urethra between them (e.g., iatrogenic strictures related to TUR procedures which typically affect the fossa navicularis and the penoscrotal junction with healthy urethra in between).

4.1.1.2 Posterior urethra

The posterior urethra is approximately 5 cm long, with three different segments [7]:

- The membranous urethra is the area of the urethra traversing the urogenital diaphragm, between the proximal bulbar and the distal verumontanum.
- The prostatic urethra runs through the prostatic gland, starting at the proximal membranous urethra and extending to the bladder neck.
- The bladder neck is surrounded by the internal urinary sphincter and is the junction between the prostatic urethra and the bladder. Stenosis (or contracture) of the bladder neck implies a prostate *in situ* (i.e., after TURP or simple prostatectomies). If the narrowing or obliteration appears at this level but after a RP, the correct term is VUAS [7].

4.1.2 *In females*

The female urethra is approximately 4 cm long and arbitrarily divided in an upper, mid and lower part [10, 119, 121, 122, 124-126, 131, 133].

4.2 According to stricture tightness

The definition of low- vs. high-grade strictures remains debatable [136-138]. A urethral plate less than 3 mm is considered a high-grade or tight stricture [139]. It has been demonstrated with a normally functioning bladder that flow rate will not diminish until the urethral lumen has a diameter below 10 Fr [137].

Table 4.1, presents a suggested classification for male patients with a normal functioning bladder. This classification was developed by the EAU Urethral Stricture Panel based on a consensus process.

Table 4.1: EAU classification according to the degree of urethral narrowing

Category	Description	Urethral lumen (French [Fr])	Degree
0	Normal urethra on imaging	-	-
1	Subclinical strictures	Urethral narrowing but ≥ 16 Fr	Low
2	Low grade strictures	11-15 Fr	
3	High grade or flow significant strictures	4-10 Fr	High
4	Nearly obliterative strictures	1-3 Fr	
5	Obliterative strictures	No urethral lumen (0 Fr)	

4.3 Strictures in transgender men and woman

4.3.1 *Trans women*

After male-to-female gender confirming surgery, the penile urethra has been resected. Meatal strictures are defined as strictures occurring at the neomeatus, which is formed between the junction of the distal bulbar urethra and the neovagina. The other segments (bulbar and posterior) are the same as in a biological man.

4.3.2 *Trans men*

Four different areas can be identified in the urethra after female-to-male gender confirming surgeries [140]:

- The native urethra is the female urethral segment which remains preserved during surgery. It goes from the bladder neck to the original external meatus.
- The fixed part (pars fixa) or perineal urethra follows the native urethra, starting at the original external meatus. This segment is reconstructed using local tissues, typically vestibular mucosa or anterior vaginal mucosa. Its course is similar to the bulbar urethral segment in males, but without being covered by spongiosal tissue.
- The anastomotic part is the area where the pars fixa joins the neophallus.
- The phallic urethra is the segment located within the neophallus or the metoidioplasty and is usually made of skin tube. Its course is similar to the penile urethra in males, but without being covered by spongiosal tissue.

5. DIAGNOSTIC EVALUATION

A comprehensive diagnostic evaluation of urethral stricture disease encompasses clinical history and examination, urinalysis (+/- culture), uroflowmetry and post-void residual (PVR) assessment, radiography and endoscopy.

5.1 Patient history

The purpose of history taking is to assess symptoms including severity and duration, possible aetiology, prior treatments, complications, associated problems, and patient factors that may impact upon surgical outcome.

The clinical presentation of urethral stricture disease is varied. In a retrospective analysis of 611 patients with an endoscopically confirmed diagnosis of urethral stricture, LUTS were the most common presentation (54.3%) followed by acute urinary retention (22.3%), urinary tract infection (UTI) (6.1%) and difficult catheterisation (4.8%) [141]. In a retrospective study of 214 patients who underwent anterior urethroplasty, weak stream was

reported as the most common individual LUTS (49%) followed by incomplete emptying (27%) and urinary frequency (20%) [142]. A further retrospective series of 614 patients undergoing anterior urethroplasty found post-void dribble to be present in 73% [143].

Genitourinary pain is a common feature, affecting 22.9-71% [29, 141]. Pain may be felt in the bladder and/or urethra, is associated with more severe LUTS, is more likely to be felt by younger men and resolves in most following reconstruction [29]. Other complaints include spraying (9%), visible haematuria (3.1-5%), urethral abscess/necrotising fasciitis (2.3%), urgency (14%) and incontinence (1-4%) [141, 142].

To establish aetiology, an enquiry about a history of pelvic, genital or perineal trauma, prior instrumentation, prior surgeries, irradiation or focal therapies and urethritis should be made. It is important to document prior surgical approaches and date of the most recent intervention (e.g., dilatation) as this may impact upon the timing of radiological evaluation or surgical treatment.

Problems of sexual function are common in patients with urethral stricture disease [144, 145] and sexual function may be impacted upon by surgical intervention [146, 147], hence the status of erectile and ejaculatory function should be established and documented using validated tools.

The performance status of the patient should be determined as it may influence the choice of treatment (curative or palliative). A past medical history should assess for factors that may impact upon tissue healing including diabetes, immunosuppression and smoking. Oral tobacco use or the chewing of betel leaves may increase the risk of morbidity at the harvest site or render oral mucosa too poor for use. Prior harvest of oral mucosa should be noted as alternative sources for tissue transfer may need to be considered [148] or alternative surgical approaches (e.g., perineal urethrostomy [PU]).

5.2 Physical examination

The abdomen should be examined for the presence of a palpable bladder. The location of any suprapubic tube should be noted to assess its potential utility for antegrade cystoscopy or the placement of a sound (to facilitate repair) [149]. Examination of the genitalia should note the presence of foreskin, the position and size of the meatus as well as any evidence of scarring suggestive of LS. Pre-operative biopsy to confirm LS may be performed if this alters management and is essential if malignancy is suspected [150].

The presence of penile or perineal fistulae should be noted. The urethra should be palpated to assess for induration suggestive of significant fibrosis. Rarely a mass may signify a urethral carcinoma. A rectal examination to assess for prostatic pathology, which may be the cause of urinary symptoms, should be undertaken. In patients with posterior urethral stenosis rectal adherence to the prostate and the mobility of the surrounding tissues should be assessed [151]. The oral cavity should be examined for the suitability of oral mucosa. Measurement of BMI will identify obese individuals who are at greater risk of leg compartment syndrome when placed in the lithotomy position for a prolonged time period [152]. Assessing hip mobility is important when considering an exaggerated lithotomy position as some patients may have limited hip flexion due to unresolved orthopaedic problems [149].

*5.2.1 **Further diagnostic evaluation***

5.2.1.1 Patient reported outcome measure (PROM)

The first validated urethral stricture surgery PROM (USS-PROM) was reported in 2011 [153]. It consists of six LUTS questions derived from the International Consultation on Incontinence Questionnaire Male LUTS (ICIQ-MLUTS) module, a LUTS-specific QoL question, the Peeling voiding chart and the EQ-5D to assess overall health-related QoL (HRQoL). The post-operative questionnaire contains an additional two questions to assess overall patient satisfaction. This PROM has been validated in several other languages (German, Spanish, Italian, Dutch, Turkish, Polish, Japanese) and is increasingly used in research studies as well as clinical practice. A further PROM is in development in North America but requires validation [154] (see section 11. Follow-up).

Summary of evidence	LE
A specific urethral stricture surgery patient reported outcome measure was found to have psychometric validity in the assessment of patient-derived benefit from surgical intervention for urethral stricture disease.	2a
Sexual dysfunction is prevalent in patients with urethral strictures and sexual function can be affected by surgical management of urethral stricture.	3

Recommendations	Strength rating
Use a validated patient reported outcome measure (PROM) to assess symptom severity and impact upon quality of life in men undergoing surgery for urethral stricture disease.	Strong
Use a validated tool to assess sexual function in men undergoing surgery for urethral stricture disease.	Strong

5.2.1.2 Urinalysis and urine culture

Urinalysis is an essential component of the work up of patients with LUTS. If infection is suggested, urine culture should be performed to confirm the diagnosis and identify the causative organism and sensitivity to antibiotics. Bacteriuria should be treated prior to surgical intervention to prevent peri-operative sepsis [155] (see section 10. Peri-operative care).

5.2.1.3 Uroflowmetry and post-void residual estimation

A reduced maximum flow rate with a prolonged plateau is characteristic of the constrictive obstruction caused by urethral stricture. However, interpretation of flow patterns is subjective and is not considered a reliable screening tool for the detection of stricture [156]. To overcome this, a statistical model based on uroflowmetry parameters was developed and was found to predict urethral stricture with a sensitivity of 80–81% and a specificity of 77–78% [156]. Uroflowmetry is usually combined with ultrasound (US) estimation of PVR to identify patients with urinary retention who may require emergent bladder drainage. Uroflowmetry parameters can also be used for monitoring patients and in the assessment of treatment response (see section 11. Follow-up).

Urodynamic studies are not indicated in the vast majority of patients with urethral stricture disease. In patients with suspected bladder dysfunction (e.g., severe storage LUTS, history of irradiation or neurological disease), an assessment of bladder function may help surgical decision making and patient counselling. Similarly, when there is concern that flow impairment or increased PVR are due to detrusor underactivity or an acontractile detrusor, a urodynamic study may help predict the likelihood that the patient would need to perform intermittent self-catheterisation (ISC) post-operatively. The only urodynamic parameter found to distinguish a diagnosis of urethral stricture from BPO is urethral closure pressure which is lower in the former due to the constrictive nature of the obstruction (22.07 vs. 28.4 cm H_2O, p=0.0039, r=0.61, BPO vs. stricture) [157].

Summary of evidence	LE
Uroflowmetry pattern interpretation by use of a statistical model was found to be predictive of urethral stricture disease.	3

Recommendation	Strength rating
Perform uroflowmetry and estimation of post-void residual in patients with suspected urethral stricture disease.	Strong

5.2.1.4 Urethrography

Retrograde urethrography (RUG) has widely been used as the investigation of choice for evaluating the stricture presence, location, length and any associated anomalies (e.g., false passages, diverticula) [158].

The reported sensitivity and specificity of RUG in the diagnosis of strictures is 91% and 72%, respectively [159]. The positive predictive value (PPV) was 89% and the negative predictive value (NPV) was 76% [159]. Most reports suggest that RUG underestimates stricture length [160, 161]. Interpretation of RUG findings by urologists were found to be more accurate at predicting urethral stricture location and length as compared to evaluation by an independent physician [162].

Limitations of RUG include difficulty assessing very distal strictures and assessing the proximal extent of strictures which are too narrow to permit passage of adequate contrast. Combining a RUG with voiding cystourethrography (VCUG) can allow adequate visualisation of the urethra proximal to the stricture and a more accurate assessment of stricture length in (nearly) obliterative strictures, stenoses and gap in pelvic fracture urethral injury (PFUI) [163, 164]. In addition, urethrography provides only a two-dimensional assessment of stricture and the results may be affected by the amount of penile stretch [165], degree of pelvic rotation and patient body habitus [166]. Risks of the procedure include infection, discomfort [157], contrast reaction from intravasation of contrast [167] in addition to the risk of radiation exposure. Urethrographic clamp devices (Brodny, Knutson) are available and were found to be less painful than using the Foley catheter technique [172].

Summary of evidence	LE
Retrograde urethrography is a widely available and easy to perform method of diagnosing and assessing urethral stricture but may underestimate stricture length.	2a
Retrograde urethrography alone is not able to assess stricture length (or gap) in obliterative strictures or stenosis.	2a
Urethrographic clamp devices are less painful than using the Foley catheter technique.	2a

Recommendations	Strength rating
Perform retrograde urethrography to assess stricture location and length in men with urethral stricture disease being considered for reconstructive surgery.	Strong
Combine retrograde urethrography with voiding cystourethrography to assess (nearly)-obliterative strictures, stenoses and pelvic fracture urethral injuries.	Strong
Use clamp devices in preference to the Foley catheter technique for urethrographic evaluation to reduce pain.	Weak

5.2.1.5 Cystourethroscopy

Cystourethroscopy allows for accurate visual detection of a suspected stricture or can rule out a stricture as cause of obstructive voiding [159]. It can detect narrowing of the urethral lumen before changes in uroflowmetry and symptoms [138]. Cystourethroscopy can also assess the presence of LS or other pathology but cannot usually assess stricture length as the calibre of most cystoscopes is greater than most symptomatic strictures [168]. To overcome this, use of smaller calibre ureteroscopes (6.5 Fr and 4.5 Fr) has been reported [168]. This also allows an assessment of the bladder prior to surgery and may identify other pathology such as bladder stones. Cystourethroscopy is particularly helpful for diagnosing proximal BMS which may be missed on RUG [169].

Retrograde urethroscopy combined with antegrade cystoscopy via the suprapubic tract may be used to evaluate PFUI and plan the surgical approach. It allows an assessment of the length of the defect, the competence of the bladder neck, the involvement of the bladder neck in scarring in addition to identifying the presence of bony spicules or other abnormalities (e.g., fistulae, stones) [170]. Combined retrograde and antegrade cystoscopy was found to provide similar estimates of length of urethral defect in patients with PFUI as combined retrograde and antegrade cystourethrography, but was more likely to detect fistulae, false passages and calculi [170].

Summary of evidence	LE
Cystourethroscopy will reliably detect the presence of a urethral stricture.	3
Combined retrograde urethroscopy and antegrade cystoscopy is more accurate than retrograde and voiding cystourethrography at identifying associated abnormalities such as fistulae, false passages and calculi in patients with PFUI.	3

Recommendations	Strength rating
Perform cystourethroscopy as an adjunct to imaging if further information is required.	Weak
Combine retrograde urethroscopy and antegrade cystoscopy to evaluate pelvic fracture urethral injuries as an adjunct to imaging if further information is required.	Weak

5.2.1.6 Ultrasound

Ultrasound of the urethra or sonourethrography (SUG) provides a non-invasive three-dimensional assessment of anterior urethral stricture disease; including stricture location, length and the degree of associated spongiofibrosis [171].

Several studies have compared SUG to RUG and cystoscopic or intraoperative findings. Sonourethrograpy was found to be more accurate at diagnosing stricture presence compared to RUG [172, 173]. Sonourethrography was also found to more accurately estimate stricture length (94% correlation with intraoperative findings) than RUG (59% correlation with intraoperative findings) ($p < 0.001$) [161]. A further study showed similar findings and found that the closest correlation for stricture length at operation was for strictures in the penile urethra [160]. Intraoperative sonourethrogram findings have also been found to change the planned reconstructive approach (based on pre-operative retrograde urethrogram) in 19% of men undergoing anterior urethral reconstruction [166]. Sonourethrography incorporating real-time elastography

can provide a qualitative and quantitative assessment of spongiofibrosis [174, 175]. The clinical relevance of assessing the degree of spongiofibrosis pre-operatively remains to be established. Three-dimensional reconstruction of sonographic images is investigational at present [176].

The advantages of SUG are that it can be performed in the outpatient setting, provides information on the degree of spongiofibrosis and its relatively low cost [171]. Limitations of the technique include lower sensitivity for detection of strictures in the bulbar urethra, operator dependency, and the need for urethral distension requiring intraurethral anaesthesia. Sonourethrography requires specialised training in the use of US and is currently not in widespread usage.

Table 5.1: Diagnostic accuracy of sonourethrography compared to other modalities and surgical findings

Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Berne-Mestre *et al*. 2018 [172]	113	Anterior and posterior	RUG, VCUG, surgical findings	SUG more accurate than RUG ($p < 0.05$)	-	-
Ravikumar *et al*. 2014 [173]	40	Anterior and posterior	RUG, VCUG, surgical findings	Anterior: SUG 100% sensitivity, 100% specificity Posterior: SUG 75% sensitivity, 50% specificity.	-	-
Kalabhavi *et al*. 2018 [161]	30	Anterior	RUG, surgical findings	-	-	SUG more accurate than RUG (r_s=0.946, $p < 0.001$ vs. r_s=0.597, p=0.001)
Krukowski *et al*. 2018 [160]	66	Anterior	RUG, surgical findings	-	-	SUG more accurate than RUG (r_s=0.73, $p < 0.001$ vs. r_s=0.55, $p < 0.001$)

N = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

5.2.1.7 Magnetic resonance imaging

Magnetic resonance imaging (MRI) has been used to image PFUIs, posterior urethral stenoses and anterior urethral strictures.

Several studies have compared MRI urethrogram to RUG and intraoperative findings. Magnetic resonance imaging urethrogram was found to be as accurate as RUG at detecting stricture site in anterior urethral strictures [177]. In terms of stricture length both MRI urethrogram and RUG reliably correlated with intra-operative findings [177]. On the other hand, a further study of patients with anterior urethral strictures found MRI urethrogram stricture length to correlate more closely with surgical findings than RUG [178].

In a mixed group of anterior urethral strictures and posterior urethral stenoses, MRI urethrogram was as accurate (sensitivity = 100%, specificity = 91.7%) as combined RUG and sonourethrography (sensitivity = 100%, specificity = 91.7%) at diagnosing strictures [179]. There was no significant difference in the measurement of stricture length [179]. In a further study of patients with posterior urethral stenosis, MRI estimation of stenosis length correlated more closely with operative findings compared to RUG [180]. In patients with PFUI, MRI measurement of pubo-urethral stump angle (angle between long axis of pubis and line between the distal end of the proximal urethral stump and lower border of inferior pubic ramus) was predictive of an elaborated approach on multivariate analysis [181].

Magnetic resonance imaging was also found to be more accurate at diagnosing associated pathologies e.g., diverticula, tumours, fistulae and stones [179]. In cases of fistulation between the urinary tract and pubic symphysis after irradiation for prostate cancer, the fistula tract can be clearly demonstrated on MRI [182]. Other imaging modalities, including computed tomography (CT), may fail to identify the tract and the problem may be misdiagnosed as isolated osteomyelitis of the pubic bone leading to medical management with antibiotics rather than surgical excision [182].

The main advantage of MRI is greater anatomical detail, which is countered by the expense of the procedure and the greater complexity in interpreting images. The technique is not commonly used for routine situations, but it may be helpful in diagnosing associated pathologies which may alter patient management.

Table 5.2: Diagnostic accuracy of MRI compared to other modalities and surgical findings

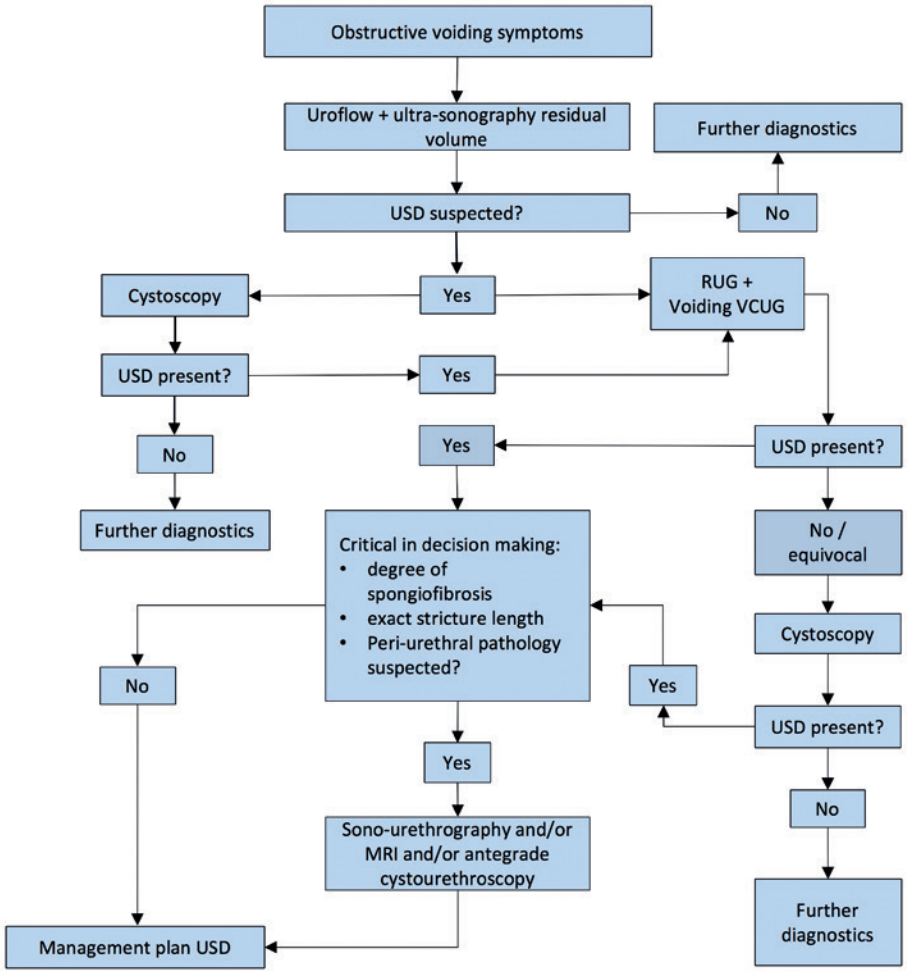
Study	N	Segment of urethra studied	Comparator	Accuracy of SUG		
				Diagnosis	Location	Length
Murugesan *et al*. 2018 [177]	32	Anterior	RUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 100% specificity)	-	-
Fath El-Bab *et al*. 2015 [178]	20	Anterior	RUG, Surgical findings	-	-	MRI more accurate than RUG.
El-Ghar *et al*. 2010 [179]	30	Anterior and posterior	RUG + SUG, Surgical findings	MRI and RUG equivalent (100% sensitivity, 91.7% specificity)	-	MRI and RUG equivalent.
Oh *et al*. 2010 [180]	25	Posterior	RUG + VCUG, Surgical findings	-	-	MRI more accurate than RUG + VCUG.

MRI = magnetic resonance imaging; n = number of patients; RUG = retrograde urethrography; SUG = sonourethrography; VCUG = voiding cystourethrogram.

Summary of evidence	LE
Magnetic resonance imaging is more accurate than retrograde urethrography and voiding cystourethrography at determining length of posterior urethral stenoses and can detect alternative associated pathologies e.g., diverticula, fistulae.	2a

Recommendation	Strength rating
Consider MRI urethrography as an ancillary test in posterior urethral stenosis.	Strong

Figure 5.1: Diagnostic flowchart of patients with suspected urethral stricture disease



MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cystourethrogram.

6. DISEASE MANAGEMENT IN MALES

6.1 Conservative options

*6.1.1 **Observation***

A stricture will usually result in diminution in flow once the calibre of the urethral lumen is ≤ 10 Fr [137]. In other strictures (> 10 Fr), the diagnosis is often made by coincidence in asymptomatic patients because of a urologic examination for other reasons (e.g., cystoscopy, need for urethral catheterisation) [137]. Purohit *et al*. performed observation and repeated cystoscopic evaluation of 42 subclinical, incidentally encountered strictures (≥ 16 Fr). After a median follow-up of 23 months, only five (12%) strictures progressed to a low-grade stricture (11-15 Fr). No patient developed symptoms and none of them needed surgical intervention [137]. These patients are candidates for observation although no evidence exist on the long-term evolution of these strictures.

In a series of anatomic stricture recurrence (≤ 16 Fr) after urethroplasty, only 65% of patients were symptomatic [138]. Some asymptomatic patients refused further intervention because they had experienced substantial improvement after their primary urethroplasty. These patients were considered as functional “success” [138]. A multicentric study of the Trauma and Urologic Reconstructive Network of Surgeons observed an important discrepancy between cystoscopic recurrence and need for further intervention [136]. Patients with a large-calibre (> 16 Fr) recurrence had a one and two-year need for intervention rate of 4% and 12%, respectively. Of note, patients with small-calibre (≤ 16 Fr) recurrence had a one and two-year need for intervention rate of only 41% and 49%. Patients who needed intervention had poorer PROMs suggesting clinical symptoms and bother. There is no information on long-term complications in patients with recurrences who did not undergo

intervention. In cases of an asymptomatic stricture recurrence, it might be an option not to intervene but to perform regular follow-up.

Care must be taken about the term “asymptomatic” stricture (recurrence) as patients might conceal their bother and symptoms by different means (not drinking, social avoidance) and might only search for medical help once concealment is no longer tenable [183].

*6.1.2 **Suprapubic catheter***

Radiation-induced urethral strictures are a difficult to treat population as stricture-free rates for urethral reconstruction are lower compared to those in non-irradiated patients [184]. Fuchs et al. evaluated 75 patients who were initially treated by suprapubic diversion for radiation-induced isolated BMS [185]. Only 51% eventually decided to undergo urethroplasty after a mean follow-up period of 25 months. Although there was no significant difference in overall performance status between patients with a chronic suprapubic catheter versus those undergoing urethroplasty, all patients with a poor performance score remained with a suprapubic catheter. Patients with concomitant stress urinary incontinence (SUI) opted more often to keep their suprapubic catheter as the SUI improved in 61% of cases. On the other hand, patients who kept their suprapubic catheter suffered from catheter-related complications in 27% of cases. Urinary diversion by ileal conduit was performed in 30% of patients who remained with a suprapubic catheter while this was only the case in 8% who underwent urethroplasty.

A suprapubic catheter is also an option in frail patients not able to undergo surgery or in patients who do not want (further) urethral surgery and are willing to accept the complications of a suprapubic catheter [186]

Summary of evidence	**LE**
Patients with asymptomatic incidental (> 16 Fr) strictures have a low risk of progression and to develop symptoms.	3
Only half of the patients initially treated with a suprapubic catheter for radiation-induced bulbomembranous strictures will proceed with urethroplasty.	3

Recommendations	**Strength rating**
Do not intervene in patients with asymptomatic incidental (> 16 Fr) strictures.	Weak
Consider long-term suprapubic catheter in patients with radiation-induced bulbomembranous strictures and/or poor performance status.	Weak

6.2 Endoluminal treatment of anterior urethral strictures in males

The ability to treat the majority of strictures by less invasive and time-consuming means, offers obvious benefits particularly when specialist surgical services are not available, or patients simply prefer a more pragmatic immediately available solution.

*6.2.1 **Direct vision internal urethrotomy***

In contemporary practice, direct vision internal urethrotomy (DVIU) is commonly performed as a first line treatment of urethral strictures [187]. It is usually performed under general or spinal anaesthesia in well-resourced countries, but shown to be well tolerated under local anaesthesia with or without sedation [188-190].

6.2.1.1 Indications of “cold knife” direct vision internal urethrotomy

6.2.1.1.1 Direct vision internal urethrotomy for primary stricture treatment

In the only high-level evidence study, Steenkamp *et al*. randomised 210 patients with seemingly comparable non-obliterative strictures at all locations of the urethra to either filiform dilatation vs. DVIU with local anaesthesia on an outpatient basis [191]. They collected objective data with RUG performed at seven follow-up visits (3, 6, 9, 12, 24, 36 and 48 months). This unique study showed that urethral dilatation is equally effective as DVIU but both procedure modalities become less effective with increasing stricture length (see section 6.2.1.1.3.1).

A Cochrane systematic review in 2012 could not identify a single prospective RCT comparing DVIU (or dilatation) with urethroplasty at the anterior urethra [192]. Since then, the randomised Open-label Superiority Trial of Open Urethroplasty Versus Endoscopic Urethrotomy (OPEN) prospectively randomised patients with a recurrent bulbar stricture between open urethroplasty and DVIU but this was for recurrent bulbar strictures only and not as primary treatment [193] (see section 6.2.1.1.2). A retrospective cohort series in boys with bulbar stricture reported a patency rate of 53% for DVIU and 80% for urethroplasty. No statistical analysis was performed and no information on stricture length was available in both cohorts which makes direct comparison hazardous [194].

Patency rates vary considerably between 8% and 77% after DVIU (predominantly without prior urethroplasty) in retrospective cohort studies with minimum follow-up of one year [64, 194-203] (Table 6.1). Median time to recurrence was less than twelve months in most series [64, 195-197, 199-201].

This large variation in patency rate can be in part explained by the heterogeneous nature of the strictures and various definitions of patency used by the authors in these series. Indication to perform DVIU is dependent on various stricture characteristics that are prognostic for a successful outcome.

Table 6.1: Results of DVIU in series with minimum follow-up > 12 months

Study	N	Age (years)	Follow-up (months)	Location	Length (cm)	Previous interventions	TTR (months)	Patency rate (%)
Santucci *et al*. [195]	76	53 (range: 17-100)	18 (range: 1-30)	Bulbar: 37 (49%) Penile: 4 (5%) Penobulbar: 1 (1%) Unknown: 34 (45%)	1.5 (0.2-5)	Primary: 100%	7	8
Pansadoro *et al*. [196]	224	62 (range: 11-90)	98 (range: 60-216)	Bulbar: 142 (63%) Penile: 37 (17%) Penobulbar: 45 (20%)	1.6 (0.1-6.5)	Primary: 88% Recurrent: 12%	< 12 56% -	32 -
Al Taweel *et al*. [199]	301	37 (range: 17-82)	36	Bulbar: 227 (75%) Penile: 50 (17%) Penobulbar: 24 (8%)	1.3 (0.4-4.2)	Primary: 47% Recurrent: 53%	10 -	8.3 -
Barbagli *et al*. [198]	136	37 (IQR: 25-48)	55 (range: 36-92)	Bulbar: 100%	1-2 cm: 45% 2-3 cm: 40% 3-4 cm: 15%	Primary: 100%	25	57
Kluth *et al*. [197]	128	64 (SD: 16)	16 (IQR:6-43)	Penile: 15 (12) Bulbar: 112 (88) Unknown: 1 (1%)	NR	Primary: 66% Recurrent: 34%	8 -	52 -
Pal *et al*. [200]	186	39 (SD:15)	1st DVIU: 58 (SD: 15) 2nd DVIU: 56 (SD: 15) 3rd DVIU: 45 (SD: 15)	bulbar: 100%	NR	Primary: 69% Repeat: 31%	8.5 -	First DVIU: 30 Second DVIU: 23 Third DVIU: 13
Diamond *et al*. [194]	53	14	30 (range: 6-64)	bulbar: 100%	NR	Primary: 100%	23	53%
Launonen *et al*. [201]	34	6 (range: 0-16)	79 (range: 7-209)	Bulbar: 74% Penile: 21% Penobubar: 6%	≤ 2 cm: 85% > 2 cm: 15% -	Primary: 100%	4	26%
Redon-Galvez *et al*. [202]	67	57 (range: 15-91)	40 (range: 12-120)	Penile:9% Bulbar: 64% VUA: 21% Membranous: 6%	≤ 1 cm: 82% > 1 cm: 18%	Primary: 90% Repeat: 10%	< 24 -	63% -
Harraz *et al*. [203]	430	50 (SD: 15)	29 (range: 3-132)	Bulbar: 100%	< 2 cm	NR, prior urethroplasty excluded	NR	58%
Yürük *et al*. [64]	193	65 (SD: 13)	36 (SD: 12)	Bulbar: 100%	< 1 cm: 140 (73%) 1-2 cm: 21 (11%) 2-3 cm: 32 (17%)	0%	87% of recurrence ≤ 3 100% of recurrence ≤ 6	77% -

DVIU = Direct vision internal urethrotomy; IQR = interquartile range; N = number of patients; NR = not reported SD = standard deviation; TTR = time to recurrence.

6.2.1.1.2 Direct vision internal urethrotomy for recurrent strictures and as salvage treatment after failed urethroplasty

In the OPEN trial, a recurrent stricture was defined as at least one previous failed intervention (endoscopic urethrotomy, urethral dilatation, urethroplasty) [204]. The previous intervention was predominantly DVIU. Despite poor recruitment, 108 and 112 patients were randomised to urethroplasty and DVIU respectively in a 24-month study protocol. Both groups had a similar improvement in voiding score symptoms after intervention. However, patients undergoing urethroplasty had a 2.6 higher odds of experiencing an improvement of ≥ 10 ml/s in their maximum urinary flow compared to those undergoing urethrotomy (p=0.001) [204]. Need for re-intervention was observed in 13.8% vs. 25.9% of cases respectively allocated to urethroplasty and DVIU resulting in a 48% lower risk for re-intervention with urethroplasty (HR: 0.52; 95% CI: 0.31-0.89; p=0.017) [204]. Of note, self-dilatation was not considered a re-intervention [204]. Direct vision internal urethrotomy is also used as salvage treatment for recurrent strictures after urethroplasty. Brown *et al*. used DVIU for stricture recurrence (mean length: 4 cm; range: 1.5-7 cm) after excision and primary anastomosis (EPA), buccal mucosa grafts (BMG) urethroplasty and penile skin graft urethroplasty [205]. Patency was obtained in thirteen out of 37 cases (35%) after a single DVIU. After free graft urethroplasty (FGU), a short, veil-like stricture (or "diaphragm") might develop at the distal or proximal end of the graft. Rosenbaum *et al*. used DVIU to a selected cohort of 43 patients with a short (< 1 cm), veil-like stricture after BMG urethroplasty [206]. After a mean follow-up of twelve months, patency rate was 51%. Farrell *et al*. performed DVIU with mitomycin C (MMC) injection in seventeen patients with a short (median 2 cm; interquartile range [IQR] 1-2.5 cm) recurrence after bulbar urethroplasty (no details on technique available) and patency was achieved in twelve (71%) patients [207].

6.2.1.1.3 Predictors of failure of "cold knife" direct vision internal urethrotomy

Several groups tried to identify prognostic factors to predict which patients are most likely to fail initial treatment (Table 6.2).

6.2.1.1.3.1 Stricture length

Stricture length was identified as an important predictive factor for recurrence in several series. For bulbar strictures, Pansadoro *et al*. found a 71% and 18% patency rate for < 1 cm and ≥ 1 cm strictures respectively (p < 0.001) [196]. In the series of Al Taweel *et al*., no patient with a stricture > 1 cm who achieved patency was stricture-free, whereas this was 27% for strictures < 1 cm (p < 0.001) [199]. Barbagli *et al*. reported an estimated five-year patency rate of 71%, 51% and 39% for 1–2 cm, 2–3 cm and 3–4 cm strictures respectively (p < 0.00001)[198]. Pal *et al*. reported no patency in case of strictures > 1 cm [200]. In their prospective study, Steenkamp *et al*. reported that for each 1 cm increase in the length of the stricture the risk of recurrence was increased by 1.22 (95% CI: 1.05-1.43) [191]. In a paediatric series, a 0% patency rate was obtained for strictures > 2 cm [201]. Redon-Galvez *et al*. reported a 25% patency rate for strictures > 1 cm, whereas strictures ≤ 1 cm had a 71% patency rate (p=0.006). This difference remained statistically significant in the multivariable analysis, when adjusted for stricture location (HR: 1.75; p=0.025) [202]. A systematic review of case series calculated a weighted average patency rate of 71.2% vs. 23.2% for strictures less and more than 1 cm respectively (p < 0.0001) [208].

6.2.1.1.3.2 Stricture tightness (calibre)

Pansadoro *et al*. reported a patency rate of 69% and 34% for strictures more than and less than 15 Fr in calibre, respectively (p < 0.001) [196]. Using pre-operative maximum urinary flow (pQ_{max}) as surrogate for urethral calibre, Barbagli *et al*. stratified patients into three groups (pQ_{max} < 5 vs. 5–8 vs. > 8 ml/s) and reported an estimated five-year patency rate of 31% versus 53% vs. 83%, respectively (p < 0.00001) and the importance of pQ_{max} was confirmed in multi-variate analysis [198]. Kluth *et al*. could not confirm the significance of pQ_{max} on the outcome of DVIU [197].

6.2.1.1.3.3 Number of strictures

Pansodoro *et al*. found poorer patency rates in case of DVIU for multiple strictures compared to a single stricture at both the bulbar (18% vs. 50%; p < 0.001) and penile urethra (8% vs. 35%; p=0.013) [196]. Pal *et al*. reported a 0% patency rate in case of multiple strictures whereas this was 35% for a single stricture (p=0.03) [200].

6.2.1.1.3.4 Stricture aetiology

Harraz *et al*. identified idiopathic stricture aetiology as an independent risk factor for failure (HR: 3.11; p=0.035) [203]. On the other hand, stricture aetiology was not a predictive factor in many other series [196, 200, 201].

6.2.1.1.3.5 Stricture location

Several series have reported a better patency rate for bulbar strictures compared to penile stricture or peno-bulbar strictures [191, 196, 199]. Kluth *et al*. could not identify stricture location as an independent prognostic factor but only 12% of patients had a stricture at the penile urethra [197].

6.2.1.1.3.6 Previous interventions

Pansodoro *et al*. [196], Al Taweel *et al*. [199] and Heyns *et al*. [209] found a 0% patency rate after two or more prior failed DVIU, whereas this occured after three and four prior failed DVIUs in the series of Santucci *et al*. [195] and Launonen *et al*. [201], respectively. Kluth *et al*. identified secondary DVIU for a recurrent stricture as an independent risk factor for stricture recurrence (HR=1.78, 95% CI: 1.05-3.03, p=0.032) [197]. Pal *et al*. found significantly better patency rates after a 1st DVIU compared to a 2nd or 3rd DVIU [200].

6.2.1.1.3.7 Other factors

Two series could not identify age, diabetes, hypertension, obesity and smoking as independent predictive factors [197, 198]. However, Harraz *et al*. identified that older age at presentation and obesity are independent predictors of failure after DVIU [203].

In the absence of well-designed, adequately powered multi-centre trials it is difficult to answer the question as to which clinical factors are predictive of failure of DVIU in men with urethral strictures. However, based on the predictors evaluated above and further supported by consensus papers [210-212], one can summarise that the best candidates are previously untreated patients with a single, short (max. 2 cm) bulbar stricture. In a selected group of patients (n=60), a patency rate of 77% was reported for a single, short, primary bulbar stricture with a minimum follow-up of five years [196]. This is confirmed by a more contemporary cohort of patients with untreated short (1-2 cm) bulbar urethral strictures, in which the estimated five-year patency rate was 71% [198].

Table 6.2: Predictors for urethral patency after direct vision internal urethrotomy

Author	Location	Length	Calibre	Multiplicity	Prior DVIU
Pansodoro *et al*. [196]	Penile: 16%	< 1 cm: 71%	< 15 Fr: 34%	Single: 50%	None: 36%
	Penobulbar: 11%	> 1 cm: 18%	> 15 Fr: 69%	Multiple: 16%	1: 6%
	Bulbar: 42%	-	-	-	> 1: 0%
Steenkamp *et al*. [191] / Heyns [209]	RR for recurrence penile vs. bulbar: 1.85 (95% CI: 0.94 to 3.67, p = 0.077)	< 2 cm: 60% (@12 months)	NR	NR	None: 50-60% (@48 months)
	-	2-4 cm: 50% (@12m)	-	-	1: 0-40% (@48 months)
	-	> 4 cm: 20% (@12 months)	-	-	2: 0% (@24 months)
Santucci *et al*. [195]	NR	NR	NR	NR	0: 8%
	-	-	-	-	1: 6%
	-	-	-	-	2: 9%
	-	-	-	-	> 2: 0%
Al Taweel *et al*. [199]	Bulbar: 11%	< 1 cm: 27%	NR	NR	0: 12.1%
	Penile: 0%	1-2 cm: 0%	-	-	1: 7.9%
	Penobulbar: 0%	> 2 cm: 0%	-	-	> 1: 0%
Barbagli *et al*. [198]	NA	1-2 cm: 71% (@60 months)	pQ_{max} < 5 ml/s: 31%	NA	0: 62%
	-	2-3 cm: 51% (@60 months)	pQ_{max} 5-8 ml/s: 53%	-	1: 37%
	-	3-4 cm: 39% (@60 months)	pQ_{max} > 8 ml/s: 83%	-	-
Kluth *et al*. [197]	Location no predictor	NR	pQ_{max} no predictor	NR	0: 60%
	-	-	-	-	≥ 1: 39%
Pal *et al*. [200]	NA	< 1 cm: 45%	NR	Single: 35%	0: 30%
	-	1-1.5 cm: 0%	-	Multiple: 0%	1: 23%
	-	> 1.5 cm: 0%	-	-	2: 13%

Launonen [201]	Bulbar: 76%*	< 2 cm: 83%*	NR	NR	0: 26%
	Penile: 71%*	> 2 cm: 0%*	-	-	1: 33%
	-	-	-	-	2: 26%
	-	-	-	-	3: 11%
	-	-	-	-	4: 0%
Redon-Galvez [202]	NR	≤ 1 cm: 71%	NR	NR	NR
	-	> 1 cm: 25%	-	-	-

DVIU = Direct vision internal urethrotomy; NA = not applicable; NR = not reported.
**patency rates are reported after repetitive treatments.*

6.2.1.2 Indications of "hot-knife" direct vision internal urethrotomy

6.2.1.2.1 Laser urethrotomy

Lasers available for urological applications including Neodymium:YAG, Argon, Holmium:YAG, Potassium titanyl phosphate (KTP) and Tm:Yag and have been used for the treatment of urethral strictures. A systematic review identified four RCTs comparing laser urethrotomy and the "cold knife" urethrotomy. All studies were limited by short-term outcome evaluation and none of these four studies specified the results based on the location of the stricture. Two of these studies reported specific recurrence rates and meta-analysis showed a risk ratio (RR) for recurrence of 0.55 (95% CI: 0.18-1.66; p=0.29), 0.39 (95% CI: 0.19-0.81; p=0.01) and 0.44 (95% CI: 0.26-0.75; p=0.003) in favour of laser urethrotomy after three, six and twelve months respectively [213]. Jin *et al*. performed a systematic review including 44 case series on laser urethrotomy or "cold knife" DVIU [208]. This included nineteen articles on laser urethrotomy and 25 articles on "cold knife" DVIU. The overall weighted average stricture-free rate was 74.9% (371/495) and 68.5% (1874/2735) for laser vs. "cold knife" DVIU, respectively (p=0.004). Although significant, the results must be interpreted with caution because of heterogeneity and because no details are provided on follow-up duration. Specifically looking at first DVIU, laser and "cold knife" DVIU obtained a stricture-free rate of 58.6% and 42.7% respectively and the difference was no longer statistically significant (p=0.09). At the bulbar urethra, laser and "cold knife" DVIU yielded a stricture-free rate of 52.9% and 60%, respectively (p=0.66) [208].

After publication of this systematic review, the EAU Guideline Panel scope search identified two additional RCTs [214, 215] and one retrospective cohort series [216]. In the RCT of Yenice *et al*., patients with a primary, bulbar stricture were randomised either to "cold knife" DVIU (n=29) or holmium:YAG laser urethrotomy (n=34). After twelve months follow-up, no significant difference in patency rate was identified (79% for "cold knife" DVIU vs. 68% for laser urethrotomy, p=0.3) [215]. In their RCT, Chen *et al*. reported a better patency rate after one year with laser (n=24) compared to "cold knife" (n=22) DVIU (respectively 88% vs. 18%; $p < 0.05$). However, after two years the benefit for laser disappeared and after five years both techniques showed a low patency rate: 9% for "cold knife" DVIU vs. 12% for laser DVIU ($p > 0.05$) [214]. In both these RCTs, operation time was slightly but significantly longer with laser DVIU as compared to "cold knife" DVIU [214, 215]. Holzhauer *et al*. evaluated in a retrospective comparative study "cold knife" (n=127) with laser (n=65) DVIU at a mean follow-up of sixteen and eighteen, respectively. They reported patency rates of 42% for "cold knife" DVIU vs. 31% for laser DVIU (p=0.1) [216].

6.2.1.2.2 Plasmakinetic (bipolar) urethrotomy

Cecen *et al*. conducted an RCT comparing plasmakinetic with "cold knife" DVIU (n=136) [217]. They reported patency rates for plasmakinetic and "cold knife" urethrotomy at nine months in respectively 86% and 70% of cases (p=0.025). At eighteen months, patency rates for plasmakinetic and "cold knife" urethrotomy were 63% and 67%, respectively (p=0.643) [217]. A prospective cohort study on primary strictures < 2 cm reported a patency rate at twelve months in 23/30 (77%) cases for plasmakinetic DVIU vs. 19/30 (63%) cases with "cold knife" DVIU (p=0.04) [218]. A retrospective case series (n=27) reported a 74% patency rate for short (1-2.5 cm) strictures after a mean follow-up of fourteen months [219]. They reported negligible blood loss during the procedure and no post-operative incontinence.

Based on the conflicting results described above and taking into account the heterogeneity of series and absence of long-term follow-up, overall, the available studies do not support the efficacy of one technique of DVIU over another. Given the similar complication rates between techniques (see section 6.2.1.3), no recommendation can be made in favour of one technique over another.

6.2.1.3 Complications of direct vision internal urethrotomy

6.2.1.3.1 Complications of "cold knife" direct vision internal urethrotomy

An overall complication rate of 6.5% was reported in a systematic review of Jin *et al*. based on twelve articles including 1,940 patients [208] (Table 6.3).

Notably, erectile dysfunction (ED) was reported in 5.3% of cases in this review [208]. In addition, Graversen *et al*. reported ED in eleven out of 104 (10.6%) patients [220]. This risk appears higher in strictures located in the penile urethra and, in addition to the poor patency rates, the use of DVIU in the penile urethra must be discouraged [212, 220].

6.2.1.3.2 Complications of "hot knife" direct vision internal urethrotomy

The systematic review of Jin *et al*. reported a total complication rate of 11.8% (39/330) [208] (Table 6.3).

6.2.1.3.3 Complications of "cold knife" versus "hot knife" direct vision internal urethrotomy

In a systematic review of RCTs comparing "cold knife" DVIU vs. laser DVIU, only 1/4 series reported complications [213]. In the laser group, an 8.9% complication rate was found due to contrast extravasation to the perineum and stricture recurrence. For the "cold knife" DVIU, a 15.5% complication rate was reported related to bleeding [213]. Two later RCT's reported similar rates of urinary extravasation [214, 215] and urinary incontinence (UI) [214] with both techniques.

The systematic review of retrospective case series of Jin *et al*. found no significant differences in the incidence rates of UI, urinary extravasation and UTI between laser and "cold knife" DVIU [208]. However, urinary retention and haematuria were more frequent with laser compared to "cold knife" DVIU [208]. Conversely, In the series of Yenice *et al*. haematuria was only reported after "cold knife" DVIU but not after laser DVIU (p=0.6) [215] (Table 6.3).

Table 6.3: Complications after "cold knife" DVIU versus laser DVIU

Study/Complication	"Cold knife" DVIU (%)	Laser DVIU (%)	p-value
Jin *et al*. [208]			
Urinary extravasation	2.9	3.1	0.938
Urinary incontinence	4.1	2.1	0.259
Urinary tract infection	2.1	2.7	0.653
Urinary retention	0.4	9	< 0.0001
Haematuria	2	5.2	0.034
Epididymitis	0.5	NR	NA
Fever	2.3	NR	NA
Scrotal abscess	0.3	NR	NA
Erectile dysfunction	5.3	NR	NA
Urinary tract irritation	NR	11.4	NA
Urinary fistula	NR	1.5	NA
Dysuria	NR	5.1	NA
Yenice *et al*. [215]			
Urinary extravasation	0	2.9	0.6
Haematuria	10	0	
Chen *et al*. [214]			
Urinary extravasation	9.1	4.2	0.5
Urinary incontinence	4.5	4.2	

DVIU = direct vision internal urethrotomy; NA = not applicable; NR = not reported.

6.2.1.3.4 Complications of direct vision internal urethrotomy versus dilatation

A Cochrane review found no significant differences for overall intra-operative complications (single dilatation vs. DVIU respectively 14% vs. 11%; RR: 0.75; 95 CI: 0.36-1.55) nor for individual complications (difficulty urinating, haematuria, false passage, pain, knotting/breaking/bending filiform leader) [191, 192]. The low rate of false passage for both DVIU and dilatation (respectively 0.96 and 0.94%) might be explained by the systematic use of a filiform leader in both groups which was inserted endoscopically in the dilatation group followed by coaxial dilatators [191, 192].

A small retrospective study comparing balloon dilatation (n=31) with DVIU (n=25) showed less urethral bleeding (6.5 vs. 32%; p=0.017) and UTI (3.2 vs. 24%; p=0.037) with balloon dilatation [221].

Apart from acute peri-operative complications described above, the stricture length was reported to increase after DVIU treatment requiring complex urethral reconstruction, but the authors of this retrospective study

clearly state the limitations of the study design in the absence of consistent baseline investigations [195]. Other authors mention that repeat urethral manipulations (DVIU and/or dilatation) can increase stricture complexity and delays time to urethroplasty [222, 223].

6.2.1.3.5 Complications of "cold knife" direct vision internal urethrotomy versus urethroplasty

The OPEN-trial reported adverse events of any type in 61% and 26.1% after urethroplasty (all types) and DVIU respectively [204]. In the urethroplasty group, mouth pain (related to oral mucosa graft [OMG] harvesting) and wound infection was noted as complication in respectively 14.6% and 4.9% of cases. Erectile dysfunction was 4.9% and 2.6% after urethroplasty and DVIU respectively. Serious adverse events were reported in 8.5% and 8.7% after urethroplasty and DVIU respectively [204].

Summary of evidence	LE
Direct vision internal urethrotomy performs poorly in penile strictures. Direct vision internal urethrotomy at the penile urethra might provoke venous leakage from the corpora cavernosa with subsequent risk of erectile dysfunction.	1b
Increased stricture length is associated with higher risk of failure of DVIU.	1b
In selected patients with a primary, single, short (< 2 cm) and non-obliterative bulbar stricture, a five-year stricture-free rate of up to 77% can be expected.	3
Direct vision internal urethrotomy has a stricture-free rate of 51-71% if performed for a short (< 2 cm) recurrent stricture after prior bulbar urethroplasty.	3
There is conflicting evidence that "hot knife" (laser, plasmakinetic) DVIU would be superior compared to "cold knife" DVIU after more than one year of follow-up.	1a

Recommendations	Strength rating
Do not use direct vision internal urethrotomy (DVIU) for penile strictures.	Strong
Do not use DVIU/dilatation as solitary treatment for long (> 2 cm) segment strictures.	Strong
Perform DVIU/dilatation for a primary, single, short (< 2 cm) and non-obliterative stricture at the bulbar urethra.	Weak
Perform DVIU/dilatation for a short recurrent stricture after prior bulbar urethroplasty.	Weak
Use either "hot" or "cold knife" techniques to perform DVIU depending on operator experience and resources.	Weak

*6.2.2 **Single dilatation***

6.2.2.1 Modalities of dilatation and results

Dilatation can be done in the office, under local anaesthesia and without complex resources [211, 224].

With dilatation, the urethral mucosa at the stricture site is stretched and the scarring is disrupted. This is opposed to DVIU where the stricture is incised. However, both treatment modalities use the same principle to achieve urethral patency: a breach of the urethral mucosa at the site of the stricture in which re-epithelialisation should occur faster than wound contraction [192].

When dilators are used to dilate bulbar urethral strictures, considerable experience is required to avoid accidental perforation of the urethra at the level of the stricture. In order to reduce the risks (esp. false passage, spongiosal perforation, urethral bleeding) of "classic" blind dilatation with rigid sounds [224], other strategies have been developed and evaluated in which the dilatation is visually controlled:

- endoscopic/fluoroscopic guidewire placement and progressive dilatation with Amplatz renal dilators [224, 225];
- endoscopic/fluoroscopic guidewire placement and balloon dilatation [221, 226];
- endoscopic/fluoroscopic guidewire placement and S-curved coaxial dilators [227].

Although no direct comparative studies of blind vs. visually controlled dilatation are available, several studies have reported a low complication rate with visually controlled modifications of dilatation. The recurrence rate with short follow-up largely varies between 7.7-64.5% (Table 6.4). Chhabra *et al*. identified focal/short (< 1.5 cm) strictures and strictures at the bulbar urethra as predictors for a favourable outcome [226].

Table 6.4: Results of visually controlled dilatation

Study	Technique	N	FU (mo)	recurrence	Definition of failure	Complications			
						Haematuria	False passage	Procedural failure	UTI
Akkoc *et al*. [224]	Amplatz	26	12-21	2 (7.7%)	Need for additional intervention	3 (11.5%)	0 (0%)	NR	NR
Chhabra *et al*. [226]	Balloon + ISD (permanent)	144	24 (3-52)	21 (15.6%)	Need for additional intervention	NR	0 (0%)	3 (2.1%)	14 (9,7%)
Kallidonis *et al*. [227]	Coaxial S-curved	310	12	90 (33%)	No recurrence @1 yr with maximum one additional procedure	11 (3.5%)	0 (0%)	7 (2.2%)	33 (10.6%)
Nomikos *et al*. [225]	Amplatz + DVIU + ISD (1 yr.)	34	12	8 (23.5%)	Stricture recurrence on urethroscopy/ urethrography	2 (5.8%)	NR	NR	3 (8.8%)
Yu *et al*. [221]	Balloon	31	15 (5-36)	20 (64.5%)	Need for subsequent urethroplasty	2 (6.5%)	0 (0%)	NR	1 (3.2%)

DVIU = direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; mo = months; N = number of patients; NA = not applicable; NR = not reported; UTI = urinary tract infection; yr = year.

6.2.2.2 Effectiveness of dilatation compared with direct vision internal urethrotomy

A systematic review identified only one prospective RCT comparing dilatation with DVIU and failed to detect any differences [191, 192]. In a small (n=56) retrospective cohort study, the three-year estimated stricture recurrence-free survival was 35.5% and 28% for respectively balloon dilatation and DVIU (p=0.21) [221].

At present, there is lack of evidence to support the claim that dilatation is superior to DVIU (or *vice versa*) and therefore, the indications for single dilatation are the same as for DVIU.

Repetitive dilatation/DVIU with curative intent (see also section 6.2.1.1.3.6 Previous interventions) should be avoided as no long-term freedom of recurrence can be expected [211] and because of the significant risk of increasing stricture length and complexity [222, 223] and prolonging the time to urethroplasty (which has better patency rates rates) [223].

Summary of evidence	LE
Visually controlled dilatation after endoscopic or fluoroscopic guidewire placement has a low complication rate.	3
Repetitive dilatations/DVIU have no long-term freedom of recurrence and increase stricture complexity.	1b

Recommendations	Strength rating
Use visually controlled dilatation in preference to blind dilatation.	Weak
Do not perform repetitive (> 2) direct vision internal urethrotomy/dilatations if urethroplasty is a viable option.	Strong

6.2.3 ***Post-dilatation/direct vision internal urethrotomy strategies***

Several strategies have been developed and evaluated to prevent wound contraction, improve the stricture-free rate and time to stricture recurrence after dilatation or DVIU.

It is noteworthy that these strategies tend to stabilise the stricture rather than to keep the patient stricture-free and the reported outcomes should be understood in this respect.

6.2.3.1 Intermittent self-dilatation

6.2.3.1.1 Results

A systematic review identified six randomised and quasi-randomised trials comparing ISD with no ISD with a follow-up between eight and 24 months [228]. Stricture recurrence was reduced in men performing ISD (85/197, 43%) vs. those who did not (128/207, 62%) (RR: 0.70 [0.48-1.00]; p=0.05). There was significant heterogeneity and the quality of included studies was very low, which led the authors to conclude there is uncertainty about the estimate [228]. This review found no significant difference in adverse events between ISD and no ISD (RR: 0.60 [0.11-3.26]; p=0.56) [228]. One trial containing 48 patients found no significant difference in six vs. twelve months duration of ISD (RR: 0.67 [0.12-3.64]) and another trial (n=59) found no significant difference from using a low-friction hydrophylic vs. a polyvinyl chloride catheter (RR: 0.32 [0.07-1.40]) [228]. Other studies have been published after this systematic review of 2014. Chhabra *et al*. reported that patients complying with ISD after dilatation had a lower need for re-intervention than those who did not, 12.3% vs. 20.5% respectively (p=0.2) [226]. After a mean follow-up of 25 months, Greenwell *et al*. found a need for subsequent intervention in 13/31 (42%) men performing ISD vs. 47/95 (49%) who did not (p=0.46). The number of reoperations in patients with need for subsequent intervention was lower in the group performing ISD vs. those who did not (2.6 vs. 3.4). No major complications were reported in both groups [229].

6.2.3.1.2 Complications

The potential benefit of ISD in stabilising the stricture must be balanced against the drawbacks. Commonly reported complications are urethral bleeding (7.1%) [230] and UTI/epididymitis (4.7%-18.1%) [231, 232]. A multicentric prospective study (n=85) reported that respectively 35% and 26% of patients had moderate to severe difficulties in catheterisation and respectively 32% and 17% of patients suffered moderate to severe pain while performing ISD. This had a serious impact on QoL which was rated moderate and poor in respectively 32% and 55% of patients [30]. Younger age was identified as predictor for poor QoL, and QoL was more impaired in proximal stricture location (posterior and bulbar) [30]. In a study of 286 patients (mainly > 60 years old) performing ISD, 20% experienced problems with ISD and 33% had at least one infection annually. After a mean follow-up of 58 months 67% still continued with ISD [233]. Khan *et al*. reported eight “drop-outs” of 30 (26.7%) men randomised to ISD [232]. Of these eight “drop-outs”, two were unable to perform ISD and one stopped because of pain.

As mentioned above, repetitive dilatation (including ISD) increases stricture complexity and delays time to urethroplasty [222, 223].

6.2.3.1.3 Intermittent self-dilatation combined with intra-urethral corticosteroids

To delay wound contraction at the stricture site, intra-urethral corticosteroids (as a catheter lubricant) have been used to improve the results of ISD. In 2014, a systematic review identified three prospective randomised controlled trials comparing ISD and local steroid (triamcinolone) ointment vs. ISD without local steroid ointment [234]. These three studies included a total 67 and 68 patients randomised to local steroid, or not, with a follow-up ranging between twelve and 36 months. There were fifteen (22.4%) recurrences in the steroid group and 25 (36.7%) in the control group (OR: 0.51; 95 CI: 0.24-1.10; p=0.09) [234]. Time to recurrence was longer in the steroid group vs. the control group (weighted mean difference = 0.29 [0.08-1.00]; p=0.05). There were no difference in adverse events between groups [234].

Since 2014, two additional RCTs have been published. Ergun *et al*. evaluated patients after DVIU for primary short (< 2 cm), bulbar (82%) or posterior (18%) strictures that were further randomised between ISD (n=30) and ISD + triamcinolone ointment (n=30) for six weeks. Stricture recurrence rate after 24 months was not significantly different between ISD and ISD + triamcinolone (respectively 33.3 and 30%) [235]. On the other hand, Regmi *et al*. found a lower stricture recurrence rate (22% vs. 46%, p=0.04) in patients performing ISD + triamcinolone (n=27) vs. ISD alone (n=28) [236]. In this study, median time to recurrence was 7.4 ± 4.5 months vs. 11.9 ± 3 months in respectively ISD alone and ISD + triamcinolone (p=0.16). Both studies reported no complications related to ointment of triamcinolone [235, 236].

In a small (n=28) cohort with LS-related strictures, an intra-urethral steroid regimen was successful (no need for subsequent escalation of therapy) in 25 (89%) patients after a mean follow-up of 25 months [150]. This regimen consisted of applying clobetasol cream 0.05% as lubricant on a calibration device (10-16 Fr catheter or dilator) twice a day during a minimum of two months. As most of these patients further continued with instillation of steroids on a calibration device, this high “success” rate must be viewed with caution and should be considered as a stabilisation of the stricture rather than a cure. Eventually, twelve (42.8%) patients could reduce the interval of instillation/dilatation and three (10.7%) of them could finally stop the treatment [150].

Summary of evidence	LE
Stricture recurrence was reduced in men performing ISD versus those who did not.	1a
Intra-urethral corticosteroids in addition to ISD delays the time to recurrence.	1a

Recommendations	Strength rating
Perform intermittent self-dilatation (ISD) to stabilise the stricture after dilatation/direct vision internal urethrotomy if urethroplasty is not a viable option.	Weak
Use intra-urethral corticosteroids in addition to ISD to stabilise the urethral stricture.	Weak

6.2.3.2 Intralesional injections

The rationale of adjuvant intralesional injections is to reduce fibroblast proliferation and excessive urethral scaring [210].

6.2.3.2.1 Steroids

A systematic review in 2014 identified five studies comparing intra-urethral submucosal steroid injection vs. no intra-urethral submucosal steroid injection after DVIU, of which two were RCTs [234]. Meta-analysis of these two RCTs with 57 and 58 patients in, respectively, the steroid and control group showed no statistical difference in recurrence rate (OR: 0.53 [0.25-1.13]; p=0.10). Time to recurrence was significantly longer in the steroid group (weighted mean difference = 4.43; 95% CI: 2.77–6.09, p < 0.00001). There were no significant differences regarding adverse events (infection, bleeding, extravasation) between both groups (weighted mean difference = 1.59; 95% CI: 0.71–3.58, p=0.26).

6.2.3.2.2 Mitomycin C

An RCT (n=40) by Moradi *et al*. reported that MMC hydrogel significantly reduced recurrent stricture formation (10% with MMC vs. 50% without MMC; p=0.001) at one year in patients with anterior strictures < 1.5 cm and no or mild spongiofibrosis on US [237]. The authors reported no significant complications related to MMC injection [237]. Another RCT (n=151) with eighteen months follow-up in predominantly bulbar strictures reported a stricture-free rate of 86% and 63% after DVIU with and without MMC, respectively (p=0.002) [238]. The mean stricture length was less than 2 cm in both groups. No significant complications, such as necrosis of the urothelium, extravasation, or systemic absorption, were recorded in the MMC group [238].

Farrell *et al*. conducted a retrospective study in 44 patients with recurrent bulbar and BMS with a median stricture length of 2 cm (IQR: 1-2.5 cm) [207]. They reported patency in 75% after a median follow-up of 26 months. No long-term complications attributed to MMC were observed.

In a prospective case-series (n=103), Kumar *et al*. evaluated adjuvant intralesional injections of a cocktail of triamcinolone, MMC and hyaluronidase after DVIU for predominantly (78%) bulbar strictures with a median follow-up of fourteen months. A stricture-free rate of 81% was reported and none of the patients suffered local or systemic side effects related to the injection [239].

Despite the encouraging results reported with MMC, the use of MMC in urethral stricture management is still off-label and not widespread. Severe complications with MMC injection are possible. Redshaw *et al*. reported in a multi-institutional series that 4/55 (7%) patients experienced serious complications with osteitis pubis, rectourethral fistula and necrosis of the bladder floor when MMC was injected after endoscopic incision to treat BNS [240]. Given this safety concern and in the absence of well-conducted and adequately powered RCTs, MMC adjuvant to DVIU should only be used in the framework of a clinical trial.

See supplementary Table S6.1 for further information.

6.2.3.2.3 Platelet rich plasma

Rezaei *et al*. conducted an RCT comparing DVIU + platelet rich plasma (PRP) (n=44) vs. DVIU + saline (n=43) in primary, bulbar strictures < 1.5 cm in length [241]. The two-year stricture-free rate was 78% vs. 56% after DVIU with or without PRP, respectively (p=0.034). Complications were frequent but not significantly different between both groups (DVIU + PRP: 70%; DVIU + saline: 79%). All complications (urethral bleeding, haematuria, urethral pain, pelvic pain, urinary leakage and genitoperineal swelling) were classified as grade 1 according to the Clavien-Dindo system. Further validation of this treatment is needed before general clinical implementation.

Summary of evidence	LE
Intralesional injections after DVIU might improve stricture-free rates on the short-term compared to DVIU alone. Experience is limited and the use of these drugs are off-label.	1a

Recommendation	Strength rating
Do not use intralesional injections outside the confines of a clinical trial.	Weak

6.2.3.3 Urethral stents

Urethral stents are designed with the aim to oppose wound contraction after dilatation or DVIU [242, 243]. Stent insertion is a short procedure (< 60 minutes) that can be done under local or spinal anaesthesia as "one-day" surgery [242, 244, 245]. Urethral stents are classified as permanent or temporary (removable, after six to twelve months).

6.2.3.3.1 Results

Permanent stainless-steel mesh stents are no longer commercially available.

An RCT comparing dilatation/DVIU only vs. dilatation/DVIU followed by temporary stent insertion for bulbar strictures reported a significantly longer stricture-free survival time in favour of dilation/DVIU followed by stent (median 292 vs. 84 days; $p < 0.001$) [246]. Only 20.6% of patients treated with a stent developed a recurrent stricture within one year vs. 82.8% in the control group. These results are corroborated by a prospective series of Wong *et al*. who found a median stricture-free survival of two months after DVIU alone vs. 23 months after DVIU followed by temporary (three months) stent for bulbar strictures [243].

Failure and need for re-intervention are frequent (30-53%) and are usually because of stricture recurrence, stent encrustation, stent migration and urethral hyperplasia. Other complications include recurrent UTI, recurrent haematuria and genito-perineal pain (Table 6.5). Although stents are mainly used to treat bulbar strictures, they have been used for posterior stenoses as well. Stents used in the posterior urethra have a high risk (82%-100%) of causing UI and this is most pronounced in patients with previous irradiation and/or strictures extending into the membranous or bulbar urethra [247]. In the bulbar urethra, the risk of UI is higher if stent placement is adjacent to the external sphincter [248]. The use of stents in the penile urethra is anecdotal. Jung *et al*. reported stent failure in 4/7 (57%) patients with a penile stricture after a mean follow-up of eight months. Of those patients who failed, no patient with distal or pan-penile strictures was rendered stricture-free [249]. In their series, stricture recurrence after stenting of the penile urethra was significantly higher when compared to the bulbar urethra [249]. Although no direct comparison is available, temporary stents tend to have fewer and less severe complications compared to permanent stents (Table 6.7).

Table 6.5: Failure rate and complications associated with urethral stents

Study	Type of stent	Duration	N	FU (months)	Stricture length (cm)	Stricture location	Previous interventions	Failure rate	Defintion failure	Complications						
										UTI	haematuria	stent encrustation/ stone formation	stent migration	urethral hyper-plasia	Local pain	UI
Abdallah *et al*. [242]	Thermo-expandable nitinol	Temporary	23	17 (6)	3.6 (1.2)	Bulbar	DVIU/ urethroplasty: all	12 (52%)	Need for re-intervention	4 (17%)	3 (13%)	3 (13%)	5 (22%)	2 (8%)	6 (26%)	NR
Jordan *et al*. [246]	Thermo-expandable nitinol	Temporary	63	12	2.7 (1.6)	Bulbar	DVIU only: all	28 (44%)	Inability to pass 16 Fr cystoscope	31 (49%)	10 (16%)	3 (4.7%)	8 (13%)	NR	19 (30%)	12 (19%)
Temeltas *et al*. [245]	Polymer-coated	Temporary	28	29 (7-46)	1.9 (0.5-3.5)	Bulbar	DVIU only: all	10 (36%)	Stricture recurrence on urethroscopy/ graphy, Q_{max} < 15 ml/s, UTI	NR	NR	1 (3.6%)	3 (11%)	NR	0 (0%)	NR
Wong *et al*. [243]	Thermo-expandable nitinol	Temporary	22	23 (9-31)	2.4 (1-4.5)	Bulbar	DVIU only: all	7 (32%)	Inability to pass 17 Fr cystoscope, Q_{max} < 10 ml/s or recurrent obstructive symptoms	0 (0%)	NR	0 (0%)	1 (4.5%)	0 (0%)	0 (0%)	NR
Atesci *et al*. [244]	Thermo-expandable nitinol	Permanent	20	144 (120 -192)	2.5 (0.5-5.5)	Bulbar	DVIU/ urethroplasty: all	6 (30%)	Need for re-intervention	NR	NR	4 (20%)	2 (10%)	0 (0%)	8 (40%)	1 (5%)
Sertcelik *et al*. [248]	Thermo-expandable nitinol	Permanent	47	101 (84-125)	2 (0.5-5)	Bulbar (45), bulbomem-branous (2)	urethroplasty (19%)/ DVIU (64%)/ railroading (17%)	22 (47%)	Need for re-intervention	NR	NR	12 (26%)	2 (4%)	7 (15%)	20 (43%)	9 (19%)
Erickson *et al*. [247]	Self-expandable super alloy mesh	Permanent	38	28 (30)	3 (1.7)	Posterior (prostate cancer related); VAUS 24; prostatic urethra (irradition) 14	DVIU only: all	20 (53%)	Need for re-intervention	7 (18%)	3 (8%)	6 (16%)	NR	NR	6 (16%)	31 (82%)

DVIU = direct vision internal urethrotomy; FU = follow-up; N = number of patients; NR = not reported; UI = urinary incontinence; UTI = urinary tract infection; VUAS = vesico-urethral anastomotic stricture; Q_{max}= maximum flow rate

6.2.3.3.2 Treatment of stent failure

In the case of stent failure, subsequent urethroplasty (usually with stent removal) is possible, but this urethroplasty is very likely to be more complex than it would have been had it been performed initially [250-252]. Due to the fact that the stainless-steel wires are fully embedded into the urethral wall, over time the urethral spongiosum is severely damaged. Horiguchi *et al*. found that a history of urethral stenting was an independent significant predictor of increased stricture complexity (OR: 13.7, 95% CI: 1.7-318.3, p=0.01) and need for more complex urethroplasty (OR: 6.9, 95% CI: 1.1-64.5, p=0.04) [222]. The majority (62%) of patients in this study had a permanent stent and tend to be difficult to remove because they are epithelialised, usually within six months [222]. The type of urethroplasty required depends on the length of the stricture and quality of local tissues [251]. In the majority of cases, it is possible to preserve the urethral plate and to perform a one-stage substitution urethroplasty [250, 251, 253]. The patency rates after different types of urethroplasty vary greatly between 16.7-100% [250-253] and this variation probably reflects variation in complexity of the stricture, rather than that the superiority of one technique of urethroplasty over another (for further information see supplementary Table S6.2). Due to these limitations, the use of stents should be avoided if subsequent urethroplasty is considered [242, 252]. Urethral stents are not a first-line treatment for urethral strictures but can be considered in co-morbid patients who have a recurrent stricture after DVIU/dilatation and are unable to have more complex urethroplasty or who refuse urethroplasty [242, 246, 247].

Summary of evidence	LE
Permanent urethral stents have a high complications and failure rate and make subsequent urethroplasty more challenging if they fail.	3
Stents have a higher failure rate in the penile urethra.	3
Temporary stents after DVIU/dilatation at the bulbar urethra prolong time to next recurrence compared to DVIU/dilatation alone.	1b

Recommendations	Strength rating
Do not use permanent urethral stents.	Strong
Do not use urethral stents for penile strictures.	Strong
Use a temporary stent for recurrent bulbar strictures after direct vision internal urethrotomy to prolong time to next recurrence only if urethroplasty is not a viable option.	Weak

6.3 Open repairs (urethroplasty): site and aetiology (clinical scenario) treatment options

*6.3.1 **The role of urethroplasty in the management of penile urethral strictures***

Due to the specific aetiology and the associated problems, strictures related to failed hypospadias repair and LS will be discussed separately. However, many series reporting on the outcome of penile strictures have a mixed aetiology also including failed hypospadias repair and/or LS [254, 255]. Due to their specific location, distal penile strictures will be discussed separately.

6.3.1.1 Staged augmentation urethroplasty

Classically called “two-stage” urethroplasty, this approach may become a multi-stage urethroplasty as revision (usually due to graft contracture) after the 1st stage has been reported in 0-20% of cases [255-258]. Therefore, the term “staged” should be used instead [259]. Revision rates before 2nd stage were 0-20%, stressing that a two-stage urethroplasty might become a multi-stage urethroplasty. In general, reconstructive urologists tend to follow this approach in men with more complex urethral stricture disease (multiple interventions in the past, unfavourable clinical findings such as significant spongiofibrosis or scarring that requires excision, poor quality of the urethral plate). An interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully [260-262].

A systematic review by Mangera *et al*. has shown an average patency rate of 90.5% with the use of all types of grafts for staged penile urethroplasties with an average follow-up of 22.2 months [263]. Patency rates of staged OMG urethroplasty in specific locations vary between 73.3 and 100% [254, 255, 257, 258]. Post-operative urethrocutaneous fistula (UCF) rates were 17.2% and 2.6% in the studies of Ekerhult *et al*. and Joshi *et al*., respectively, and either not reported or unclear in the remaining studies [254, 255].

6.3.1.2 Single-stage augmentation urethroplasty

Single-stage urethroplasty offers the option for reconstruction of the stricture without the need for multiple operations, the associated peri-procedural risks and the cosmetic and functional implications that by definition follow the first part of staged urethroplasties [264-266]. There is some evidence to suggest a considerable

number of patients (50% or more in some studies) who were offered 1st stage urethroplasty never returned for the 2nd stage because they were either satisfied with their functional status after the 1st stage (this particularly applied to older men or patients with multiple failed procedures in the past) or they were disappointed with the need for another operation [264, 265].

In the systematic review of Mangera *et al*., overall patency rate for all types of single-staged graft urethroplasties is 75.7% with an average follow-up of 32.8 months [263].

The patency rate for different one-stage techniques in specific are:

- dorsal OMG (n=190): 70-100% [258, 267-272];
- ventral OMG (n=47): 55-92.6% [273, 274];
- dorsal + ventral OMG (n=10): 80% [271];
- double (dorsal + ventral) onlay with penile/scrotal skin graft /OMG (n=14/8/4): 88.5% [268];
- dorsal penile skin graft (n=44): 62-78% [268, 269];
- penile skin flap (n=315): 67-100% [268-270, 275, 276].

No high-level evidence exists to state that one technique is superior to another but it seems that the dorsal graft location is more commonly used compared to the ventral one. Mangera *et al*. reported that the patency rate was better with OMG compared to other grafts (mainly penile skin) [263]. Jiang *et al*. showed that combined (dorsal + ventral) BMG onlay had significantly better stricture-free rates for penoscrotal strictures (patency rate 88.9% vs. 60.9% with single-onlay approach); however, follow-up was significantly shorter in the double-onlay group [277]. Few studies have reported dedicated results on sexual function parameters that do not appear to be significantly impaired post-operatively [257, 278, 279].

A critical factor with respect to single-staged procedures is the careful selection of patients, as men with long and complex strictures might not be good candidates for single-stage reconstruction and attempts to offer single-staged operations in these patients might lead to high recurrence rates. Sometimes, this selection can only be done based on intra-operative findings. Therefore, any scheduled single-staged procedure might be converted into a staged one [264, 280]. Palminteri *et al*. highlighted the fact that single-stage augmentation urethroplasties in men with LS-related strictures enlarge rather than remove the diseased segment of the urethra and therefore there is always a risk of recurrence in the future [281]. The role of previous interventions (especially multiple urethrotomies or history of previous urethroplasties) remains unclear as several studies on single-staged operations do not provide information on previous procedures, or excluded patients with operations in the past [270, 279]. Although favourable outcomes in patients with previous history of urethrotomies/urethroplasties were reported by Barbagli and Kulkarni, in the study by Pfalzgraf *et al*. all recurrences post-previous urethroplasty took place in the single-stage group while Ekerhult *et al*., identified prior history of urethral operations as a risk factor for recurrence in the group of single-stage procedures [254, 257, 258, 268]. In addition to previous urethral surgery, high BMI has also been identified as a poor prognostic factor after single-stage penile urethroplasty [254].

6.3.1.3 Anastomotic urethroplasty in men with penile urethral strictures

Historically, the use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively [262, 282]. Nevertheless, it has been performed in selected patients with very short strictures (usually < 1 cm) with a 93% patency rate, with satisfactory QoL and sexual function and without any case of chordee [283].

Summary of evidence	**LE**
Stricture-free rates for single-stage penile augmentation urethroplasties range from 70%-100% for dorsal OMG augmentation, 67-100% for penile skin flap (PSF) augmentation, 55-92.6% for ventral OMG augmentation and 62-78% for dorsal SG augmentation. Overall stricture-free rates for staged OMG penile augmentation urethroplasties range from 70-100%.	2b
In staged urethroplasties, an interval of at least four to six months has been proposed before proceeding to the tubularisation of the urethra, provided that the graft has healed uneventfully.	4
The use of anastomotic urethroplasty in the management of urethral stricture disease has been discouraged due to the risk of chordee post-operatively. Anastomotic urethroplasty can be offered in selected cases of very short (< 1 cm), inury-associated penile strictures.	3
In case of adverse intra-operative findings, a single-stage approach might not be feasible and must be converted into a staged approach.	3

Recommendations	Strength rating
Offer men with penile urethral stricture disease augmentation urethroplasty by either a single-stage or staged approach taking into consideration previous interventions and stricture characteristics.	Strong
Offer an interval of at least four to six months before proceeding to the second stage of the procedure provided that outcome of the first stage is satisfactory.	Weak
Do not offer anastomotic urethroplasty to patients with penile strictures > 1 cm due to the risk of penile chordee post-operatively.	Strong
Counsel patients with penile strictures that single-stage procedures might be converted to staged ones in the face of adverse intra-operative findings.	Strong

6.3.1.4 Specific considerations for failed hypospadias repair-related strictures

The term "failed hypospadias repair" (FHR) includes a wide range of abnormalities after previous attempts for reconstruction, such as glans deformity, recurrent urethral stricture, glans/urethral dehiscence, UCF and penile chordee [284-286]. The management of FHR is challenging as the urethral plate, penile skin and dartos fascia are often deficient/non-existent. Management of these patients is often made more difficult due to incomplete health records and a lack of critical information (original meatal site, number and type of previous repairs) [260, 287]. In addition, multiple operations might need to be offered to reach satisfactory outcomes [284]. As a result, FHR should always be considered as a complex condition and it is advised that FHR management takes place in high-volume centres [285, 286, 288, 289].

"Hypospadias cripples" is a term widely used to describe the group of men with multiple previous failed attempts to correct the condition resulting in unfavourable results such as severe scarring, penile deformity and shortening, hair or stones in the urethra, UCF, chordee and functional disorders (e.g., urinary or sexual dysfunction). This term should be avoided and a more neutral one should replace it as it further stigmatises men with hypospadias who have been shown to have reduced self-esteem and confidence due to unsatisfactory cosmesis, and problematic urinary and sexual function. Moreover, it has been reported that FHR patients experience high rates of disappointment after failure of attempted repair and a sense of helplessness as they are frequently advised that their failed hypospadias is too complex to correct and they should not pursue further repair [285-287, 290, 291].

Two main approaches are applicable: single-stage or staged procedures. In general, it is advised that staged procedures should be followed when the urethral plate is inadequate for a single-stage operation. Surgeons should consent patients for both types of urethroplasty as the surgical approach might need to be modified intra-operatively depending on favourable/unfavourable intra-operative findings. Besides poor-quality of the urethral plate, these unfavourable findings include high degree of scarring and presence of concomitant LS, UCF and/or chordee. It is not uncommon for men with FHR to have scarred skin or concurrent LS and thus, skin grafts or flaps should be avoided as the risk of recurrence due to LS is very high (90% in long-term follow-up reported by Depsaquale *et al*. [36]) [292, 293].

Staged repairs (using mainly BMG) reported patency rates ranging from 71-95% [256, 290, 292, 294, 295], while single-stage repairs had patency rates from 80-100% [292, 294, 296-299]. It needs to be highlighted that, as FHR is an umbrella term that covers various clinical conditions apart from urethral stricture disease only (such as UCF, chordee, penile deformity), "success" rates as reported by the authors in their studies do not represent urethral patency rates only. Unfortunately, the number of previous operations is either not reported or refers to the whole FHR study group collectively rather than to the subgroups of staged/single-staged procedures.

A comparative analysis is reported by Barbagli *et al*. in 345 FHR patients at five-year follow-up. Overall failure-free survival rate was 48% for all urethroplasties, and in subanalysis, staged techniques had significantly lower treatment failure-free survival rates compared to single-stage techniques [300]. However, it is unclear whether these groups were comparable in terms of baseline characteristics such as age, length of stricture, number of procedures, comorbidities etc. [300]. If the patients in the staged group had a more unfavourable background, this on its own could explain the final outcome rather than the surgical approach itself.

Kozinn *et al*. reported a 16% and 14% revision rate after the 1st and 2nd stage, respectively, and observed that these revision rates were higher in the FHR group compared to non-FHR patients with penile strictures [256]. There is conflicting evidence whether FHR as aetiology is a poor prognostic factor in the outcome of urethroplasty for penile strictures [254, 301-303]. Concomitant UCF can be successfully managed at the same time of urethroplasty [300].

For further information see supplementary Table S6.3.

Summary of evidence	LE
Men with FHR have history of multiple interventions, and poor quality tissues, and might require complex procedures for a satisfactory functional and cosmetic outcome.	4
Men with FHR may have low self-esteem due to urinary and sexual dysfunction and unsatisfactory cosmesis.	2b
Men with FHR can have scarred penile skin or concurrent LS and outcomes with skin grafts or flaps can be unsatisfactory.	3

Recommendations	Strength rating
Men with failed hypospadias repair (FHR) should be considered complex patients and referred to specialist centres for further management.	Weak
Propose psychological and/or psychosexual counselling to men with unsatisfactory cosmesis and sexual or urinary dysfunction related to FHR.	Weak
Do not use penile skin grafts or flaps in failed FHR patients with lichen sclerosus or scarred skin.	Strong

6.3.1.5 Specific considerations for lichen sclerosus-related penile urethral strictures

Given the fact that LS affects the skin, the use of genital skin as a flap or graft is not advised as the risk of disease recurrence has been reported to be high (50-100%) and while most of recurrences tend to occur within the first two to three post-operative years, late recurrences have been reported [304].

Main strategies are single-stage or staged oral mucosa graft urethroplasty.

The EAU Urethral Strictures Guidelines Panel conducted a systematic review [305] to explore the role of single-stage oral mucosa graft urethroplasty in the management of LS-related urethral strictures and to compare its outcomes with alternative management options [surgical dilatations +/- intermittent self-dilatation (ISD); surgical dilatations + local steroids +/- ISD ; staged oral mucosa urethroplasty; penile skin urethroplasty; meatotomy/meatoplasty; urethrotomy (Otis, DVIU); perineal urethrostomy; urinary diversion (e.g., suprapubic catheterisation)].

In total, fifteen studies met the inclusion criteria, recruiting a total of 649 patients (366 from five non-randomised comparative studies and 283 from ten single-arm retrospective observational studies). Single-stage oral mucosa graft urethroplasty resulted in success rates ranging from 65% to 100% after a 12-67 months mean or median follow-up. For staged oral mucosa graft urethroplasty, the most commonly reported comparator, the success rates were somewhat lower and varied between 60% and 79%. Methodological issues (mainly selection bias) could explain the difference in success rates rather than the intervention itself. Complications were uncommon (0-12%) and mainly comprised Grade 1-3 events.

Due to the overall very poor quality of evidence, the systematic review did not provide a clear answer as to whether single-stage oral mucosa graft urethroplasty is superior to other management options, although careful patient selection is highlighted. In the absence of adverse local tissue conditions a single-stage approach could lead to high success rates with an improvement in voiding symptoms and QoL.

Summary of evidence	LE
Lichen sclerosus is a skin condition that can lead to scarring, and recurrence rates after skin graft/flap augmentation urethroplasties have been reported to be high (50-100%).	4
Single-stage OMG urethroplasty provides patency rates between 65 and 100% and is not inferior to staged OMG urethroplasty.	3

Recommendations	Strength rating
Do not use genital skin in augmentation penile urethroplasty in men with lichen sclerosus-related strictures.	Strong
Perform single-stage oral mucosa graft urethroplasty in the absence of adverse local conditions in men with lichen sclerosus-related strictures.	Weak

6.3.1.6 Distal urethral strictures (meatal stenosis, fossa navicularis strictures)

Open repair of distal urethral strictures can be in the form of Malone meatoplasty, skin flap meatoplasty or graft (skin [SG]/OMG) urethroplasty.

For short distal meatal strictures, the Malone meatoplasty (dorsal + ventral meatotomy) provides a technique with patency rates up to 100%, and 83% patient-reported satisfaction with the cosmetic results [306].

Skin flap meatoplasty showed excellent patency rates ranging from 85-100% based on three studies comprising 53 patients [307-309]. In addition, based on their results, patient satisfaction with post-operative outcomes and cosmesis was high, there were no cases of ED and functional complaints were minimal (mainly spraying of the urine flow). Barbagli *et al*. in their study from 2008, had lower success (57%) with the use of skin flaps; however, this was in only seven patients [268].

Patency rates with the use of grafts (OMG or SG) ranged from 69-91% in 85 patients overall [268, 297, 308, 310]. Where reported, patients were satisfied with cosmesis, and mild spraying of the urine flow self-resolved. Although tubularised grafts in a single-stage procedures are not routinely recommended (see also section 9. Tissue transfer), one series reported a 89.9% patency rate for this approach ("two-in one approach") in selected patients with mainly distal penile strictures [311].

For further information see supplementary Table S6.4.

Summary of evidence	LE
Post-meatoplasty/urethroplasty patency rates in men with meatal stenosis or fossa navicularis/distal urethral strictures range between 57-100% depending on type of surgical intervention with high patient satisfaction and minimal complications.	3

Recommendation	Strength rating
Offer open meatoplasty or distal urethroplasty to patients with meatal stenosis or fossa navicularis/distal urethral strictures.	Weak

6.3.2 ***Urethroplasty for bulbar strictures***

6.3.2.1 "Short" bulbar strictures

The length of a "short" bulbar stricture is poorly defined. In general, "short bulbar strictures" are those amenable to stricture excision and subsequent tension-free anastomotic repair. The limit is usually around 2-3 cm but can be longer depending on the patient's anatomy and stricture location within the bulbar urethra [312].

In fit patients, the choice of urethroplasty is between EPA (transecting or non-transecting) and FGU.

6.3.2.1.1 Excision and primary anastomosis

6.3.2.1.1.1 Excision and primary anastomosis with transection of corpus spongiosum (transecting EPA)

Transecting EPA (tEPA) is based on the full thickness resection of the segment of the bulbar urethra where the stricture and surrounding spongiofibrosis is located. Reconstruction is performed by a tension-free spatulated anastomosis.

6.3.2.1.1.1.1 Patency rates

The International Consultation on Urological Diseases (ICUD) performed an extensive review of the literature and reported a composite patency rate of 93.8% for tEPA [313]. Based on this, they endorsed tEPA as treatment of choice for short bulbar strictures if other techniques have an expected patency rate below 90%. However, ED was not taken into account for this advice and, as discussed below, ED is a concern with tEPA.

After publication of the ICUD review, several other series have been published and the reported patency rates (76-97%) are in line with the findings of the ICUD review [314-326].

Usually, no need for further intervention is used to evidence that the urethra is patent. In the few studies using an anatomic definition for failure (an inability to pass a 16 Fr endoscope) tEPA urethroplasty achieves a similar patency rate, ranging between 85.5% and 97% [138, 319, 325, 327] (Table 6.12). The median time for recurrence after tEPA is between 3.5 and thirteen months [138, 316, 317].

Several authors suggested that tEPA is the technique of choice for short post-traumatic bulbar strictures with complete obliteration of the urethral lumen and full thickness spongiofibrosis [327, 328]. These strictures are a specific entity and usually the result of a straddle injury with complete or nearly complete rupture of the bulbar urethra. These obliterations are predominantly short and can be treated with tEPA yielding a patency rate of 98.5% as reported in the series of Horiguchi *et al*. [329]. They also reported an improvement in erectile function after urethroplasty measured one year post-operatively. Straddle injury (and perineal trauma) are a common aetiology in papers published about tEPA; however, separate data on the outcomes for this specific aetiology is usually lacking.

For further information see supplementary Tables S6.5 and S6.6.

6.3.2.1.1.1.2 Complications

Granieri *et al*. [318] specifically focused on complications after bulbar urethroplasty. Peri-operative complications (haematoma, neuralgia), infectious complications, anatomic complications and voiding complications were not significantly different between EPA, augmented anastomotic repair (AAR) and FGU. Erectile dysfunction after bulbar urethroplasty is usually transient, with improvement after three to six months [330]. Chordee is one of the complications attributed to EPA urethroplasty, but is rarely reported. A large series (352 patients) reported an incidence of 0.3% [327]. Another large series (94 patients) reported five cases (5.3%), with a mean stricture length of 2 cm (range 1.5-4) in patients with this complaint [314].

Other complications of tEPA are a cold feeling in the glans (1.6-3.2%) and decreased glandular tumescence (6%) [330, 331]. These latter complications (as well as ED) might be attributed to complete transection of the corpus spongiosum at the level of the stricture, thereby disrupting the antegrade blood flow of the urethra and corpus spongiosum. To spare this, the non-transecting EPA (ntEPA) has been described [332] and later modified [333].

6.3.2.1.1.2 Non-transecting excision and primary anastomosis (ntEPA)

6.3.2.1.1.2.1 Patency rates

Except for straddle injuries that are usually associated with complete obliteration of the lumen and full thickness scarring of the corpus spongiosum [313, 327], ntEPA is a good alternative for short bulbar strictures of all other aetiologies. With median follow-ups ranging between 17.6 and 37.1 months, the patency rates reported are 93.2-99%; with the lack of further intervention as success criteria [326, 328, 334]. Even with the anatomic criteria -16 Fr cystoscopy passage- the success rate achieved was 97.9% at twelve months [327] (see supplementary Table S6.7).

Two comparative analyses evaluated tEPA vs. ntEPA. Waterloos *et al*. reported patency rates of 88.4% and 93.2% respectively for tEPA and ntEPA (p=0.33) but with significantly longer follow-up for tEPA (118 vs. 32 months, $p < 0.001$). Of patients scheduled for ntEPA, 11.1% were converted to tEPA, highlighting that ntEPA is not always possible. Chapman *et al*., using anatomic success criteria (16 Fr cystoscope passage), reported patency in 93.8% of tEPA vs. 97.9% of ntEPA. Follow-up was also significantly shorter at 74.1 (SD: 45.4) months for tEPA vs. 37.1 (SD: 20.5) months for ntEPA ($p < 0.001$) [327].

6.3.2.1.1.2.2 Complications

When erectile function after urethroplasty was assessed (at six months), ntEPA had significantly lower ED rates (a decrease of > 5 points on the sexual health inventory for men [SHIM] scale) compared to tEPA (4.3 vs. 14.3%, respectively) [327]. Urethral transection performed during tEPA was the only factor associated with sexual dysfunction in multivariate analysis [327]. Other series reported ED lasting for more than six months in 2-6% of cases after ntEPA [328, 334, 335]. Grade ≥ 2 Clavian-Dindo complications were 3.6-8.1% vs. 4.3-6.8% respectively for tEPA and ntEPA, without reaching statistical significance [326, 327].

To date, no trials comparing ntEPA with FGU have been published to report on comparative patency outcomes and complications.

6.3.2.1.2 Free graft urethroplasty

Despite the very high patency rates of EPA, FGU has been performed for short bulbar strictures as well. This is mainly driven by reports of ED after EPA. A meta-analysis of ten papers [336] comparing tEPA with BMG FGU for short strictures, found that tEPA is better than BMG FGU in terms of patency rates (91.5% vs. 70%), whilst BMG FGU has less erectile complications (9% vs. 25%). However, the methodology of this meta-analysis must be disputed as it was performed on cohort studies without risk of bias assessment and without further specification of timing of assessment of ED. On the other hand, two prospective, non-randomised papers [138, 337] comparing tEPA with BMG FGU, found no significantly different patency rates for EPA compared

to BMG FGU (87-90% vs. 84-87%, respectively) and no significant differences in erectile complications for tEPA compared to BMG FGU (6.7% vs. 2.2%, respectively). However, the operation technique used was dependent upon the length of the stricture, with tEPA utilised for shorter strictures (< 2 cm) and BMG for longer (> 2 cm) [337] or when a tension-free anastomosis was not possible [138]. Appropriate choice of procedure for stricture length and other patient and stricture parameters appear to equalise outcomes. Another prospective trial [338] involving both penile and bulbar strictures could not find any influence on erectile function of urethral transection. A prospective study on ejaculatory function following different urethroplasties by Erickson *et al*. [339] found no overall difference in ejaculatory score pre- and post-operatively, although patients with a poor score pre-operatively improved significantly and those with a good score pre-operatively did not decrease post-operatively.

Dogra *et al*. [278] looked prospectively at sexual function in 87 patients after different urethroplasties (EPA, penile/bulbar substitution) and found a 20% reduction in sexual function in all groups, which resolved after six months.

Details on where to place the graft during FGU are discussed below.

Summary of evidence	**LE**
For short post-traumatic strictures tEPA has good patency rates.	3
For short bulbar strictures not related to straddle injury tEPA, ntEPA and FGU have the same patency rates, but ntEPA and FGU have less erectile dysfunction than tEPA.	3

Recommendations	**Strength rating**
Use transecting excision and primary anastomosis (tEPA) for short posttraumatic bulbar strictures with (nearly) complete obliteration of the lumen and full thickness spongiofibrosis.	Strong
Use non-transecting excision and primary anastomosis or free graft urethroplasty instead of tEPA for short bulbar strictures not related to straddle injury.	Weak

6.3.2.2 "Longer" bulbar strictures

6.3.2.2.1 Free graft urethroplasty

For strictures not amenable to EPA, FGU is the technique of choice and buccal mucosa is, at the moment, the most widely used graft. Other grafts (and flaps) are possible and discussed in the tissue transfer chapter. Patency rates of FGU of the bulbar urethra are 88-91% with twelve to 40 months follow-up [263, 340].

During bulbar urethroplasty, the bulbospongiosus muscle is usually separated at the midline which may cause damage to the muscle and perineal nerves. This might subsequently provoke post-void dribbling and ejaculation disorders. In order to reduce this, the muscle and nerve-sparing perineal approach has been introduced [341]. Although it is mostly used in graft urethroplasty, this approach is also possible for EPA as well [342]. Elkady *et al*. [335] randomised 50 patients between a muscle and nerve-sparing perineal approach vs. a classic perineal approach and found no difference in operative time (100 vs. 105 min), but significantly less dribbling (4% vs. 36%, p=0.01), and significantly less ejaculatory changes (8% vs. 40%, p=0.02) in the nerve and muscle-sparing group. Fredrick *et al*. [342] did the same in 50 patients in a multicentric study with bulbar urethroplasty but could not find a statistical difference regarding post-void dribbling and ejaculatory changes. Due to the limited and conflicting evidence, no recommendation can be made about the routine use of nerve and muscle-sparing modification during bulbar urethroplasty.

See supplementary Table S6.8 for further information.

6.3.2.2.2 Augmented anastomotic repair

Augmented anastomotic repair is also an option for these strictures. It has been mainly performed in cases where the stricture was just too long (+/- 2-4 cm) for tension-free EPA [324]. It can also be performed for longer strictures with a shorter (nearly) obliterative segment [343]. In this case, only the most obliterative segment is excised, the urethral plate is anastomosed and the urethra is further reconstructed with an onlay graft [343]. Patency rates after AAR vary between 91.1 and 91.9% with twelve to 28 months follow-up [318, 324] (see supplementary Table S6.9).

A non-transecting alternative has also been described to overcome the previously mentioned inconveniences related to spongiosal transection (augmented non-transecting anastomotic bulbar urethroplasty [ANTABU]). With this technique, Bugeja *et al*. [344] reported a 100% patency rate in sixteen patients after a median follow-up of thirteen months. One patient (6.7%) suffered permanent ED.

Summary of evidence	LE
For strictures not amenable to EPA, FGU provides a 88-91% patency rate.	1b
Augmented anastomotic repair provides good patency rates for bulbar strictures with a nearly obliterative segment.	3

Recommendations	Strength rating
Use free graft urethroplasty for bulbar strictures not amendable to excision and primary anastomosis (EPA).	Strong
Use augmented anastomotic repair for bulbar strictures not amenable to EPA but with a short, nearly obliterative segment within the whole strictured segment.	Weak

6.3.2.2.3 Location of the graft during urethroplasty for bulbar strictures

The best location for graft positioning into the bulbar urethra remains to be determined. There are many techniques described with ventral, lateral, dorsolateral or dorsal graft as an onlay or an inlay. Onlay means from the outside onto the urethra, inlay means from the inside after opening the urethra.

Regarding the site of graft placement, the Panel has conducted a systematic review assessing the literature from 1996 onwards, including studies with at least 20 patients and a minimum of twelve months follow-up [345]. This yielded one RCT, four non-randomised comparative series and 36 case series comprising 3,683 patients. The RCT of Vasudeva *et al*. compared ventral (n=40) with dorsal (n=40) onlay BMG urethroplasty and reported a patency rate of 90 and 92.5% respectively at twelve months follow-up (p=0.51) [340]. The non-randomised comparative studies could not identify any significant differences in patency rates for dorsal onlay vs. ventral onlay, dorsal inlay vs. ventral onlay or dorsal onlay vs. ventral onlay vs. dorsolateral onlay. Case series reported a patency rate of 62.1-98.3% for dorsal onlay, 74.3-94.4% for ventral onlay and 78.4-92% for dorsal inlay. There are no arguments to assume a higher risk of ED with one of the four techniques. Post-void-dribbling was reported in 0-28.1% with dorsal onlay and in 20-21% with ventral onlay. Other complications were also similar in incidence between techniques. Urethrocutaneous fistula and urethral diverticulum were only reported with the ventral onlay technique although this consisted of only two and one cases, respectively.

Double ventral-dorsal onlay, proposed by Palminteri *et al*. [139] for high-grade strictures, yielded a patency rate of 91% after 22 months follow-up.

Summary of evidence	LE
Location of the graft has no impact on patency rates.	1b

Recommendation	Strength rating
Use dorsal, dorsal-lateral or ventral approach according to surgical practice, expertise and intra-operative findings.	Strong

6.3.2.3 Staged urethroplasty for bulbar urethral strictures

6.3.2.3.1 Indications

Staged urethroplasty may be considered when:

- there are locally adverse conditions such as fistula, false passage, abscess, cancer [280, 346, 347];
- there has been a previously unsuccessful complex urethroplasty including failed hypospadias repair [256, 346];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [346];
- the stricture is radiotherapy induced [256];
- the stricture is consequent to LS [256] (this is controversial and for some groups LS is a contraindication for a staged urethroplasty [302]; Kozinn *et al*. recommend leaving at least ten months between 1st stage and 2nd stage re-tubularisation in patients with LS to allow graft complication to develop) [256];
- there is severe spongiofibrosis [348].

6.3.2.3.2 Outcomes

Patency rates of 33.3-94.6% at mean follow-up of 11.2-50 months have been described for staged urethroplasty in series which include men with bulbar urethral stricture disease [256, 302, 325, 348-350]. Grafts (mesh graft, preputial skin, oral mucosa) can be used in staged augmentation as well as marsupialisation [325,

348]. In patients affected by LS, a 52.2% patency rate for staged urethroplasty was reported whereas this was 86% for single-stage buccal mucosa urethroplasty ($p < 0.01$) [302]. It is highly likely that different stricture and patient characteristics contributed to the differences reported and this should be kept in mind when interpreting the data. Of note, 19-45.5% of patients planned for staged urethroplasty declined to proceed to 2nd stage re-tubularisation [256, 349].

Early complications after staged procedures include wound dehiscence, UTI, epididymitis, scrotal abscess and penile numbness. Specific to 2nd stage Johanson urethroplasty UCF occurs in 3-15%. The actual incidence of UCF is probably higher as many small fistulae close spontaneously with conservative management and are not formally reported [302, 325, 348].

Late complications of 1st stage urethroplasty include a need for revision in up to 19% - consequent to recurrence of LS in graft(s) (8.8%), graft contracture (6.6%) and stomal stenosis (3.3%) [256]. Late complications of 2nd stage urethroplasty include post-micturition dribble in 14-18%, SUI in up to 16%, penile curvature in up to 9%, ED in up to 4%, urethral diverticulum formation in 1% and cold glans [302, 348, 350]. Stress urinary incontinence (SUI), penile curvature and ED appear to be particularly associated with mesh graft stage urethroplasty [348, 350].

After their procedure, 86% and 96.6% of men with respectively mesh graft and buccal mucosa graft staged urethroplasty were satisfied. The patient groups included in the review were too small to detect significant differences [348]. All are retrospective series – with heterogenous indications, stricture locations (not exclusively bulbar), stricture lengths and patient groups. It is consequently difficult to draw meaningful conclusions from the little data that are available.

See supplementary Table S6.10 for more information.

Summary of evidence	LE
Staged urethroplasty for bulbar strictures and for strictures involving the bulbar urethra yields patency rates of 33.3-90% depending upon patient and stricture characteristics and patient satisfaction is high with all types of staged urethroplasty.	3
Lichen sclerosus is a relative contraindication for staged urethroplasty in the literature with lower long-term urethral patency rates of 52.2% compared to urethral patency rates of 64.3% in non-lichen sclerosis patients.	3
Up to 45.5% of men elect not to proceed to 2nd stage re-tubularisation after successful 1st stage.	3
Up to 19% of men required revision of their 1st stage urethroplasty.	3

Recommendations	Strength rating
Offer staged urethroplasty to men with complex anterior urethral stricture disease not suitable for single stage urethroplasty and who are fit for reconstruction.	Weak
Do not perform staged bulbar urethroplasty for lichen sclerosis if single stage urethroplasty is possible.	Weak
Consider staged procedure in patients unsure about perineal urethrostomy versus urethral reconstruction.	Weak
Warn men that staged urethroplasty may comprise more than two stages.	Weak

6.3.2.4 Risk factors for adverse outcomes

In four series specifically dedicated to risk factors for failure after urethroplasty using multivariate analysis, there is conflicting evidence about several factors (aetiology, comorbidity, stricture length, prior therapy) that might be predictive for failure after urethroplasty (Table 6.6). Advanced age does not appear to be a risk factor for urethroplasty failure in the majority of studies, with the exception of Viers *et al*. 2017 [354] retrospective case series which found that the risk for recurrence was significantly higher beyond the age of 60 (< 50 yrs 94%, > 70 yrs 74%) in 184 patients having a wide variety of urethroplasties. Previous radiation therapy was also found to be a risk factor for stricture recurrence in both Viers' [354] retrospective case series and Ahyai's 2015 series [355] – with only a 71% patency rate at a median follow-up of 29 months in those with previous radiotherapy. Based on these data, a clear and evidence-based recommendation cannot be formulated.

Table 6.6: Risk factors for failure after urethroplasty based on multivariable Cox regression analyses

Study	N	Population	Comorbidity HR (95% CI)	Length HR (95% CI)	Aetiology HR (95% CI)	Prior stricture therapy HR (95% CI)
Breyer *et al*. 2010 [351]	443	Mixed	NS	NS	NS	Prior DVIU: 1.7 (1.0-3.0) Prior urethroplasty: 1.8 (1.1-3.1)
Kinnaird *et al*. 2014 [352]	604	Mixed	NS	≥ 5 cm: 2.3 (1.2-4.5)	Iatrogenic: 3.4 (1.2-10.0) LS: 5.9 (2.1-16.5) Infectious: 7.3 (2.3-23.7)	NS
Chapman *et al*. 2017 [319]	596	Isolated bulbar strictures	Overall comorbidity: 2.4 (1.1-5.3) Obesity: 2.9 (1.3-6.5)	1.2 (1.1-1.3)	Infectious: 3.7 (1.3-10.6)	NS
Verla *et al*. 2020 [353]	474	Anterior strictures	NS	NS	NS	NS

CI = confidence interval; HR = hazard ratio; LS = Lichen sclerosus; N = number of patients; NR = not reported NS = not significant.

6.3.2.5 Management of recurrence after bulbar urethroplasty

Kahokehr *et al*. [324] followed nearly 400 patients after urethroplasty and found a recurrence rate of 6% (n=25). Ninety-two percent of the failed cases were treated successfully with DVIU and only 8% needed another open reconstruction. However, they did not mention characteristics of the recurrent cases nor the duration of follow-up.

Rosenbaum *et al*. [356] and Javali *et al*. [357] retrospectively analysed the outcomes of BMG FGU for ReDo urethroplasty in 51 and 21 patients respectively using the other cheek as donor side. Patency rates were 82-86%, which is in the range of primary cases.

Vetterlein *et al*. [358] compared primary (no previous open urethroplasty) vs. ReDo (previous open urethroplasty with BMG) vs. secondary (previous open urethroplasty without use of BMG) cases in a retrospective series of 534 patients with BMG FGU. The patency rates in primary and ReDo cases were comparable (87%) whilst the outcome in secondary cases was worse (71%).

A small series (n=37) reported on the use of EPA for revision surgery after failed urethroplasty in strictures of 2.1 (range 1-3.5) cm length on average. Patency rates using EPA after failed primary EPA (51%) and after any other technique of urethroplasty (49%) were 95 and 94% respectively with a mean follow-up of 30 months [317].

Summary of evidence	LE
Buccal mucosa free graft urethroplasty after failed urethroplasty achieves the same patency rates as primary cases.	3

Recommendation	Strength rating
Use oral mucosa free graft urethroplasty for ReDo urethroplasty in case the of a long stricture.	Strong

6.3.3 ***Urethroplasty for penobulbar or panurethral strictures***

The possibilities for reconstruction are various and often include combinations of different techniques or grafts other than OMG. The patency rates are usually lower than in shorter reconstructions (Table 6.7). Hussein *et al*. [359] performed a RCT comparing skin grafts vs. skin flaps in strictures of mean length 15 cm and found no difference in patency rates (72% vs. 79%) or complications.

Warner *et al*. [302] performed a multi-institutional review in 2015 including 466 patients with stricture length > 8 cm and found an overall patency rate of 77.5%.

As discussed previously, Kozinn *et al*. [256] reported on the outcome of staged urethroplasty in a cohort of which 54.9% had panurethral strictures (Table 6.7).

Kulkarni *et al*. [360] proposed a one-stage completely perineal approach with invagination of the penis and one-sided urethral dissection. After 59 months the overall patency rate was 83.7% in 117 men with a mean stricture length of 14 cm.

Another option in patients refusing or unfit for complex reconstructive surgery is PU (see section 6.3.4 Perineal urethrostomy).

Table 6.7: Study characteristics and patency rates of series on penobulbar strictures

Author	Study	Length in cm (min, mean, range)	Technique	N	FU months (mean, range)	Patency
Hussein *et al*. 2011 [359]	RCT	NR, 15, 9-21	Skin graft vs. flap	37	36, 12-60	72 vs. 79%
Hussein *et al*. 2016 [361]	Prospective	NR, 8, NR	BM vs. skin dorsal onlay	69	56, NR	90 vs. 84%
Warner *et al*. 2015 [302]	Retrospective review	> 8, 12.5, 8-24	BM/staged/skin	466	20, 12-344	77.5%
El Dahshoury *et al*. 2009 [362]	Retrospective	NR, 18, 15-20	Skin flap	30	24, NR	87%
Mathur *et al*. 2010 [363]	Retrospective	NR, 12, 8-16.5	Tunica albuginea graft	86	36, NR	89%
Meeks *et al*. 2010 [364]	Retrospective	NR, 11, 4-24	Abdominal skin graft	21	28, 11-52	81%
Kulkarni *et al*. 2012 [360]	Retrospective	NR, 14	BM dorsal onlay	117	59, NR	83.7%
Tabassi *et al*. 2014 [365]	Retrospective	NR, 14.4, NR	BM dorsal onlay	117(37)	19, NR	84%
Xu *et al*. 2017 [298]	Retrospective	> 8, 12, 8-20	BM/LM/combination	81	>12, 41, 15-86	83%
Alsagheer *et al*. 2018 [366]	Retrospective	> 8, 11.3	BM onlay vs. skin flap	50	NR, 16, NR	70 vs. 77%
Kozinn *et al*. 2013 [256]	Retrospective	NR, 9.6, 4-17	Staged urethroplasty	91	15, 12-69	90.1%

BM = buccal mucosa; LM = lingual mucosa; FU = follow-up; N = number of patients; NR = not reported; RCT = randomised controlled trial.

Summary of evidence	LE
Publications about panurethral urethroplasties generally come from high volume centres.	4
Different materials and techniques might be needed for reconstruction.	3

Recommendations	Strength rating
Offer panurethral urethroplasties in specialised centres because different techniques and materials might be needed.	Weak
Combine techniques to treat panurethral strictures if one technique is not able to treat the whole extent of the stricture.	Weak

6.3.4 ***Perineal urethrostomy***

6.3.4.1 *Indications*

Perineal urethrostomy offers a permanent or temporary solution for restoration of voiding in men with complex urethral stricture disease in whom:

- there are no further options to restore urethral patency either due to multiple previous failed urethroplasties [302, 346] or multiple co-morbidities precluding a more expansive surgical undertaking after failed endoscopic management [367];
- there is a lack of certainty on behalf of the surgeon regarding the most appropriate form of urethroplasty for the patient [346];
- following urethrectomy and/or penectomy for cancer [368].

6.3.4.2 *Types of perineal urethrostomy*

Johanson described an inverted anterior scrotal funnel PU in 1953. This was later modified by Gil-Vernet and Blandy to utilise a posteriorly based scrotal flap. Both these techniques utilise an inverted U or lambda incision. The Gil-Vernet-Blandy PU has been further modified with the addition of dorsal and/or ventral free OMG augment to allow use of PU in men with strictures consequent to radiotherapy [369] or LS [258] and/or in men with PU stenosis or stricture extending into the proximal bulbar or membranous urethra ("augmented Blandy") [367].

More recently, the '7 flap' PU utilising a unilateral posteriorly based scrotal flap has been developed for use in the very obese, or in men of all BMI with stricture extension into the proximal bulbar or membranous urethra [370]. Initially this was performed with transection of the distal bulbar urethra but latterly the technique has been modified to a non-transection technique with loop mobilisation of the bulbar urethra ("loop PU") [371]. The "7-flap" utilises a midline incision – which has been shown to have a significantly reduced side-effect profile in terms of superficial wound infection (1.9% c.f. 18.6%) and superficial wound dehiscence (11.9% c.f. 23.3%) than the inverted U or lambda incision [372, 373] and may be associated with improved urethroplasty (and by inference PU) outcomes, at least in the short term (0% failure c.f. 6.2% failure at six months) [372]. Operative time is similar for all types of PU with mean operative time varying between 97.2 minutes to 112 minutes [368, 374].

The utilisation of PU is increasing [375] – constituting 4.5% of 403 procedures for complex urethral stricture disease in a tertiary centre in 2008 and 38.7% in 2017 [376]. Perineal urethrostomy patients are generally older than those having urethroplasty with a median of 62.6 years of age for men having PU in Fuchs *et al*. 2018 series compared with a median of 53.2 years for men having anterior urethroplasty [376]. Between 18.7% and 73.4% of men having staged urethroplasty for complex anterior urethral stricture decline to proceed to 2nd stage re-tubularisation after a successful 1st stage and remain voiding from the PU of their 1st stage urethroplasty [256, 346, 349].

6.3.4.3 *Outcomes*

6.3.4.3.1 Patency rates

Patency rates of 70-95% at mean/median follow-up of 20–63 months have been described [302, 346, 354, 367-369, 371, 374, 376]. All reports are retrospective series – all of which are heterogenous in terms of indications and patients. There is consequently little data available to determine which is the best technique for PU.

McKibben *et al*. reported a patency rate of 92.9% in 42 patients for "7-flap" PU at median follow-up of 53.6 months, whilst they had a 100% patency rate with loop PU in 20 patients at a median follow-up of thirteen months [371].

Lumen *et al*. in 2015 reported a 74.3% patency rate for Johanson PU compared with an 87.5% patency rate for Gil-Vernet-Blandy PU (p=0.248), but with a significantly longer follow-up after Johanson PU (median 36 vs. nine months) [368]. Barbagli *et al*. published the largest series of PU patients to date – including 173 men (all of whom had been planned to have a staged urethroplasty for their complex anterior urethral stricture disease and 127 (73.4%) of whom declined to proceed with 2nd stage re-tubularisation). The median follow-up in this series was 62 months and the patency rate was 70% - confirming that patency rates for PU (and indeed for all urethroplasty [269, 322] reduce with time [346].

See supplementary Table S6.11 for further information.

6.3.4.3.2 Complications

Perineal urethrostomy complications occur in 2.5-11.4% and include superficial wound dehiscence, scrotal abscess, UTI and urosepsis, bleeding, and transient scrotal pain and numbness [302, 368, 377]. The majority of

complications are Clavien-Dindo grades 1 (2.9-18.8%) and 2 (0-2.9%). Grade 3 complications are rare and only occur in 5.7-6.2%. In the medium-term 22.2-30.8% of men with PU report post-micturition dribble [368].

6.3.4.3.3 Patient reported outcomes

Barbagli *et al*. reported that 168/173 (97.1%) of men were satisfied or very satisfied with the outcome of their Gil-Vernet-Blandy PU and would have the procedure again at median 62 months follow-up. Of these, 166/173 (95.9%) felt they had excellent or good results from their Gil-Vernet-Blandy PU, 145/173 (85%) felt it caused them no problems and 141/173 (82%) felt it caused their partner no problems [346]. The Trauma and Urologic Reconstructive Network of Surgeons (TURNS) collaborative found no significant change in sexual function and a significant improvement in urinary symptoms following PU in a small group of patients [378] whilst Lumen *et al*. found satisfactory or acceptable International Prostate Symptom Score (IPSS) outcomes in 26/32 (81.25%) of men with Johanson or Gil-Vernet-Blandy PU at a median follow-up of 32 months and nine months, respectively.

McKibben *et al*. found a mean patient global impression of improvement (PGI-I) of 1.3 in nineteen patients with either loop PU or "7-flap" PU [371] at median 31 months follow-up.

6.3.4.3.4 Risk factors for patency failure of the perineal urethrostomy

Lichen Sclerosus, trauma and infection urethral strictures have poorer outcomes from PU, with PU patency failure in 36.7-67% at a median 62 months follow-up [346, 377]. Worse outcomes were also observed in patients with previous failed urethroplasty and multiple previous endoscopic and open treatments [346, 368, 369].

Barbagli *et al*. found that stricture length was inversely related to PU patency, as was patient age [346]. Conversely Viers *et al*. found outcomes worsened with age, reporting patency rates of 100% in men < 50 years old compared with 83% in men aged 60-69 years old [354]. Lopez *et al*. found increased risk of PU failure in men with ischaemic heart disease which makes sense and would be a putative explanation for the age-related worsening of outcomes noted by Viers *et al*. [377].

Failure of PU is most commonly treated with surgical revision of PU using V-Y plasty, augmentation or complete ReDo but can also be managed with periodic dilatation or urinary diversion [346, 367, 368].

For further information see supplementary Table S6.11.

Summary of evidence	LE
Perineal urethrostomy provides very good short- and long-term outcomes for men with complex urethral stricture disease.	1a
Perineal urethrostomy provides very good short and long-term outcomes for men who are unable to have complex reconstruction due to co-morbidities.	2b
All types of PU yield equivalent very good outcomes.	4
Augmented Gil-Vernet-Blandy or "7-flap" PU yield very good outcomes in men with extension of their urethral stricture disease into the proximal bulbar or membranous urethra.	2
"7-flap" PU yields very good results in obese men.	3

Recommendations	Strength rating
Offer perineal urethrostomy as a management option to men with complex anterior urethral stricture disease.	Strong
Offer perineal urethrostomy for men with anterior urethral stricture disease who are not fit or not willing to undergo formal reconstruction.	Weak
Choose type of perineal urethrostomy based on personal experience and patient characteristics.	Weak
Consider augmented Gil-Vernet-Blandy perineal urethrostomy or "7-flap" perineal urethrostomy in men with proximal bulbar or membranous urethral stricture disease.	Weak
Consider "7-flap" urethroplasty in obese men.	Weak

*6.3.5 **Posterior urethra***

6.3.5.1 Non-traumatic posterior urethral stenosis

6.3.5.1.1 Treatment of non-traumatic posterior urethral stenosis

Several treatment modalities including conservative management (see section 6.1 Conservative options), endoluminal, open or minimally invasive surgical procedures are currently available, depending on patient's goals and health status.

6.3.5.1.2 Endoluminal management of non-traumatic posterior urethral stenosis

6.3.5.1.2.1 Dilatation of non-traumatic posterior urethral stenosis

This can be done under loco-regional anaesthesia [379-383]. Dilatation is used for VUAS [379-384] or radiation-induced BMS [112, 385] and in the majority of reported cases, patients were not previously treated for their stricture (see supplementary Table S6.12). Patency rates vary widely between 0% and 89% [112, 379-385]. The risk of *de novo* UI was low (0-11%) and no other complications were reported. It is of note that most series report on visually controlled dilatation [379-383] in VUAS without complete obliteration.

6.3.5.1.2.2 Endoscopic incision/resection of non-traumatic posterior urethral stenosis (Table 6.8)

Incisions can be performed at multiple locations according to surgeon's preference [386]. However, aggressive incisions at the six and twelve o'clock positions should be avoided because of the risk of respectively rectal injury and urosymphyseal fistulation [182, 387-389]. The risk of urosymphyseal fistulation is especially a concern after previous radiotherapy [390]. Direct vision internal urethrotomy is mainly performed in patients with primary or recalcitrant VUAS although one series performed it in a mix of patients with VUAS and BNS [391] and two series reported it for radiation-induced BMS [112, 385]. Direct vision internal urethrotomy/dilatation for non-irradiated BMS are usually included in series reporting on anterior strictures (see section 6.2 Male endoluminal treatment of anterior urethral strictures). Patency after a 1st "cold/hot knife" DVIU ranges between 25-80% [379, 382, 384, 386, 391-396]. Laser incision yields a 69-100% patency rate [382, 384, 397, 398]. In a retrospective and unbalanced series, LaBossiere *et al*. found better patency rates for laser incision as compared to dilatation, "cold knife" DVIU and transurethral resection (TUR) [382]. Redshaw *et al*. reported inferior patency rates for "cold knife" incision vs. "hot knife" incision followed by MMC for BNS (50 vs. 63%; p=0.03) [240] (see supplementary Table S6.13). Urinary incontinence largely varies between 0 and 53% but some series have not assessed urinary continence before DVIU [392, 394]. In series where pre-DVIU continence data were available, *de novo* urinary continence after DVIU ranges between 0% and 10% [379, 384, 393, 395, 397]. Noteworthy, of 21 patients that were incontinent pre-DVIU in the series of Giannarini *et al*., eleven (52%) patients became continent and eight (38%) patients experienced improvement after DVIU [393]. In the series of Lagerveld, 1/5 (20%) patients noticed improvement of UI after DVIU [397]. As most recurrences will occur early [393, 394], it is advised to wait for three to four months after DVIU [386, 394, 399] to proceed with incontinence surgery if necessary, although others wait for twelve months [400]. The presence of recurrence must be ruled out by cystoscopy prior to incontinence surgery [386, 394, 399, 400].

Another option is to resect the stenosis. Popken *et al*. reported a 47% patency rate with TUR for untreated VUAS and no patient suffered *de novo* SUI [395]. Kranz *et al*. compared the results of TUR in 87 and 60 patients with respectively VUAS after RP and BNS after TURP. After a median follow-up of 27 (range: 1-98) months, patency rate was 40.2% for VUAS and 58.3% for BNS (p=0.031). The rate of *de novo* incontinence was significantly higher in patients treated for VUAS compared to BNS (13.8 vs. 1.7%; p=0.011) [401]. Kravchick *et al*. reported a higher incontinence rate after TUR compared to "cold knife" DVIU and dilatation for VUAS (50% vs. 13% vs. 0%, respectively; p=0.005) [383]. However, the number of patients were small and a selection bias of more severe cases towards TUR might be possible [383]. Alternatively, thermal damage to the adjacent external sphincter during TUR (especially with monopolar current) might be the cause of incontinence [383]. Brodak *et al*. compared TUR by bipolar resection (n=22) with holmium laser incision and vaporisation (n=17). After a mean follow-up of 42 months, two (9.1%) and four (23.5%) patients suffered a recurrence with bipolar and laser resection respectively (p=0.37). After six months, patients treated with bipolar resection had a significant better Q_{max} compared to laser treatment (13 vs. 6.1 ml/s; $p < 0.001$) [398]. Bipolar plasma vaporisation produced an 82% patency rate at a mean 24 months follow-up in 28 patients with VUAS who previously failed endoscopic treatment [402].

Cut-to-the-light technique for a complete obliterative stricture is not advised because of the very-low likelihood of durable patency and for the risk of false passage towards the rectum [399, 403, 404].

Repetitive DVIU was often able to stabilise the stricture [112, 379, 382, 385, 391-393, 401], but ultimately 6-10% required urinary diversion [394] or chronic suprapubic cystostomy [385, 391].

Transurethral resection can be performed for prostatic obstruction due to sloughing after high-energy treatments (HIFU, cryoablation) [96]. Transurethral resection for obstructive necrotic debris after radiotherapy is possible but is of limited role. Risk of recurrence is 50% and risk of *de novo* UI is 15-25% [96].

Table 6.8: Results of endoluminal incision/resection for posterior non-traumatic stenosis

Study	Modality	Type	N	Previous treatment (%)	FU (months)	Patency° (%)	Urinary incontinence (%)	Complications (%)
Merrick *et al*. [385]	Dilatation/ "Cold knife" DVIU	Radiation-induced BMS	29	0	NR	69	NR	NR
Sullivan *et al*. [112]	Dilatation (n=15) / "Cold knife" DVIU (n=20)	Radiation-induced BMS	39	0	16 (2-48)	51	11	NR
Brede *et al*. [394]	"Cold knife" DVIU	VUAS	63	Dilation 33 Incision 38 Both 29	11 (1-144)	73	52*	NR
Yurkanin *et al*. [392]	"Cold knife" DVIU	VUAS	61	Dilatation 100	31 (1-77)	87	12**	NR
Giannarini *et al*. [393]	"Cold knife" DVIU	VUAS	43	0	48 (23-80)	74	0	NR
Ramchandani *et al*. [379]	"Cold knife" DVIU	VUAS	10	0	NR	80	10	0
Hayashi *et al*. [384]	"Cold knife" DVIU	VUAS	6	Dilatation: 100	NR	50	NR	NR
	Holmium laser DVIU	VUAS	3	Dilatation + DVIU: 100	11-37	100	0	NR
Lagerveld *et al*. [397]	Holmium laser DVIU	VUAS	10	None: 40 Endoscopic (dilatation +/- DVIU +/- ISD): 60	18 (3-29)	100	0	0
Ramirez *et al*. [391]	"Hot knife" DVIU	VUAS: 74% BNS: 26%	50	None: 22	16	72	9	NR
Gousse *et al*. [396]	"Hot knife" DVIU	VUAS	15	None	15 (6-26)	80	100***	NR
Bang *et al*. [386]	"Hot knife" DVIU	VUAS	37	NR	13 (2-33)	65	100***	NR
Popken *et al*. [395]	"Cold knife" DVIU	VUAS	6	None	12-72	50	0	NR
	TUR	VUAS	15	None		47	0	NR
Kranz *et al*. [401]	TUR	VUAS	87	NR	27 (1-98)	40.2	13.8	NR
	TUR	VUAS	60	NR		58.3	1.7	NR
Brodak *et al*. [398]	TUR (bipolar)	BNS	22	DVIU 45	42 (14-72)	91	NR	NR
	Holmium laser DVIU	VUAS	17	DVIU: 12		76	NR	NR
Ozturk *et al*. [402]	TUR (bipolar)	VUAS	28	Dilatation: 75 DVIU: 25	24 (6-66)	82	0	0
LaBossiere *et al*. [382]	Holmium laser DVIU	VUAS	70	NR	10	69	NR	NR
	"Cold knife" DVIU	VUAS	8	NR		25	NR	NR
	TUR	VUAS	36	NR		39	NR	NR

BNS = bladder neck stenosis; DVIU = Direct vision internal urethrotomy; FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; NR = not reported; TUR = transurethral resection; VUAS = vesico-urethral anastomosis stricture.

°patency rate after 1st endoluminal treatment evaluated in the study.

** requiring incontinence surgery (artificial urinary sphincter or male sling).*

*** slightly problematic urinary incontinence by questionnaire post DVIU (no data on pre DVIU continence).*

****all incontinent pre-operatively.*

6.3.5.1.2.3 Post-dilatation/direct vision internal urethrotomy strategies for non-traumatic posterior urethral stenosis

6.3.5.1.2.3.1 Intermittent self-dilatation for non-traumatic posterior urethral stenosis

As for anterior strictures, ISD can be offered to patients for recurrent posterior stenosis after dilation/DVIU in order to stabilise the stenosis. This is especially relevant for patients unfit/unwilling to undergo surgery or in patients with radiation-induced BMS [112, 382, 385, 405]. Although ISD may be acceptable to many urologists and patients, it usually is associated with a reduced QoL and poor patient compliance [30].

6.3.5.1.2.3.2 Intralesional injections for non-traumatic posterior urethral stenosis

In order to stabilise the luminal fibrosis and consequently to reduce the risk of recurrence, injection of antifibrotic agents at the time of endoluminal treatment has been proposed. The majority of patients in these studies were patients with recalcitrant/recurrent non-obliterative VUAS/BNS. Two series used corticosteroids [383, 399], whilst the others used MMC [240, 400, 403-406]. Patency rates with corticosteroid injections range between 50 and 100% [383, 399]. Patency rates with MMC vary between 50 and 79% [240, 400, 403-406]. No trials comparing endoluminal treatment with or without adjuvant intralesional injections were identified.

See supplementary Table S6.13 for further information.

Complications are low across most studies, but all studies were retrospective in nature. Redshaw *et al*. also reported grade 3 complications in four out of 55 (7%) patients, including osteitis pubis (n=2), bladder neck necrosis (n=1) and rectourethral fistula (n=1) in one multi-institutional study [240]. Three of these patients ultimately required urinary diversion with additional faecal diversion in one patient [240]. Given the severity of these complications, although rare, MMC should not be used outside the framework of a clinical trial [407].

6.3.5.1.2.3.3 Urethral stent for non-traumatic posterior urethral stenosis

Stents have been used anecdotally in the posterior urethra [247, 248, 382]. Patency rate are relatively low (47-60%) [247, 248, 382] at the cost of a high-risk for UI (19-82%) [247, 248].

Summary of evidence	**LE**
For non-obliterative VUAS and radiation-induced BMS, visually controlled dilatation and DVIU yield a patency rate of respectively 0-89% and 25-100% with a low complication rate. It can be performed under loco-regional anaesthesia.	3
During DVIU, deep incision might provoke injury to the rectum at the six o' clock position and might provoke urosymphyseal fistulation at the twelve o'clock position.	3
For BNS, TUR and "hot-knife" incision yield a patency rate of respectively 58.3 and 72% with a low complication rate.	3
Repetitive endoluminal treatments in non-obliterative VUAS, radiation-induced BMS or BNS have the ability to stabilise the posterior stenosis and are easy to perform compared to reconstructive surgery.	3
Any form of endoluminal treatment might be associated with *de novo* UI (up to 25%) or worsening of existing UI (up to 15%).	3
Vesico-urethral anastomosis stricture, BMS and BNS with complete obliteration are not included in present series and endoluminal treatment is unlikely to be successful.	3
Urethral stents at the posterior urethra have a rather low patency rate (47-60%) and incontinence rate (19-82%).	3

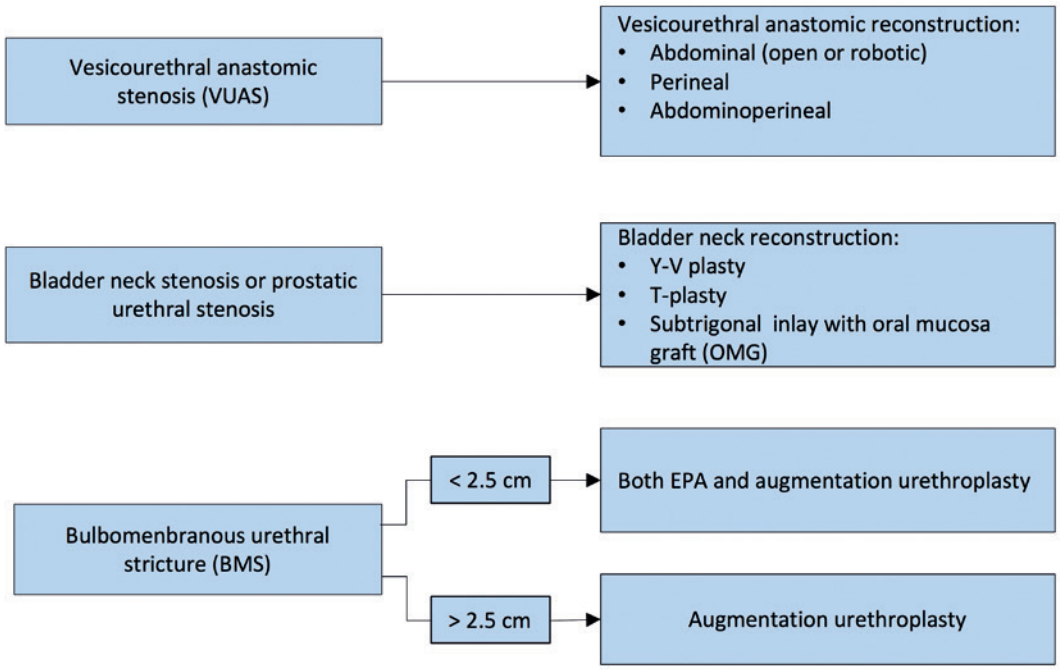
Recommendations	**Strength rating**
Perform visually controlled dilatation or direct vision internal urethrotomy (DVIU) as 1st line-treatment for a non-obliterative vesico-urethral anastomosis stricture (VUAS) or radiation-induced bulbomembranous strictures (BMS).	Weak
Do not perform deep incisions at the six and twelve o' clock position during DVIU for VUAS or radiation-induced BMS.	Strong
Perform transurethral resection (TUR) or "hot-knife" DVIU as 1st line-treatment for patients with non-obliterative bladder neck stenosis (BNS) after surgery for benign prostatic obstruction.	Strong
Perform repetitive endoluminal treatments in non-obliterative VUAS or BNS in an attempt to stabilise the stricture.	Weak
Warn patients about the risk of *de novo* urinary incontinence (UI) or exacerbation of existing UI after endoluminal treatment.	Weak

Do not perform endoluminal treatment in case of VUAS, BMS and BNS with complete obliteration.	Strong
Do not use stents for strictures at the posterior urethra.	Weak

6.3.5.1.3 Lower urinary tract reconstruction for non-traumatic posterior urethral stenosis

If endoluminal treatment (repeatedly) fails or in case of a completely obliterated posterior stenosis [403, 404, 408, 409], lower urinary tract reconstruction may be considered in fit patients motivated to undergo surgery (Figure 6.1). The choice of lower urinary tract reconstruction will depend upon the length, location, calibre and aetiology of the stenosis, continence status, bladder function, previous radiotherapy, patient's preference and surgeon's expertise.

Figure 6.1: Options for lower urinary tract reconstruction of non-traumatic posterior urethral obstruction (stenosis/stricture)



6.3.5.1.3.1 Redo vesico-urethral anastomosis for vesico-urethral anastomotic stenosis after radical prostatectomy

After excision of the stenosis, ReDo vesico-urethral anastomosis (ReDo VUA) can be performed. This may be performed via a retropubic, perineal, combined abdominoperineal or robot-assisted approach. Nikolavsky *et al*. proposes a retropubic approach for VUAS involving the bladder neck, a perineal approach for short VUAS with intact bladder neck and an abdominoperineal approach for long segment (> 3 cm) VUAS with bladder neck involvement [408]. The ReDo VUA must be performed in a tension-free fashion which can be achieved either by mobilisation of the bladder (retropubic approach), mobilisation of the bulbar urethra with corporal splitting and inferior pubectomy if necessary (perineal approach) or both (abdominoperineal approach)[408, 410]. Dinerman *et al*. reported a robot-assisted abdominoperineal approach in a case with 4.5 cm long complete obliteration [411]. Kirshenbaum *et al*. reported a pure robot-assisted abdominal approach. Regardless of the approach, the procedure is technically demanding due to the location deep under the pubic symphysis, and the proximity of the external sphincter [410]. As a consequence, the surgical morbidity must be taken into account. As most patients with VUAS were healthy enough to undergo RP, most patients will likewise remain fit and eligible for VUAS surgical reconstruction [408, 410].

Table 6.9: Outcomes of ReDo vesico-urethral anastomosis

Study	N	Approach (%)	Previous RT (%)	FU (months)	Length (cm)	Patency (%)	Incontinence (%)	Complications (%)
Nikolavsky *et al*. [408]	12	Perineal: 25 Abdominal: 67 Abdominoperineal: 17	25	76 (14-120)	2.5 (1-5)	67	58	Persistent extravasation due to anastomotic dehiscence grade 3b: 8.3 (prior RT)
Mundy *et al*. [410]	17	Transperineal	0	NR	NR	88	100	NR
	6		100	NR	NR	67	100	NR
Schuettfort *et al*. [412]	22	Transperineal	0	45 (4-77)	NR	91	100*	Rectal injury: 4 Lower leg paresthesia: 4
	1		100		NR	0	100*	
Pfalzgraf *et al*. [413]	20	Retropubic	NR	63 (15-109)	NR	60	65**	UTI: 5 Fever: 5 Renal failure: 5 (all grade 2)
Giudice *et al*. [414]	10	Perineal: 5 Abdominal: 4 Combined: 1	NR	30 (4-106)	NR	80	70	NR
Dinerman *et al*. [411]	1	Robot-assisted abdominoperineal	0	12	4.5	100	0***	0
Kirshenbaum *et al*. [409]	5	Robot-assisted abdominal (±VY-plasty)	0	14 (5-30-)	NR	60	0	Pubovesical fistula: 20 grade 3b

FU = follow-up; N = number of patients; NR = not reported; RT = radiotherapy; UTI = Urinary tract infection.

* *incontinent before ReDo VUA.*

** *de novo incontinence in four out of eleven patients.*

****social continent (1 pad/day).*

ReDo VUA in non-irradiated patients yields patency rates of 60-91% (Table 6.9) [408-410, 412-414]. Prior radiotherapy is a risk factor for failure [410, 412]. In addition, radiation-induced bladder toxicity might provoke reduced bladder capacity, low bladder compliance, bladder spasms and pain, and urethral necrosis making reconstruction futile (see below) [390, 410, 415]. ReDo VUA should only be done in patients with adequate bladder function and in the absence of (peri)-urethral pathology (urethral necrosis, calcification, fistulation). Flaps (gracilis flap, peritoneal flap) to support and protect the anastomosis may be beneficial in irradiated patients [408].

With the transperineal approach, UI is inevitable, as this approach disrupts the external sphincter [409, 410, 412, 414]. With the retropubic approach, Pfalzgraf *et al*. reported *de novo* incontinence in only four out of eleven (36%) patients [413]. In the series of Nikolavsky *et al*. where a retropubic approach was predominantly used, incontinence rate was 58% [408]. Kirshenbaum *et al*. reported no incontinence in five patients treated by robot-assisted retropubic approach [409]. Giudice *et al*. reported incontinence in one out of four patients treated with the retropubic approach [414]. Therefore, some authors [96, 408, 409] have proposed a preference for the retropubic approach in patients with good pre-operative urinary continence, although both approaches have never been directly compared for UI. In addition, the lack of perineal dissection by a retropubic approach will preserve the perineal anatomy and vascularisation which makes subsequent artificial urinary sphincter (AUS) less demanding [409]. Artificial urinary sphincter implantation should be deferred because of the risk of VUAS recurrence and difficulty of treating any recurrent VUAS with the cuff of the AUS in place [394, 410]. The exact timing of AUS placement is not consensual in the literature but most advise waiting at least three to six months to ensure stability of the VUA patency [390, 407, 410, 412, 413].

Due to the complexity of this pathology the EAU Urethral Strictures Panel advises that VUAS reconstruction should be performed only in experienced high-volume centres, particularly after prior radiotherapy or other energy ablative treatments.

Summary of evidence	LE
ReDo VUA has patency rates of 60-91% in non-irradiated patients and 67% in irradiated patients with obliterative VUAS or VUAS refractory to endoluminal treatment.	3
Urinary incontinence is inevitable after transperineal ReDo VUA. Artificial urinary sphincter placement can be offered after three to six months if patency of ReDo VUA is ensured.	3
De novo incontinence with retropubic ReDo VUA is 0-58%.	3

Recommendations	Strength rating
Perform ReDo vesico-urethral anastomosis (VUA) in non-irradiated patients and irradiated patients with adequate bladder function with obliterative vesico-urethral anastomosis stricture or vesico-urethral anastomosis stricture refractory to endoluminal treatment.	Weak
Warn patient that urinary incontinence (UI) is inevitable after transperineal ReDo VUA and that subsequent anti-UI surgery might be needed in a next stage, after at least three to six months.	Strong
Offer ReDo VUA by retropubic approach if the patient is pre-operatively continent.	Weak

6.3.5.1.3.2 Posterior stenosis after surgery for benign prostatic obstruction

6.3.5.1.3.2.1 Bladder neck reconstruction for bladder neck stenosis after surgery for benign prostatic obstruction

The bladder neck is augmented by advancement of local bladder flaps (Y-V or T-plasty) with or without resection of scar tissue. They are used for BNS refractory to endoscopic treatments [409, 416-418]. Patency rates vary between 83% to 100% with fourteen to 45 months follow-up [409, 416-418]. There is a trend to perform bladder neck reconstruction by minimally invasive approach (laparoscopic, robot-assisted)[409, 417, 418]. *De novo* incontinence rate ranges from 0% to 14% [409, 416-418]. Satisfaction among patient is high with 88.5% of patients stating that they are pleased with the surgery, with an improvement of QoL in 75% of patients [416, 418]. Recently, a robot-assisted augmentation technique with subtrigonal buccal mucosa inlay has been successfully reported in a case report, but this technique requires further investigation [419].

See supplementary Table S6.14 for further information.

6.3.5.1.3.2.2 Bulbomembranous strictures after surgery for benign prostatic obstruction

Bulbomembranous urethral strictures (BMS) after TURP or simple prostatectomy are managed as bulbar strictures and can be treated by EPA or augmentation urethroplasty with a graft, taking into account the length and tightness of the stricture [79, 420]. As reconstruction is in the proximity of the external sphincter and the bladder neck was already damaged during BPO surgery, the risk of incontinence (up to 25%) is present [79].

Summary of evidence	LE
Bladder neck reconstruction with Y-V or T-plasty for treatment refractory BNS has patency rates of 83-100%.	3
Incontinence occurs in up to 14% with bladder neck reconstruction and up to 25% after reconstruction of BMS after previous surgery for BPO.	3

Recommendations	Strength rating
Perform bladder neck reconstruction with Y-V or T-plasty for treatment refractory bladder neck stenosis (BNS).	Weak
Warn patients about *de novo* urinary incontinence after reconstruction for BNS or bulbomembranous urethral strictures with previous benign prostatic obstruction surgery as aetiology.	Strong

6.3.5.1.3.3 Radiation/high-energy induced posterior strictures

6.3.5.1.3.3.1 Bulbomembranous strictures secondary to radiation/high energy sources

The major challenge in treating radiation-induced strictures is the consequent tissue damage with impaired healing capacity, involving not only the stricture itself but also the adjacent proximal and distal areas of the scar [410, 421]. Additionally, proximity of the stricture to the external sphincter can further complicate surgery [79]. Due to these challenges, patients with radiation-induced BMS have long been considered poor candidates for urethral reconstruction, and have been treated with urinary diversion if endoscopic treatments failed or were not possible [410].

Most radiation-induced BMS are short and in these cases EPA is possible [79, 184, 422, 423]. Reported patency rates vary between 67% and 95% [79, 184, 423, 424]. *De novo* UI was reported in 33-36% of cases [79, 184, 423, 424] and this seems to be higher compared to the rates reported for bulbar and traumatic-posterior strictures (see sections 6.3.2 and 6.3.5). Chung *et al*. reported *de novo* incontinence in twelve out of 36 (33%) patients with EPA for radiation-induced BMS vs. four out of 33 (12%) patients with EPA for PFUI (p=0.05) [424].

Excision and primary anastomosis has the advantage of avoiding the use of a graft or a local flap in an area of poor vascular health. However, EPA will not be possible for BMS with a long bulbar segment and in these cases, augmentation urethroplasty will be necessary despite the aforementioned concerns [184, 423, 425, 426]. Glass *et al*. used a cut-off of 2.5 cm to proceed with augmentation urethroplasty, whilst this was 2 cm by Meeks *et al*. [423, 426]. Some authors have even used augmentation urethroplasty as their standard technique for radiation-induced BMS [355]. Both dorsal [420, 425] and ventral onlay [355, 426] have been described to treat radiation-induced BMS. In the absence of a robust vascular graft bed, the support by a gracilis flap has been proposed during ventral onlay graft urethroplasty [426, 427]. Patency rates with augmentation urethroplasty vary between 50 and 83% [184, 355, 423, 425] with *de novo* incontinence ranging between 11 and 50% [184, 355, 425] (see supplementary Table S6.15). Rourke *et al*. reported a patency rate of 91% vs. 75% for respectively EPA and augmentation urethroplasty but this difference did not reach statistical significance (p=0.31) [425]. Of note, strictures treated with augmentation urethroplasty were significantly longer compared to those treated by EPA (respectively 6.1 vs. 2.1 cm; $p < 0.001$). They reported no significant differences in *de novo* urinary incontinence (26 vs. 25%; p=1), new onset ED (35 vs. 0%; p=0.06) or other adverse events (30% vs. 33%; p=1) [425].

6.3.5.1.3.3.2 Prostatic strictures secondary to radiation/high energy sources

Radiotherapy and high-energy modalities (cryoablation, HIFU) might provoke prostatic necrosis, sloughing and obstruction [96]. Cases refractory to TUR and with good bladder capacity might be salvaged by prostatectomy taking into account the morbidity associated with salvage RP (rectal injury, VUAS, incontinence) [96, 421]. Mundy *et al*. treated nine patients with patency in six, (67%) and one (11%) needing an AUS for severe incontinence [410].

Cases with impaired bladder function, urethral necrosis and/or peri-urethral pathology should be considered for supravesical diversion, especially if a suprapubic catheter is not tolerated due to bladder pain or spasms [390, 407, 410, 415].

Recently, a "pull-through" procedure has been reported as an alternative to cutaneous diversion for reconstruction of the devastated posterior urethra associated with a defunctionalised bladder after radiation where tissue vascularity and quality is poor [428]. This novel technique of total lower urinary tract reconstruction combines salvage cystectomy, ileal neobladder formation and urethral pull-through. An AUS was implanted in a 2nd stage. All eight patients maintained a patent posterior urethra after a median follow-up of 58 (range 16-84) months. Five patients experienced low-grade complications after the 1st stage, but no high-grade complications were reported. Four out of eight (50%) patients experienced cuff erosion with need for removal and subsequent reimplantation. After a median of two revision surgeries (range 0 to 4), all patients achieved social continence enhancing QoL [428]. This technique requires further validation before its use can be recommended.

Summary of evidence	**LE**
Patency rates with EPA and augmentation urethroplasty are respectively 67-95% and 50-83% in case of radiation-induced BMS.	3
Radiation-induced BMS longer than 2-2.5 cm are rarely amenable for EPA.	3
De novo incontinence and new onset ED after urethral surgery for radiation-induced BMS are reported in respectively 11-50% and 0-35% of cases.	3
Salvage prostatectomy is able to achieve patency in 67% of patients for prostatic strictures after irradiation or high-energy treatments but morbidity is substantial.	4

Recommendations	**Strength rating**
Use either excision and primary anastomosis (EPA) or augmentation urethroplasty for short (< 2.5 cm) radiation-induced bulbomembranous strictures (BMS) refractory to endoscopic treatment depending on surgeon's experience.	Weak

Perform augmentation urethroplasty for long (> 2.5 cm) radiation-induced BMS.	Weak
Warn patients about the risk of *de novo* incontinence and new onset erectile dysfunction after urethroplasty for radiation-induced BMS.	Strong
Offer salvage prostatectomy in motivated and fit patients with adequate bladder function in case of a prostatic stricture due to irradiation or high-energy treatment.	Weak

6.3.5.1.4 Extirpative surgery and urinary diversion for non-traumatic posterior urethral stenosis

In complex and/or recurrent cases [408], lower urinary tract reconstruction is not possible or not indicated due to severe necrosis, calcification and significant morbidity, especially severe pain [407]. Intractable haematuria or fistulation might be other reasons to abandon the urethral outlet. Typically, the patient has a history of pelvic irradiation or high energy prostate cancer treatment and several previous attempts to achieve cure. Moreover, and equally important, any of the options used to deal with a devastated posterior urethra are dependent upon good bladder capacity, compliance and function allowing for bladder preservation as well as healthy distal ureters [390, 407]. The last resort therapeutic option is urinary diversion (continent or incontinent) with or without cystectomy [410, 415]. Different techniques have been described and the choice between them largely depends on the bladder capacity, presence of local symptoms, performance status and expectations of the patient. Cystectomy during urinary diversion is able to palliate symptoms of intractable bladder pain, spasms and haematuria which are especially prevalent after pelvic radiotherapy [429-432]. The satisfaction rate was reported to be 100% and the overwhelming majority of patients would have undergone this extirpative surgery an average of thirteen months sooner in a study of fifteen patients by Sack *et al*. [433]. In a report by Faris *et al*., 27% of the patients also required bowel diversion due to intractable gastrointestinal morbidity, highlighting the complexity of this pathology [415].

Summary of evidence	**LE**
Urinary diversion can improve QoL in patients with a devastated lower urinary tract with a high satisfaction rate.	3
Cystectomy is able to palliate symptoms of intractable bladder pain, spasms and haematuria.	3

Recommendations	**Strength rating**
Perform urinary diversion in recurrent or complex cases with loss of bladder capacity and/or incapacitating local symptoms.	Weak
Perform cystectomy during urinary diversion in case of intractable bladder pain, spasms and/or haematuria.	Weak

6.3.5.2 Post-traumatic posterior stenosis

The acute and early management of PFUIs is discussed in the EAU Guidelines on Urological Trauma. A non-obliterative stenosis is the result of a partial injury at the membranous urethra, or occurs after unsuccessful early realignment of a partial or complete injury. An obliterative stenosis is the consequence of a complete injury with a distraction defect between the ruptured urethral ends. The gap between these ends fills up with dense fibrotic tissue [6].

The deferred management of PFUI is at earliest three months after the trauma. After that period, the pelvic haematoma has nearly always resolved, the prostate has descended into a more normal position, the scar tissue has stabilised [434] and the patient is clinically stable and able to lie down in the lithotomy position [434, 435].

6.3.5.2.1 Endoluminal treatment for post-traumatic posterior stenosis

6.3.5.2.1.1 Endoluminal treatment as primary treatment for post-traumatic posterior stenosis

Endoluminal treatment (dilation, DVIU) of an obliterative stenosis using the cut-to-the light principle will not be successful [43] and has a risk of creating a false passage towards the bladder base or rectum [436]. For a non-obliterative, short (≤ 1.5 cm) stenosis, one attempt of endoluminal treatment (endoscopic incision or dilation) can be performed. Kulkarni *et al*. reported a 92.3 and 96.5% stricture-free rate with “cold knife” and holmium laser urethrotomy, respectively (median follow-up respectively 61 and 57 months) [437]. These results are challenged by Barbagli *et al*. who reported a 51% stricture-free rate with holmium laser urethrotomy but with no data on length of follow-up available [438]. Cai *et al*. compared patient outcomes between bipolar plasma vaporisation and “cold knife” DVIU in 53 patients with posterior traumatic (80%) and iatrogenic (20%) urethral strictures with significantly different stricture-free rates of 81.5% vs. 53.8% at a mean follow-up of 13.9 months, respectively [439]. No severe complications were reported in either group. A statistically significant shorter operative time was found in the bipolar group [439]. Barratt *et al*. calculated a composite

stricture-free rate of 20% after all types of endoscopic treatments (but with a mix of obliterative and non-obliterative stenoses) [43]. *De novo* UI was reported in 4% of cases [43]. Repetitive endoluminal treatments are unlikely to be curative and must be discouraged as this delays the time to definitive cure and can lead to more complications [440, 441].

6.3.5.2.1.2 Endoluminal treatment after failed urethroplasty for post-traumatic posterior stenosis

In case of a non-obliterative and short (≤ 1 cm) recurrence after failed urethroplasty, endoluminal treatment can be performed [442, 443]. Although a 1st and 2nd DVIU can be successful with a stricture-free rate of 22.9-77.3% and 0-60% respectively, three or more incisions are never successful (see supplementary Table S6.16) [442-446]. Therefore, repetitive endoluminal treatments (dilations and/or endoscopic incisions) can only be considered as a palliative option [443, 447].

Summary of evidence	LE
Endoluminal treatment of obliterative stenoses is not successful and may create false passages towards bladder or rectum.	3
Endoluminal treatment of short, non-obliterative, stenoses has a 20-96.5% stricture-free rate.	3
A 1st DVIU has stricture-free rates of 22.9-77.3% for a short and non-obliterative recurrence after excision and primary anastomosis.	3

Recommendations	Strength rating
Do not perform endoscopic treatment for an obliterative stenosis.	Strong
Perform one attempt at endoluminal treatment for a short, non-obliterative stenosis.	Weak
Do not perform more than two direct vision internal urethrotomies and/or dilatations for a short and non-obliterative recurrence after excision and primary anastomosis for a traumatic posterior stenosis if long-term urethral patency is the desired intent.	Weak

6.3.5.2.2 Urethroplasty for post-traumatic posterior stenosis

In view of the complexity and difficulty of urethroplasty and the fact that the best results are obtained with its first attempt, this surgery must be performed in high-volume centres [448-450]. It has been calculated that to achieve and maintain sufficient experience in the reconstruction of PFUI, one centre per twelve million inhabitants is sufficient (for well-resourced countries) [449].

6.3.5.2.2.1 First urethroplasty for post-traumatic posterior stenosis

6.3.5.2.2.1.1 Indication and technique of urethroplasty for post-traumatic posterior stenosis

Progressive perineal EPA is the standard treatment for an obliterative stenosis and for a non-obliterative stenosis as first attempt, or after failure of primary endoluminal treatment [43, 451].

Although both a midline and inverted U-incision are possible to gain access to the posterior urethra, a midline incision is associated with a significant reduction in trauma to the superficial perineal and posterior scrotal nerves and vessels, in the rate of surgical site infections (3.1 vs. 16.4%) and reduced length of hospitalisation [373].

A combined transpubic abdomino-perineal approach is only necessary in complicated cases such as those with associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury [436]. Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure [452]. Although also considered complex situations, iatrogenic recto-urethral fistula (after misdirected endoscopic treatment), traumatic recto-urethral fistula < 5 cm from the anus, UCF and urinoma cavity can usually be corrected by a progressive perineal approach only [436, 453].

6.3.5.2.2.1.2 Patency rate after urethroplasty for post-traumatic posterior stenosis

The overall patency rate after deferred EPA is 85.7% [43]. Complete excision of scar tissue is a strong predictor for freedom of stricture whereas number (3-5 vs. 6-7) and size (3.0 vs. 4.0 cm) of sutures are not [454]. One retrospective cohort study showed a significantly improved patency rate if dorsal anterior urethral spatulation was performed compared to ventral anterior urethral spatulation [455]. Another retrospective study showed an improved patency rate after eversion of the urethral mucosa of both urethral ends before anastomosis ("valgus urethral mucosa anastomosis") [456]. The findings of both studies have yet to be confirmed in a prospective fashion.

To preserve the antegrade arterial inflow of the bulbar urethra and reduce the surgical trauma of "classic" deferred EPA, bulbar artery sparing EPA has been described [457]. Initial patency rates vary between 88.5-100% with 20-45 months of follow-up (see supplementary Table S6.17) [457-459]. Xie *et al*. only used this technique for distraction defects less than 2.5 cm [459]. No evidence exists to date whether bulbar artery sparing EPA is superior to the "classic" EPA in terms of patency rate and potency and continence rates.

In case of a very deep location of the proximal urethral end that makes anastomotic suturing impossible, Badenoch described a pull-through technique which has a 33.3-96.5% patency rate after 43-126 months of follow-up (see supplementary Table S6.18 for further information) [437, 460, 461]. With the aim to reduce stricture recurrence, Wong *et al*. advise a 1.5 cm segment overlap of the bulbar stump within the prostatic urethra during the pull-through technique [460]. To facilitate the suturing at the proximal part of the urethra located deep under the pubic bone, the robotic approach is under exploration but there is no evidence so far of improved outcome with this approach [462].

Patency rate in children varies between 75 and 89.8% (Table 6.10). The statement that EPA in children is associated with poorer results [463] cannot therefore be generally accepted [464].

Table 6.10: Outcomes of EPA in children

Study	N	Follow-up (months)	patency rate	Erectile dysfunction	Incontinence	Abdomino-perineal
Podesta *et al*. [465]	49	78 (60-264)	44 (89.8%)	3 (6.1%)	9 (18.4%)	21 (43%)
Waterloos *et al*. [466]	7	57 (8-198)	6 (85.7%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Singh *et al*. [463]	5	26 (12-42)	4 (80%)	NA	0 (0%)	0 (0%)
Singla *et al*. [467]	28	36 (3-58)	21 (75%)	-	1 (3.6%)	1 (3.6%)
Voelzke *et al*. [468]	18	13 (1-71)	16 (88.9%)	-	-	1 (5.6%)

N = number of patients; NA = not applicable.

6.3.5.2.2.1.3 Sexual function, urinary continence and rectal injury after urethroplasty for post-traumatic posterior stenosis

Regarding erectile function, a prospective study by Hosseini *et al*. found no significant difference before, and three or six months after EPA for posterior traumatic stenosis [469]. Another prospective study by Tang *et al*. also demonstrated no significant overall change in ED after urethroplasty. However, in the subgroup of patients with pre-operative non-vascular ED, a significant post-operative increase in ED was observed [470]. A meta-analysis of retrospective studies showed a significant decline of the rate of ED from 43.27% before to 24.01% after posterior urethroplasty ($p < 0.001$) [471]. Assessment of erectile function and its definitive treatment (e.g., penile prosthesis) should be performed two years after the trauma because of the potential return of normal erectile function within that time [472, 473].

After deferred EPA, antegrade ejaculation is present in 98.3-100% of cases [474, 475]. Decreased ejaculatory volume and/or diminished ejaculatory force were reported in 17.2-18.7% of cases but it cannot be assessed whether this is due to the trauma or due to the surgery [474, 475].

Continence after PFUI and urethroplasty is generally attributed to a competent bladder neck [43]. On the other hand, as most ruptures occur at the bulbomembranous junction just below the external sphincteric mechanism, at least a part of the external sphincter mechanism can be spared during urethroplasty [476]. Therefore, incontinence is rare with deferred EPA (6.8%) and is usually due to incompetence of the bladder neck although an incompetent bladder neck will not necessarily result in incontinence after urethroplasty [43, 476].

Rectal injury is a relative rare (0-10.2%) but a severe complication after deferred EPA (see supplementary Table S6.19) [434, 446, 452, 455, 477-481]. The risk of rectal injury tends to be higher in complicated cases or cases with previous urethral manipulations [434, 477, 482] .

6.3.5.2.2.2 ReDo-urethroplasty for post-traumatic posterior stenosis

In case of a recurrent stenosis, a repeat ("ReDo") urethroplasty is possible. In the majority of cases, especially if not all consecutive length-gaining manoeuvres have been used during the 1st EPA, another EPA can be performed [465, 477, 478, 483, 484]. The Badenoch pull-through technique is again an option if no adequate mucosa-to-mucosa suturing is possible (See supplementary Table S6.18) [460, 461]. In case of excessive dead space after resection of the fibrosis, gracilis muscle [482] or omental flaps (laparoscopically harvested if urethroplasty was performed using perineal approach only) [436, 480] have been advised to fill up this space

and support the anastomosis. These flaps, or alternatively bulbospongious muscle or local subcutaneous dartos flaps, are also useful to separate the suture lines in case of a concomitant recto-urethral fistula [436, 448, 453, 482]. If the urethra cannot be anastomosed in a tension-free fashion despite the aforementioned manoeuvres or in cases of ischemic narrowing/necrosis of the bulbar urethra, options are a tubed preputial island flap, staged BMG urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty [448, 478, 483, 485]. In case of entero-urethroplasty, the sigmoid colon is preferred above ileum (which is in turn better than stomach) because of the proximity of the vascular pedicle to the perineum. Entero-urethroplasty should only be done in the presence of a competent bladder neck because subsequent implantation of an AUS is nearly impossible [485].

Patency rate of different types of ReDo-urethroplasty varies between 37.5-100% (Table 6.11) [443, 448, 450, 477, 478, 480, 483-485]. An alternative is to abandon the normal urinary outlet and opt for Mitrofanoff-vesicostomy, PU (if local perineoscrotal skin is suitable) or permanent suprapubic diversion [478, 485].

Table 6.11: Outcome of different types of ReDo-urethroplasty

Study	Type	N	Follow-up (months)	Patency rate
Bhagat *et al*. [483]	Progressive perineal EPA	28	29 (12-108)	36 (83,72%)
	Transpubic EPA	12		
	Tubed preputial flap	1		
	Staged BMG + local flap	2		
Fu *et al*. [477]	Progressive perineal EPA	55	36 (18-47)	33 (60%)
Garg *et al*. [478]	Progressive perineal EPA	40	31 ± 11	30 (75%)
	Transpubic EPA	2	25	2 (100%)
	Tubed preputial flap	1	25	1 (100%)
	Staged BMG + local flap	2	17	1 (50%)
	Radial forearm free flap	1	15	1 (100%)
Gupta *et al*. [484]	Progressive perineal EPA	52	54 (10-144)	42 (80.8%)
Koraitim M. [443]	Progressive perineal EPA	4	168 (12-300)	4 (100%)
	Transpubic EPA	5		5 (100%)
Kulkarni *et al*. [480]	Progressive perineal EPA	15	18 (6-24)	14 (93.3%)
Kulkarni *et al*. [448]	Progressive perineal EPA	541	68 (12-240)	412 (79.1%)
	Tubed preputial flap	37		30 (81%)
	Staged BMG flap	10		6 (60%)
	Staged BMG + local flap	15		13 (86.6%)
	Entero-urethroplasty	2		2 (100%)
	Radial forearm free flap	3		3 (100%)
	Pedicled anterolateral thigh flap	1		1 (100%)
Mundy *et al*. [485]	Entero-urethroplasty	11	NA	7 (63.6%)
Podesta *et al*. [465]	Transpubic EPA	4	120 (72-204)	4 (100%)
Singh *et al*. [450]	Progressive perineal EPA	8	31 (13-90)	3 (37.5%)
Singh *et al*. [463]	Progressive perineal EPA	37	26 (12-42)	32 (86.5%)
Singla *et al*. [467]	Progressive perineal EPA	1	NA	1 (100%)
	Tubed preputial flap	2	NA	2 (100%)

BMG = buccal mucosa graft; EPA = excision and primary anastomosis; N = number of patients; NA = not applicable.

Summary of evidence	LE
The best results are obtained after the 1st urethroplasty.	4
The overall stricture-free rate after EPA is 85.7%. By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed.	3
After failed endoluminal treatment, EPA is the standard treatment for a non-obliterative stenosis.	3
Both a midline and inverted U perineal incision equally gain access to the posterior urethra but a midline incision is associated with less anatomical damage to local vessels and nerves, reduced risk of surgical site infection and hospital stay.	2b

Total pubectomy during transpubic abdomino-perineal reconstruction has a higher complication rate (bleeding, pelvic instability, dead space) compared to partial (superior or inferior) pubectomy with no gain in surgical exposure.	4
By using the progressive perineal approach, a combined transpubic abdomino-perineal approach is usually not needed except for very long distraction defects and in case of complicated situations, which include associated para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	3
If the urethra cannot be anastomosed in a tension-free fashion or in case of ischaemic narrowing/ necrosis of the bulbar urethra, options are a tubed preputial island flap, staged buccal mucosa graft urethroplasty with flap, staged buccal mucosa dartos flap, radial forearm free flap urethroplasty or entero-urethroplasty.	3
In case of excessive dead space after resection of the fibrosis, local flaps have been advised to fill up this space and support the anastomosis. These flaps are also useful to separate the suture lines in case of a concomitant recto-urethral fistula.	3

Recommendations	Strength rating
Perform open reconstruction for post-traumatic posterior stenosis only in high-volume centres.	Weak
Perform progressive perineal excision and primary anastomosis (EPA) for obliterative stenosis.	Strong
Perform progressive perineal EPA for non-obliterative stenosis after failed endoluminal treatment.	Strong
Perform a midline perineal incision to gain access to the posterior urethra.	Strong
Do not perform total pubectomy during abdomino-perineal reconstruction.	Strong
Reserve abdomino-perineal reconstruction for complicated situations including very long distraction defect, para-urethral bladder base fistula, trauma-related recto-urethral fistula, and bladder neck injury.	Weak
Perform another urethroplasty after 1st failed urethroplasty in motivated patients not willing to accept palliative endoluminal treatments or urinary diversion.	Weak
Use a local tissue flap to fill up excessive dead space or after correction of a concomitant recto-urethral fistula.	Weak

7. DISEASE MANAGEMENT IN FEMALES

7.1 Signs and symptoms of female urethral strictures

The symptoms of female urethral strictures are non-specific and therefore generally non-diagnostic. Female urethral stricture presents with mixed filling and voiding symptoms with frequency in 60.2%, urgency in 51%, poor flow in 42%, incomplete emptying in 42%, UI in 36% (stress, urge or mixed), nocturia in 26%, UTI in 20% and straining to void in 16%. It very rarely presents with urethral pain (3%), terminal dribble (1%), haematuria (1%) or renal failure (1%) (see supplementary Table S7.1) [10, 18, 119, 121, 122, 127, 129, 131, 133, 486-489].

There is often a significant delay in diagnosis of FUS from time of development of symptoms with mean delays of 4.3-12 years described (range 1-30 years) [124, 131].

7.2 Diagnosis of female urethral strictures

Twenty-four studies detail investigations leading to a diagnosis of FUS (see supplementary Table S7.2) [8, 10, 119-122, 125-131, 133, 488-497]. In all cases a full history was taken and a detailed pelvic examination was performed to assess for prolapse, masses, scars and vulval dermatological disorders such as LS, lichen planus or vulvo-vaginal atrophy. Flow rate and US PVR assessment was evaluated in eighteen (75%) and seventeen (71%) studies respectively. Lateral VCUG was performed routinely in fifteen studies (63%) and as required in one study (4%). Cystourethroscopy was performed routinely in thirteen studies (54%) and as required in two studies (8%). Urodynamics (UDS) were performed routinely in four studies (17%) and as required in seven studies (30%) whilst video-urodynamics (VUDS) were performed routinely in three studies (13%) and urethral calibration (to < 14 Fr) also in three studies (13%). Pelvic MRI was performed as required in four series (17%) whilst transrectal US (TRUS) and renal US were each performed routinely in two series (8%) and intravenous urography (IVU) in ten (4%).

Flow rate and PVR assessment make inherent sense as initial non-invasive screening tools and allow for simple monitoring of effect of treatment. Voiding cystourethrography and/or VUDS will permit diagnosis of BOO [18, 496], visualisation of ballooning above the proximal end of the FUS [129], and delineation of alternate or co-existent diagnoses such as detrusor overactivity (DO) and SUI [122], although VCUG, VUDS and UDS require the ability to insert a 6 Fr catheter and may not be possible without preliminary urethral dilatation in all cases of FUS [489]. Likewise, passage of a cystourethroscopy will require a preliminary dilation in the majority of cases even when a paediatric uretero-renoscope is utilised [120]. Cystourethroscopy will allow for formal identification of the distal end of the FUS and will also allow for exclusion of a functional cause of BOO [129]. Magnetic resonance imaging is performed mainly to exclude alternate pathology such as urethral diverticulum and urethral carcinoma and also allows assessment of the degree of urethral fibrosis associated with FUS [489, 498]. Proponents of TRUS utilise it in lieu of MRI and also for visualisation of the dilated urethra above the proximal end of the FUS [499].

7.3 Treatment of female urethral strictures

*7.3.1 **Minimally invasive techniques for treatment of female urethral strictures***

Several minimally invasive treatments have been reported; these include urethrotomy, dilatation, meatotomy and meatoplasty. Meatotomy and meatoplasty are essentially the same procedure in the female urethra and the term 'meatoplasty' will be used throughout this document.

7.3.1.1 Urethrotomy for treatment of female urethral strictures

No papers were found detailing the use and outcomes of urethrotomy specifically for the management of FUS. Internal urethrotomy or dilation was used by Massey and Abrams [500] to treat a variety of pathologies, including FUS, causing symptoms of obstructed voiding, and resulted in symptomatic improvement in 80% of patients. As this study included women with a variety of complaints and did not assess urodynamic parameters, the results in the patient subset with true urethral stricture are unclear. If utilised, urethrotomy in the female urethra involves incisions at three, nine and occasionally twelve o'clock [500].

7.3.1.2 Urethral dilatation for treatment of female urethral strictures

With this treatment, the urethra is dilated to between 30 Fr and 41 Fr Some patients will continue with ISD. Romman *et al*. 2012 [488] and Popat & Zimmern [489] also described suture plication of bleeding areas of the meatus if required post-urethral dilatation.

Four studies described the results after 12-59 months follow-up of, in total, 183 patients having dilatation only. Patency rates ranges from 7.5 to 51% (see Table 7.1) [122, 123, 488, 489]. In another four studies that included, in total, 31 patients that continued to perform ISD, stabilisation of the stricture with "patency" was obtained in 37.3-100% of cases at 12-21 months of follow-up (see Table 7.1)[8, 127, 130, 494].

New onset SUI (0.8%) and other complications are very rare after dilation (see supplementary Table S7.3). Due to the low complication rate, the minimally invasive nature of the technique and the reasonable success rate, it is acceptable to start with urethral dilation as a first-line treatment for an uncomplicated FUS.

7.3.1.3 Meatoplasty for treatment of female urethral strictures

Meatal stenosis is extremely rare, with only 2/58 (3%) of females evaluated for voiding dysfunction found to have true meatal stenosis [501]. Only three meatoplasty papers were identified containing 60 patients (see supplementary Table S7.4): one [502] detailed meatoplasty outcomes in a series of 58 girls whilst the 2nd was from a study analysing outcomes of various forms of FUS treatment that included one case of meatoplasty [503], and the third was a case report [127]. The patency rate of meatoplasty in girls is excellent with 97% of the 58 girls in Hesing's series having a successful outcome with no reported side effects at twelve months. Forty-eight of 50 patients experienced resolution of their recurrent UTIs and improved voiding symptoms one year after meatoplasty [502]. None of these studies reported incontinence or other acute complications. For short meatal strictures, meatoplasty is the first-line treatment option.

*7.3.2 **Urethroplasty for treatment of female urethral strictures***

Twenty-five papers report the outcomes of urethroplasty for FUS disease in 231 patients in total after the scope search of the Panel. The Panel have analysed the outcomes of these urethroplasty according to flap or graft type as: vaginal graft, vaginal flap, labial/vestibular graft, labial/vestibular flap and buccal or lingual graft.

In female urethroplasty, a dorsal approach is via a stricturotomy at twelve o'clock, a ventral approach is via a stricturotomy at six o'clock and circumferential is a full circumference reconstruction.

7.3.2.1 Vaginal graft augmentation urethroplasty for treatment of female urethral strictures

There were four studies reporting vaginal graft urethroplasty including 37 patients [10, 492, 497, 504]. All 37

vaginal graft urethroplasties were performed via a dorsal approach in women with a mean/median age of 47.5-60.6 years (range 35-70). In these studies, patency rates of 73-100% were reported after 22-27 months follow-up (Table 7.1). No complications and no new onset UI were reported.

See supplementary Table S7.5 for further information.

7.3.2.2 Vaginal flap augmentation urethroplasty for treatment of female urethral strictures

Vaginal flap urethroplasty was reported in 70 women and was always via a ventral approach, utilising an inverted U vaginal flap inlay in five studies (n=52) [121, 122, 125, 486, 487], a lateral C vaginal flap in three studies (n=17) [119, 127, 131] and one vaginal island flap urethroplasty in one patient [125]. At a mean/median follow-up time of 30-80.7 months, patency rates of 67-100% were reported (Table 7.1). Eight (11.4%) patients had a simultaneous pubo-vaginal sling (PVS), four (5.7%) had a simultaneous Martius fat pad flap interposition and one (1.4%) had a simultaneous excision of urethral diverticulum. Five (7.1%) patients developed new onset UI, two (2.9%) developed UTIs and two (2.9%) described temporary intravaginal direction of their urinary stream.

See supplementary Table S7.6 for further information.

7.3.2.3 Labial/vestibular graft augmentation urethroplasty for treatment of female urethral strictures

There were four papers detailing the outcomes of 31 patients having labial or vestibular graft urethroplasty (see supplementary Table S7.7); nineteen had ventral labial minora graft [126, 133, 491] and twelve had dorsal labial graft [130]. At a mean follow-up of 15-24 months, patency rates of 75-100% were reported with ventral grafting whilst this was 100% with dorsal grafting at six to fifteen months follow-up (Table 7.1). One (5.2%) ventral graft patient developed a UTI post-surgery. There were no other complications (including UI).

7.3.2.4 Labial/vestibular flap urethroplasty for treatment of female urethral strictures

There were two papers detailing the outcomes of nineteen patients having labial/vestibular flap urethroplasty: two had a ventral labia minora flap [505] and seventeen had a dorsal vestibular flap [11]. At a follow-up of 24 months the two ventral flap patients (100%) remained stricture-free whilst fifteen (88%) dorsal flap patients remained stricture-free at a mean of twelve months follow-up (Table 7.1 and supplementary Table S7.8). There were no adverse short- or long-term effects reported in either group.

7.3.2.5 Buccal and lingual mucosal graft augmentation urethroplasty for treatment of female urethral strictures

There were twelve papers detailing the outcomes of 73 patients, all treated with BMG except in the series of Sharma *et al*. who used lingual mucosa graft (LMG) in fifteen patients at the dorsal urethra [120]; 44 patients with dorsal onlay oral (buccal or lingual) mucosa graft (DOOMG) [120-122, 125, 128, 490, 496, 504, 506]; 27 with ventral onlay BMG (VOBMG) [121, 129, 507, 508] and two with circumferential BMG urethroplasty [121]. At a mean/median follow-up of 6-28 months, 62.5-100% of DOOMG urethroplasty patients were stricture-free whilst 50-100% of VOBMG patients were stricture-free at a mean of 10-24 months follow-up. Both circumferential BMG patients were stricture-free at a mean of 21 months follow-up (Table 7.1). Seven (15.9%) DOOMG patients suffered a low-grade short-term adverse effect and no patients in any subgroup developed sustained new onset UI.

For further information see supplementary Tables S7.9, S7.10 and S7.11.

7.3.2.6 Anastomotic urethroplasty

Anastomotic urethroplasty has only been described in two cases in the literature – both in women with very short mid-urethral stricture and both of whom were stricture-free at four and 24-months follow-up respectively. None of them suffered from UI post-operatively [121, 493] (see supplementary Table S7.12).

Table 7.1: Summary of available evidence on treatment of female urethral strictures

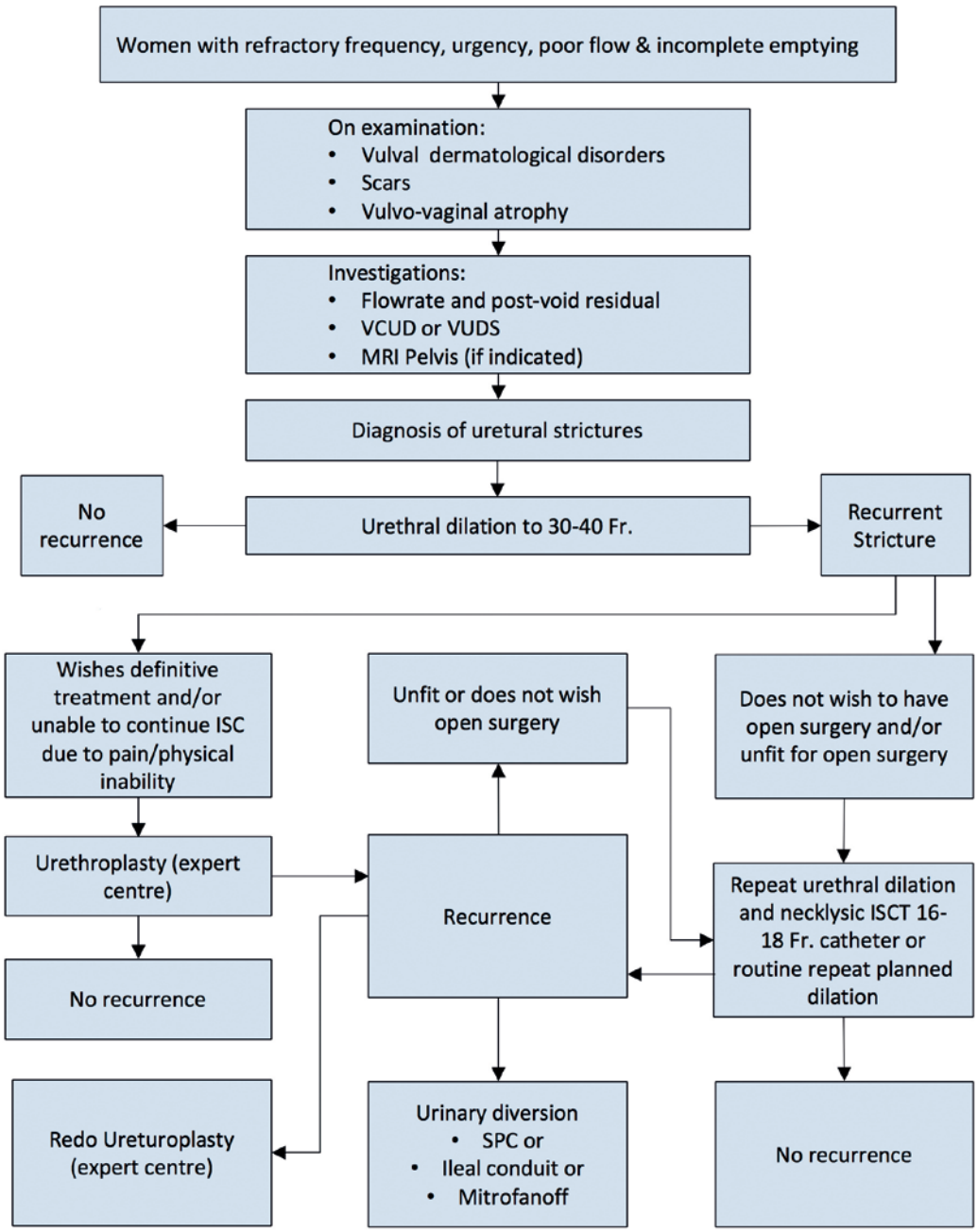
Treatment	No. of studies	N	Patency rate (%)	UI (%)	Mean/Median FU Months	Refs
Urethral Dilatation	4	183	7.5-51	0	12-59	[122, 123, 488, 489]
Urethral Dilatation + ISD/ planned repeat dilatation	4	31	37.3-100*	1.9	12-21	[8, 127, 130, 494]
Dorsal Vaginal graft urethroplasty	4	37	73-100	0	22.4-27	[10, 492, 497, 504]
Ventral Vaginal flap urethroplasty	8	70	67-100	7	30-80.7	[119, 121, 122, 125, 127, 131, 486, 487]
Ventral Labial/Vestibular graft urethroplasty	3	19	75-100	0	15-24	[126, 133, 491]
Dorsal Labial/Vestibular graft urethroplasty	1	12	100	0	6-15	[130]
Ventral Labial/Vestibular flap urethroplasty	1	2	100	0	24	[505]
Dorsal Labial/ Vestibular flap urethroplasty	1	15	88	0	12	[11]
Dorsal BMG urethroplasty	9	44	62.5-100	0	6-28	[120-122, 125, 128, 490, 496, 504, 506]
Ventral BMG urethroplasty	4	27	50-100	0	10-24	[121, 129, 507, 508]

FU = follow-up; ISD = intermittent self-dilatation; N = number of patients; UI= urinary incontinence.

Summary of evidence	LE
Female urethral stricture symptoms are long standing and non-specific, the most commonly reported are frequency, urgency, poor flow, incomplete emptying and urinary incontinence. It is important to exclude FUS in female patients with LUTS.	3
Urethral dilatation alone to 30-41 Fr provides low stricture-free rates of mean 35% at mean follow-up 36.3 months.	3
Urethral dilatation and ISC or planned repeat dilatation provides stricture-free rates of 75%.	3
Urethroplasty provides stricture-free rates of 81-92%. No one particular type of urethroplasty is superior to another.	3
Meatotomy/meatoplasty for short meatal strictures has a success rate of 95% at twelve months follow-up.	3

Recommendations	Strength rating
Perform flow rate, post-void residual and voiding cystourethrogram or video-urodynamics in all women with refractory lower urinary tract symptoms.	Strong
Perform urethral dilatation to 30-41 Fr as initial treatment of female urethral stricture (FUS).	Weak
Perform repeat urethral dilatation and start planned weekly intermittent self-dilatation (ISD) with a 16-18 Fr catheter for the 1st recurrence of FUS.	Weak
Perform urethroplasty in women with a 2nd recurrence of FUS and who cannot perform ISD or wish definitive treatment. The technique for urethroplasty should be determined by the surgeon's experience, availability and quality of graft/flap material and quality of the ventral versus dorsal urethra.	Strong
Treat meatal strictures by meatotomy/meatoplasty.	Weak

Figure 7.1: Women with refractory frequency, urgency, poor flow and incomplete emptying



ISC = intermittent self-catheterisation; MRI = magnetic resonance imaging; VUDS = video-urodynamics.

8. DISEASE MANAGEMENT IN TRANSGENDER PATIENTS

8.1 Treatment of strictures in trans men

In trans men, stricture treatment depends on the time after neophallic reconstruction, stricture location, stricture length and quality of local tissues [509].

8.1.1 Management of strictures early after neophallic reconstruction

Urethral surgery on tissues in the acute phase of inflammation and wound healing is not indicated and should be postponed until any healing problems of the neophallus have been resolved and scar tissue formation in the urethra has been stabilised. This usually takes six months [27, 140]. Endoscopic incision for short (< 3 cm)

urethral strictures has been performed, mainly at the anastomotic site, with a maximum stricture-free rate of only 16.7% when performed within six months after neophallic reconstruction [510]. Insertion of a suprapubic catheter is the first-line treatment in cases of obstructive symptoms severely affecting the patient's QoL, recurrent UTI or retention. The alternative is perineostomy, which is a specialist procedure and should be performed by a urologist familiar with transgender urethral anatomy. The perineostomy may be closed at the time of formal urethral reconstruction [140].

*8.1.2 **Treatment of meatal stenosis in trans men***

Intermittent urethral dilatation is an option, as palliative treatment, for low-grade meatal stenosis with the interval of dilatation depending on the interval of stricture recurrence. Patients with high-grade meatal stenosis, those who refuse ISD, or those who want a durable solution should be offered simple meatotomy. Patency is 75% (mean follow-up 39 months) but the drawback is that the meatus will be in a hypospadiac position [140]. Alternatively, a staged urethroplasty can be offered [140].

*8.1.3 **Treatment of strictures at the neophallic urethra***

Endoscopic incision of a short stricture at the neophallic urethra has been reported but evidence is very scarce and the long-term results seem to be disappointing (34% patency rate after median follow-up of 51 months) [510].

Single-stage graft urethroplasty is only possible if the graft can be supported and covered by the healthy surrounding fatty tissue of the neophallus. Experience is very limited and reported patency rate is 50% after a mean follow-up of 102 months [140].

The standard treatment for these strictures is staged urethroplasty with or without graft augmentation [140, 509] (BMG or full thickness SG) [27, 140]. A patency rate of 69.7% has been described with these techniques (mean follow-up: 25 months) [140].

For complex (e.g., fully obliterated) or recurrent strictures at the neophallic urethra, a complete urethral substitution of this part needs to be performed. Different suitable flaps have been described (radial forearm free flap, superficial circumflex iliac artery free flap, pedicled groin flap). Double-face grafts with the ventral graft supported by rotating a part of the neoscrotum or by a gracilis flap have been successfully reported in a very limited number of patients [509].

*8.1.4 **Treatment of strictures at the anastomosis neophallic urethra-fixed part of the urethra***

Short, non-obliterative, strictures can be treated by endoscopic incision. A first endoscopic incision has a 45.5% patency rate but this dropped to 0% in case of three or more attempts (median follow-up of 51 months) [510]. Therefore, repetitive endoscopic incisions should be discouraged unless with palliative intent.

For very short (< 1 cm) low-grade strictures, Heineke-Mikulicz urethroplasty is an option reporting a 57.9% patency rate after a mean follow-up of 44 months [140].

If endoscopic incision fails or if the stricture is nearly or completely obliterative, options are EPA or graft augmentation urethroplasty. In case of short (< 2-3 cm) strictures, EPA yields a 57.1% patency rate (mean follow-up of 35 months) [27, 140]. If EPA is not possible, usually for strictures longer than 2 cm, a ventral onlay BMG urethroplasty demonstrated a 50% patency rate (median follow-up of 9.5 months) [511]. In case of insufficient ventral tissue during graft urethroplasty, it is advised to support this graft by a local fasciocutaneous flap [512]. An alternative (especially after failure of the previous techniques) can be a staged approach but no data are currently available [511].

*8.1.5 **Treatment of strictures at the fixed part of the urethra***

This part of the urethra has a more reliable blood supply and the dorsal part of the urethra is supported by the corporal bodies of the clitoris. Therefore, single-stage dorsal inlay graft urethroplasty is possible for strictures at this site. Experience however is very limited [140, 509].

Staged repair with or without a dorsal graft is a reliable treatment for these rare strictures [140].

*8.1.6 **Definitive perineostomy in trans men***

The vast majority of trans men have a strong desire to void in a standing position [509]. Therefore, definitive perineostomy should only be offered to those with refractory strictures or to patients with strictures who do not wish to have complex reconstructive surgery [27, 140].

8.2 Peri-operative care after treatment of strictures in trans men

Anecdotally, after endoscopic incision and urethroplasty, the urethral catheter is maintained for two to three weeks [510, 511]. Peri-catheter urethrography is advised before catheter removal as it might be challenging to reinsert the urethral catheter in case of urinary extravasation [511].

8.3 Strictures in trans women

It is acceptable to start with dilation of a short and non-obliterative stricture in trans women although no long-term data about the effectiveness are available [28, 513]. If this is not possible or if it fails, a short (< 1 cm) meatal stricture can be treated by Y-V meatoplasty with an 85% stricture-free rate [514]. Somewhat longer (1-2 cm) meatal strictures can be treated by a neovaginal advancement flap (inverted U or "7-flap") with no recurrence observed after 37 months median follow-up [515].

Summary of evidence	LE
After neophallic reconstruction, local tissues go through the different stages of wound healing and stable wound healing is usually achieved after six months.	3
After two attempts, endoscopic incision is no longer successful in trans men.	3
Two-stage urethroplasty for strictures at the neophallic urethra has a stricture-free rate of 69.7%.	3
Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women has a stricture-free rate of 85%.	3

Recommendations	Strength rating
Do not perform endoscopic incision or urethroplasty within six months after neophalloplasty.	Strong
Do not perform more than two endoscopic incisions for strictures in trans men unless with palliative intent.	Strong
Perform staged urethroplasty for strictures at the neophallic urethra if open reconstruction is indicated.	Weak
Perform Y-V meatoplasty for short (< 1 cm) meatal stenosis in trans women if open reconstruction is indicated.	Weak

9. TISSUE TRANSFER

9.1 Comparison of grafts with flaps

One small RCT (LS excluded) comparing OMG with PSF found no significant difference in urethral patency rate [516]. Penile skin flaps had a higher urogenital morbidity (superficial penile skin necrosis, penile torsion, penile hypoesthesia and post-void dribbling) and longer operation time compared to OMG. Furthermore, patient dissatisfaction was significantly higher with penile flaps [516]. Another small RCT (LS excluded) comparing penile skin grafts with PSF confirmed these findings with longer operation time and more superficial penile skin necrosis in the group of the flaps whereas the urethral patency rate was similar between both groups [359]. Several retrospective series also found a comparable urethral patency rate between PSF and grafts [268, 270, 275, 517] (Table 9.1).

Table 9.1: Comparative studies of grafts versus flaps used in urethroplasty for anterior urethral strictures

Study	Type of study	Follow-up (mo.)	Flap		Graft		p-value*
			Type	Urethral patency	type	Urethral patency	
Barbagli *et al*. [268]	Retrospective	55	LIF	12/18 (67%)	OMG/PSG	36/45 (80%)	0.32
Dubey *et al*. [516]	RCT	22-24	LIF	22/26 (84.6%)	BMG	24/27 (88.9%)	0.70
Fu *et al*. [270]	Retrospective	>12	All types	166/199 (83.4%)	LMG	80/94 (85.1%)	0.71
Hussein *et al*. [359]	RCT	36	TIF	15/19 (78.9%)	PSG	13/18 (72.2%)	0.25
Lumen *et al*. [275]	Retrospective	42-43	All types	23/29 (79.3%)	OMG/PSG	63/75 (84%)	0.57

Sa *et al*. [517]	Retrospective	28 (18-60)	TIF	28/34 (82.3%)	BMG	67/82 (81.7%)	0.851

BMG = buccal mucosa graft; Excl. = excluded; LIF = longitudinal island flap; LMG = lingual mucosa graft; LS = lichen sclerosus; mo = months; NR = not reported; OMG = oral mucosa graft; PSG = penile skin graft; TIF = transverse island flap; RCT = randomized controlled trial.
** if not reported: recalculated by EAU Urethral Strictures Panel with chi²-statistics.*

Due to their robust vascular pedicle, flaps can be used as a tube as well as a patch in a single-stage approach [448]. Castagnetti *et al*. showed that grafts used as a tube have significantly higher complication rates as compared to onlay grafts (OR: 5.86; 95% CI: 1.5-23.4) [518]. A review by Patterson *et al*. also reported high (circa 50%) complication and recurrence rates for tubularised grafts [519]. Iqbal *et al*. have shown an encouraging 87% stricture-free rate in 23 patients who were offered single-stage circumferential skin flap urethroplasty [279]. Therefore, if there is a need to reconstruct a complete urethral segment with a tissue-transfer tube in a one-stage operation, flaps are usually the preferred option. As flaps carry their own vascular supply to the reconstruction site, they do not rely on the local vascularisation of the recipient site. Therefore, they need to be considered in case of poor urethral vascularisation (e.g., after irradiation or dense scarring after previous urethroplasty) [275, 520]. In addition, flaps survive well in the presence of active urinary infection [521].

Grafts and flaps should not be considered competitors in urethral surgery. A combination of a flap with a graft is possible for complex, multifocal or penobulbar strictures [275, 522, 523].

Summary of evidence	LE
Flaps have a higher urogenital morbidity, but a comparable patency rate compared to grafts.	1b
Grafts have a significantly higher complication rate compared to flaps when complete tubularisation in a single-stage approach is needed.	1b
Flaps do not rely on the local vascularisation of the recipient site.	3

Recommendations	Strength rating
Use a graft above a flap when both options are equally indicated.	Strong
Do not use grafts in a tubularised fashion in a single-stage approach.	Strong
Use flaps in case of poor vascularisation of the urethral bed.	Weak

9.2 Comparison of different types of flaps

Different local flaps have been described. Penile skin flaps are generally hairless, although the ventral penile skin can be hair-bearing around the raphe in some ethnic groups/phenotypes. They can be harvested as a transverse preputial skin flap [524], a transverse distal PSF [362, 521, 525, 526] or as a longitudinal island flap [527]. Urethral patency rates vary between 74.2 and 100% [270, 362, 521, 524-527]. Complications include skin necrosis (0-3.8%), fistula (0-7%), penile deformity (0-7%), post-void dribbling (0-79%) and sacculation (0-16.5%) (see supplementary Table S9.1). As there are no direct comparative series available about these flaps it is not possible to determine which performs better.

Hair-bearing perineal and scrotal flaps have been described as well. Fu *et al*. demonstrated that PSF had a significantly better urethral patency rate compared to scrotal and perineal skin flaps (respectively 87.7%, 69% and 66.7%) [270]. The hair-bearing perineal and scrotal skin flaps are associated with hairball formation and chronic infection which may cause failure of the repair. A study of Blandy with long-term follow-up reports 3% revision for calculi and 3% revision for diverticula [528].

An alternative is to epilate the needed scrotal skin prior to tissue transfer [529, 530] or to patch an OMG to the underlying dartos tissue of the scrotum after incision of the scrotal skin and use this patch as a flap in a second attempt [448].

Summary of evidence	LE
Hair-bearing flaps have a lower urethral patency rate compared to non-hair-bearing flaps.	3

Recommendation	Strength rating
Do not use hair-bearing perineal or scrotal flaps unless no other option is feasible.	Strong

9.3 Comparison of different types of grafts

Buccal mucosa is at present the most commonly used graft. Urethral patency rates of buccal mucosa vary between 75.6% and 91.7% with 16-75 months of follow-up (see supplementary Table S9.2) [531-537].

Penile skin is another popular graft, especially in uncircumcised men where the foreskin is an abundant source of graft material.

In case of LS, Trivedi *et al*. demonstrated a significantly higher urethral patency rate when using non-genital mucosal grafts for reconstruction (82.6%) compared to genital skin grafts (4%) [538]; therefore, the use of genital skin in LS cases is not indicated.

There is no RCT comparing buccal mucosa with penile skin. A secondary analysis of a meta-analysis comparing dorsal with ventral onlay graft urethroplasty found a superior urethral patency rate for buccal mucosa compared to penile skin (88.1% vs. 79%; $p < 0.001$). In this secondary analysis, no data were available about the stricture aetiology, stricture length, follow-up duration or other potential confounders between both groups [539]. A pooled analysis of non-RCTs comparing buccal mucosa (n=483) with penile skin (n=428) found a better urethral patency rate for buccal mucosa (respectively 85.9% vs. 81.8%). However, the results might be biased because of the longer follow-up time and longer stricture length in the penile skin group [540]. Lengthy skin grafts (up to 20 cm) can be taken from the foreskin in a spiroid fashion which is clearly more difficult with oral mucosa grafts.

The main disadvantage of BMG harvesting is the oral morbidity and because of this morbidity, lingual mucosa has been proposed as alternative. A systematic review and meta-analysis of comparative studies comparing LMG with BMG (four prospective, two retrospective studies) showed no significant differences in urethral patency rate and overall long-term complication rate [541-543]. These studies revealed that LMG was associated with more difficulties in eating/drinking, speaking, tongue protrusion and dysgeusia [541, 542]. In 13.8-20%, speaking problems remained after six months [541, 542]. A retrospective study of Xu *et al*. reported difficulties in tongue movements, numbness over the donor site and speaking difficulties in 6.2%, 4.9% and 2.5% of patients, respectively after twelve months [298]. On the other hand, BMG harvesting provoked more oral tightness which was present in up to 24% of patients after six months [541, 542]. Chauhan *et al*. showed that immediate and early donor site complications were more common in the BMG group, except for bleeding being more common in the LMG group. Numbness (61%), difficulty in chewing (54%), swelling (48%) and articulation (40%) were the most common problems during the first week. Late donor site complications were rare [544]. Pal *et al*. describes more short-term complications (difficulty in tongue movement and slurring of speech) in the LMG group, compared to the BMG group. Long-term complications (after three months) at the donor site (persistent pain, perioral numbness, tightness of mouth, salivary disturbance, scarring of the cheeks) were only seen in the BMG group [545]. For long strictures, buccal mucosa can be combined with lingual mucosa [298].

The use of lower lip mucosa was described, especially when smaller grafts are needed, and has similar qualities to lingual mucosa. However, a narrative review based on the experience from retrospective series showed that these grafts have a higher post-operative donor site morbidity and can lead to permanent sequelae (persistent discomfort, neurosensory deficits, salivary flow changes and important aesthetic changes) at the donor site, which have not been described with lingual mucosa [546].

Beyond the oral mucosa and penile skin graft, a multitude of other autologous grafts have been described. These include: postauricular skin [523, 547], abdominal skin [364], split-thickness mesh graft from the thigh [348], inguinal skin [297] and colonic mucosa [548] (Table 9.2). Manoj *et al*. only used the postauricular skin when both genital skin and oral mucosa were not usable [547]. Marchal *et al*. used postauricular skin in addition to oral mucosa to reconstruct lengthy strictures [523]. Meeks *et al*. reported the use of abdominal skin graft mainly in patients with lengthy strictures where OMG harvesting would be insufficient, in case of prior OMG urethroplasty or if OMG was refused by the patient [364]. Pfalzgraf *et al*. reported a comparable urethral patency rate for split-thickness mesh graft and BMG (respectively 84 and 83%), but more penile deviation (9% vs. 0%) and lower satisfaction (83.3 vs. 96.7%) with split-thickness mesh graft [348]. Xu *et al*. used colonic mucosa for lengthy (> 10 cm) strictures. Urethral patency rate was 85.7% but graft harvest requires an abdominal procedure and 1/35 (2.9%) patient developed a colonic-abdominal fistula [548]. Due to the limited experience with grafts other than oral mucosa and penile skin, they should only be considered if oral mucosa and penile skin are not available, indicated or desired.

Table 9.2: Outcome of case series of other autologous grafts

Study	Type of graft	N	Follow-up (months)	Stricture length (cm)	Urethral patency (%)
Bastian *et al*. 2012 [297]	Inguinal skin	34	70 (3-86)	8 (1.5-14)	91
Manoj *et al*. 2009 [547]	Postauricular skin	35	22 (3-48)	8.9 (3-15)	89
Meeks *et al*. 2010 [364]	Abdominal wall skin	21	28 (11-52)	11 (4-24)	81
Pfalzgraf *et al*. 2010 [348]	Split thickness skin graft	57/68	32	NR	84
Xu *et al*. 2009 [548]	Colonic mucosa	35	53.6 (26-94)	15.1 (10-20)	85.7

N = number of patients; NR = not reported.

Summary of evidence	LE
Patency rates of buccal mucosa and lingual mucosa are comparable.	1a
Different types of oral grafts have different types of oral morbidity and some of the oral complications might last in the long-term.	1a
Patency rates with penile skin grafts are 79-81.8% versus 85.9-88.1% with buccal mucosa.	3
In LS related strictures, the use of genital skin graft is associated with poor patency rates (4%).	3

Recommendations	Strength rating
Use buccal or lingual mucosa if a graft is needed and these grafts are available.	Weak
Inform the patient about the potential complications of the different types of oral grafting (buccal versus lingual versus lower lip) when an oral graft is proposed.	Strong
Use penile skin if buccal/lingual mucosa is not available, suitable or accepted by the patient for reconstruction.	Weak
Do not use genital skin graft in case of lichen sclerosus.	Strong

9.4 Tissue engineered grafts

9.4.1 Cell-free tissue engineered grafts

These grafts are derived from cadaveric or animal sources (e.g., porcine small intestine submucosa (SIS), acellular bladder matrix, acellular dermal matrix), are completely cell-free and serve as a scaffold for host cell ingrowth [549]. The main advantage suggested for their use is the off shelf availability [549].

A small RCT (n=30) comparing acellular bladder matrix with BMG reported a urethral patency rate of respectively 66.6% and 100%. The poorer results of acellular bladder matrix were the most apparent in cases of an unhealthy urethral bed [550]. Palminteri *et al*. reported a global urethral patency rate with SIS graft in 19/25 (76%) cases [551]. In this series SIS graft urethroplasty failed in all cases with a stricture length > 4 cm [551]. On the other hand, Xu *et al*. reported adequate urethral patency in 26/28 patients (92.8%) after a median follow-up of 25 months. Of note, only one patient in this series underwent previous urethroplasty suggesting only minor spongiofibrosis in the remaining patients [552]. Other series have included only a limited number of patients with short follow-up. In these series, urethral patency rates vary between 20 and 100% [549].

Summary of evidence	LE
Patency rate of cell-free tissue engineered grafts decreases with large stricture length and unhealthy urethral bed.	1b

Recommendation	Strength rating
Do not use cell-free tissue engineered grafts in case of extensive spongiofibrosis, after failed previous urethroplasty or stricture length > 4 cm.	Weak

9.4.2 Autologous tissue engineered oral mucosa grafts

These grafts contain a matrix seeded with autologous oral mucosa cells. Production requires a small oral mucosa biopsy (@ 0.5 cm^2) and the graft is further manufactured in the lab. The main advantage suggested is the reduction of oral donor site morbidity whereas the main disadvantages are costs and the strict time frame between manufacturing and implantation of the graft [549].

The clinical use of autologous tissue-engineered OMG was evaluated in a prospective, multicentre study including 99 patients [553]. Estimated 12- and 24-months urethral patency rate was 67.3 and 58.2%, respectively. Oral adverse events were minimal. No comparative studies with acellular grafts or native OMGs are available nor are there any data about the cost-effectiveness [549].

Summary of evidence	LE
Safety, patency rate and cost-effectiveness of autologous tissue-engineered grafts is currently under research.	3

Recommendation	Strength rating
Do not use autologous tissue-engineered oral mucosa grafts outside the frame of a clinical trial.	Strong

9.5 Management of oral cavity after buccal mucosa harvesting

The post-operative morbidity of closure vs. non-closure of the buccal mucosa harvesting site has been evaluated by a number of prospective RCTs.

The results are summarised in Table 9.3. Based on these findings, no clear recommendation can be provided whether or not to close the harvesting site and the decision can be left to the treating physician.

Oral rinsing with chamomile [554] or chlorhexidine [542, 555] solution has been suggested in the first post-operative days without any evidence that this reduces pain or other oral complications.

Table 9.3: Effect of non-closure compared to closure on oral morbidity after buccal mucosa harvesting

Study	Early oral pain	Eating/ drinking problems	Altered taste	Altered salivation	Oral tightness	Perioral numbness	Oral bleeding	Slurred speech
Soave *et al*. [554]	=	=	=	=	=	=	=	=
Rourke *et al*. [556]	=	↓	NR	NR	↓	↓	=	NR
Muruganandam *et al*. [557]	↓	=	NR	=	=	=	=	NR
Wong *et al*. [555]	=	↑	NR	NR	=	=	=	NR
Lumen *et al*. [542]	↑	NR	NR	NR	NR	NR	NR	NR

↓ = less morbidity with non-closure; ↑ = more morbidity with non-closure; = = no significant difference; NR = not reported

10. PERI-OPERATIVE CARE OF URETHRAL SURGERY

10.1 Urethral rest

After any form of urethral manipulation (urethral catheter, ISD, dilatation, DVIU), a period of urethral rest is necessary in order to allow tissue recovery and stricture "maturation" before considering urethroplasty. This improves the ability to identify the true extent of the fibrotic segments during subsequent surgery. If the patient develops incapacitating obstructive symptoms or urinary retention, a suprapubic catheter should be inserted. Terlecki *et al*. propose diagnostic evaluation after two months and urethroplasty after three months of urethral rest. These timings are based on the general principles of wound healing [558]. In their study, it has been shown that these periods allow for reliable stricture evaluation during urethrography which is, in turn, important to ensure selection of the most appropriate urethroplasty technique [558]. Utilising this strategy, similar outcomes were obtained compared to patients with stable previously unmanipulated strictures [558]. However, the optimal duration of urethral rest for all patients is not known and the degree of associated infection and inflammation should be taken into account as well with longer periods of rest in those with greater degrees of infection and inflammation.

Summary of evidence	LE
After any form of urethral manipulation, a minimum period of three months urethral rest is necessary to allow for tissue healing before performing urethroplasty.	3

Recommendation	Strength rating
Do not perform urethroplasty within three months of any form of urethral manipulation.	Weak

10.2 Antibiotics

Post-operative wound infection and UTI are common post-operative complications and infection at the site of reconstruction may contribute to failure of urethroplasty. The vast majority of reconstructive urologists perform urine culture one to two weeks prior to surgery [559]. Urine culture is superior to urine-analysis which can be omitted in the pre-operative evaluation [559]. If infection or colonisation is present, a therapeutic course with antibiotics is recommended pre-operatively. In case of an indwelling catheter general principles would suggest at least an attempt to suppress the colonisation with pre-operative antibiotics [559]. These practices are in accordance to the strong recommendations of the EAU Guidelines on Urological Infections:

- "Screen for and treat asymptomatic bacteriuria prior to urological procedures breaching the mucosa."
- "Treat catheter-associated asymptomatic bacteriuria prior to traumatic urinary tract interventions."

An intra-operative prophylactic regimen with antibiotics (according to local antibiotic resistance profiles) is effective in reducing the rate of post-operative surgical site and UTIs [559]. Although most urologists continue with post-operative antibiotics upon and even beyond catheter removal, there is no evidence that such a prolonged administration would reduce the infective complication rate [559]. The EAU guidelines on urological infections do not routinely recommend the use of antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. There is no evidence that this recommendation would not apply to catheter removal after urethral surgery.

Summary of evidence	LE
An intra-operative prophylactic regimen with antibiotics is effective in reducing the rate of post-operative surgical site and urinary tract infections.	4

Recommendation	Strength rating
Administer an intra-operative prophylactic regimen with antibiotics at time of urethral surgery.	Strong

10.3 Catheter management

After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period and it should be removed within 72 hours [560].

After one-stage urethroplasty and closure of the urethral plate after staged urethroplasty, urinary extravasation at the site of reconstruction must be avoided [561]. For this purpose, urinary diversion by either transurethral catheter or suprapubic catheter with urethral stent can be used. With respect to the type of catheter material, a prospective randomised (but underpowered) trial comparing silicone vs. hydrogel coated latex transurethral catheters showed no significant difference in the time to stricture recurrence nor in the overall recurrence rate [561]. The size of the urethral catheter utilised usually varies varies between 14 Fr and 20 Fr [562, 563]. Systematic use of anticholinergic drugs has not shown a significant reduction in the rate of involuntary pericatheter voiding whilst catheterised [564].

After urethroplasty an indwelling catheter is commonly left *in situ* for two to three weeks [563, 565]. After three weeks of urethral catheterisation, an extravasation rate of 2.2%-11.5% at urethrography has been reported after different types of urethroplasty [565-568]. However, success with early catheter removal under three weeks has also been reported. A study after EPA for non-complicated anterior strictures demonstrated no significant difference in extravasation (6.8 vs. 4.5%) and recurrence rates (4.9 vs. 5.2%) between catheter removal at one or two weeks respectively [569]. Poelaert *et al*. reported an extravasation rate of 3.5% vs. 8.3%, when the catheter was removed ≤ 10 days or > 10 days respectively after all types of urethroplasty (n=219) (p=0.158) [562]. Importantly, patients who had a duration of catheterisation of > 10 days had longer and more complex strictures [562].

Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation [565, 567]. Importantly, some authors have identified urinary extravasation as a predictive factor for stricture recurrence [562, 570]. Other series, however, could not confirm the prognostic significance of urinary extravasation but they included any form of extravasation (including minor leaks) [567, 568]. Grossgold *et al*. found that high-grade leaks (defined as length ≥ 1.03 cm and width ≥ 0.32 cm) were significantly associated with higher restricture rates. This study also found length of extravasation ≥ 1.03 cm alone to be an independent predictor of restricture [570]. In cases of persistent and significant urinary extravasation, the catheter should be maintained or reinserted and the examination repeated after one week [565]. However, low-grade ("wisp-like") extravasation does not appear to affect long-term restricture rate and the catheter can be removed in these cases without subsequent urethrogram [567, 570]. In case of any doubt about the significance of extravasation, it is safe to keep the catheter in for an additional week and ReDo the assessment.

The assessment of urinary extravasation is achieved by either pericatheter retrograde urethrography (pcRUG), classic RUG or VCUG [565]. Voiding cystourethrography (after catheter removal) is the most physiologic examination as it shows the urethra under normal intra-urethral pressures and using this test residual urethral narrowing is most accurately identified. This has been found to be a strong prognostic factor for failure in a series evaluating bulbar FGU [568]. In contrast, pcRUG is associated with supraphysiological intra-urethral pressures and a potentially higher chance of false positive results [565, 570]. Although there is no evidence that one imaging modality is superior to the other, pcRUG should be performed if there is a high-risk of leakage as it avoids the need for catheter reinsertion through a recently reconstructed urethra in case of a positive exam. High risk of leakage depends on the complexity of urethroplasty (e.g., stricture length > 10 cm, panurethral repair) [567, 570]. External clinical signs of impaired wound healing (e.g., abscess formation, wound dehiscence) are also associated with a high risk (71.4%) of leakage [562]. In cases of attempted VCUG where the patient is not able to void during fluoroscopy after catheter removal, RUG should be performed [570].

Although limited evidence for urethroplasty care in trans men exists, one study advised a three week period of transurethral catheterisation with pcRUG upon catheter removal [511].

After perineostomy or the 1st stage of staged urethroplasty, the catheter can be removed without need for urethrography after three to five days [346, 567].

Summary of evidence	LE
Prior to catheter removal after urethroplasty, it is important to assess for urinary extravasation with urethrography to avoid ensuing complications including peri-urethral inflammation, abscess formation and fistulation.	2b
After uncomplicated DVIU, there is no advantage in maintaining the catheter for a prolonged period.	3
Early catheter removal may be appropriate for a subset of patients with short, uncomplicated, strictures.	3

Recommendations	Strength rating
Perform a form of validated urethrography after urethroplasty to assess for urinary extravasation prior to catheter removal.	Strong
Remove the catheter within 72 hours after uncomplicated direct vision internal urethrotomy or urethral dilatation.	Weak
Consider 1st urethrography seven to ten days after uncomplicated urethroplasty to assess whether catheter removal is possible, especially in patients with bother from their urethral catheter.	Weak

11. FOLLOW-UP

11.1 Rationale for follow-up after urethral surgery

The rationale for following-up patients after urethral stricture surgery is to detect and manage any complication or recurrence. As with any surgical procedure, following urethroplasty some patients will present with complications at short to medium follow-up: approximately 38% with bulbar urethroplasties [318] and up to 54% for all anterior urethroplasties [571]. Most of these complications (92%) would be classified as Clavien

grade 1 or 2 [318]. Even though urethroplasty techniques provide the highest chances for successful treatment of urethral strictures, some patients will experience recurrence [322]. For further details on particular outcomes in each urethral segment, please review the individual chapters of this Guideline.

Summary of evidence	LE
After urethroplasty surgery, recurrent strictures appear with different frequency depending on stricture features and urethroplasty techniques.	3

Recommendation	Strength rating
Offer follow-up to all patients after urethroplasty surgery.	Strong

11.2 Definition of success after urethroplasty surgery

The “traditional academic” definition of post-operative success after urethroplasty has been considered as “The lack of any post-operative intervention for restricture” [572]. This definition, despite being widely used [302, 318] is problematic as it ignores asymptomatic or even symptomatic recurrences in patients not willing to undergo further surgeries [572]. There is some variation as to what is considered intervention with some groups accepting endoscopic treatments as success, while considering failure only as the requirement for a ReDo urethroplasty [303].

A more objective definition of success is the “anatomic success”, defined as “Normal urethral lumen during RUG or cystoscopy, regardless of patient symptoms”. Using this definition, stricture recurrence or anatomical failure is considered by some groups as urethral narrowing found to be endoscopically impassable – without force – with a 16 Fr flexible endoscope [138, 573]. This definition is certainly more strict, with up to 35% of cystoscopic recurrences after bulbar urethroplasty remaining asymptomatic, and thus would have been considered as successful if a “lack of further intervention” definition was used [138]. Other groups consider cystoscopic recurrence as any stricture that is visible on post-operative cystoscopy, even the so-called “large-calibre re-strictures” (> 17 Fr) [136]. Not all anatomic recurrent strictures would need further treatment [572]. It was suggested to intervene when the anatomic recurrence is associated with recurrence of symptoms, stricture-related high post-void residuals or a stricture calibre of < 14 Fr – even if these are asymptomatic [572].

Over the last ten years, the evaluation of urethral surgery outcomes has shifted towards a “patient-reported definition of success”. The aim of any urethral intervention is to allow patients to return to a normal state of voiding while maintaining QoL [574] or to minimise symptoms, reduce disability, and improve HRQoL by restoring normal urinary function [575]. Even if the surgeon reconstructed a wide and patent urethra, if patients experience pain, sexual dysfunction or perceive their urinary function as not improved, they will not rate their outcome as successful [572]. On a multivariate analysis including both patient-reported and clinical parameters, urine flowmetry parameters failed to demonstrate significant contribution to satisfaction [576]. Kessler *et al*. reported that only 78.3% of patients with clinical success described themselves as (very) satisfied. More dissatisfaction significantly appeared with penile curvature, penile shortening, worsening of erectile function and impairment of sexual life [577]. Conversely, 80% of patients defined as clinical failures considered themselves as (very) satisfied with their outcomes [577]. Regardless of anatomic success after urethroplasty, post-operative pain, sexual dysfunction and persistent LUTS were independent predictors of patient dissatisfaction [576]. Improvement in voiding function (i.e., statistical improvement on IPSS) alone does not predict patient satisfaction after urethroplasty [578]. On a multivariate analysis including both patient-reported and clinical parameters, after adjusting for disease recurrence and age, persistence in voiding symptoms (weak stream), genitourinary pain, and post-operative sexual function alterations were the greatest independent drivers of post-operative dissatisfaction [576]. In addition, penile shortening (OR: 2.26; CI: 95% 1.39-3.69) and chordee (OR: 2.26; CI: 95% 1.44-4.19) were independent predictors of patient dissatisfaction after urethroplasty [578] (Table 11.1).

Table 11.1: Predictors of patient dissatisfaction after urethral surgery

Predictor/Symptoms	Measure of effect	Authors
Weak/very weak urinary stream	< 0.001	Kessler TM *et al*. J Urol 2002 [577]
Penile curvature	0.001	
Penile shortening	0.001	
Worsening of erectile function	0.001	
Impairment of sexual life	< 0.001	
Sexual activity alteration	OR: 4.36 (1.54 – 12.37)*	Bertrand LA *et al*. J Urol 2016 [576]
Erection confidence (SHIM)	OR: 1.53 (1.12 – 2.07)*	
Inability to ejaculate (MSHQ)	OR: 1.52 (1.15 – 2.01)*	
Urethral pain	OR: 1.71 (1.05 - 2.77)*	
Bladder pain	OR: 2.74 (1.12 – 6.69)*	
Urinary strain (CLSS)	OR: 3.23 (1.74 – 6.01)*	
Hesitancy (IPSS)	OR: 2.01 (1.29 – 3.13)*	
Voiding quality of life (IPSS)	OR: 1.96 (1.42 – 2.72)*	
Haematuria	10	Maciejewski CC *et al*. Urology 2017 [578]
Urinary extravasation	9.1	

** p < 0.05; ** p < 0.001.*
SHIM = Sexual Heath Inventory for Men; MSHQ = Male Sexual Health Questionnaire;
CLSS = Core Lower Urinary Tract Symptom Score; IPSS = International Prostate Symptoms Score.

Due to this evident discrepancy between surgeon's assessment and patient assessment, PROMs have been developed for the follow-up after urethroplasty [153, 575].

A complete approach for urethral surgery outcomes would combine both anatomic, endoscopic, and patient-reported success [320, 572]. As a Panel, we suggest using a functional definition of success in clinical practice, namely "lack of symptoms and/or need for further interventions".

Collecting standardised documentation of the patient's subjective assessment of their symptoms and objective anatomic outcomes would be limited for academic purposes, in order to allow comparison of surgical outcomes among reconstructive urologic surgeons and centres. Those objective and subjective outcomes measures should therefore be assessed and reported (simultaneously but separately) when evaluating urethroplasty results [572].

11.3 Follow-up tools after urethral surgery

*11.3.1 **Diagnostic tools for follow-up after urethral surgery***

11.3.1.1 Calibration during follow-up after urethral surgery

The difference between calibration and urethral dilatation is usually subjective as soft strictures may be dilated during calibration [579]; therefore, urethral calibration should be used with caution for follow-up after urethroplasty. Dedicated calibration bougies should be used and not dilatators.

11.3.1.2 Urethrocystoscopy during follow-up after urethral surgery

Urethrocystoscopy has been considered the most useful tool to confirm the presence or absence of a recurrent stricture [136, 580], as up to 35% of patients with re-strictures remain asymptomatic [138]. Also, the cystoscope could be a measure to calibrate the strictured lumen, bearing in mind the most commonly used endoscopes: 15.7 Fr (5 mm diameter) or 17.3 Fr (5.5 mm diameter) [580]. Urethrocystoscopy allows differentiation of recurrences as diaphragm/cross-bridging – responding to simple intervention, or significant urethral restrictures – requiring repeated interventions or ReDo surgeries [581]. Endoscopic assessment at three months after anterior urethroplasty can predict the risk for further re-intervention at one year. Compared to normal endoscopy, large calibre (> 17 Fr) restrictures have a HR of 3.1 (1.35-7.29) for repeat intervention while small calibre (< 17 Fr) restrictures have a 23.7 HR (12.44-45.15) adjusted for age, stricture length, location and aetiology [136]. The main problem with using urethrocystoscopy for routine follow-up is the low compliance of patients as only 54% of patients underwent endoscopy at one year after urethroplasty, even when it was a part of a study protocol [138].

11.3.1.3 Retrograde urethrogram and voiding cystourethrogram during follow-up after urethral surgery

Retrograde urethrogram combined with VCUG are commonly used to confirm suspected recurrence [582, 583] or as part of a routine protocol to assess post-operative urethral patency [584, 585].

11.3.1.4 Urethral ultrasound – Sonourethrography during follow-up after urethral surgery

The use of SUG as a follow-up tool is not very common. It would be a reliable tool for diagnostic recurrent strictures [582].

11.3.2 ***Screening tools for follow-up after urethral surgery***

These tools are used to assess whether there is suspicion of stricture recurrence and need for subsequent diagnostic evaluation (see section 5. Diagnostic evaluation).

11.3.2.1 Flow-rate analysis during follow-up after urethral surgery

Evaluating the Q_{max} is the commonest follow-up tool. Different cut-off points from Q_{max} 15 ml/s or 12 ml/s were suggested to consider the intervention as a failure or to trigger a confirmatory test for recurrence [584]. There is no clear threshold, and 19% of patients with Q_{max} < 14 ml/s would still have a patent urethra, allowing passage of 15 Fr cystoscope [139].

Flow rates may be affected by operator error, BPO/LUTS, bladder dysfunction, and variations in bladder capacity. Further limitations of uroflowmetry include the need for a minimum voided volume of 125 to 150 ml to reach a voided flow rate that reliably predicts an abnormality [579]. Even in controlled settings, the percentage of patients with adequate pre- and post-operative uroflowmetry analysis is only 31% [585]. Comparing both pre- and post-operative Q_{max} levels was suggested, and a difference in Q_{max} of 10 ml/s or less is found to be a reliable screen tool for recurrence (sensitivity 92%, specificity 78%). This measure also has strong reproducibility (R=0.52) [585]. Unfortunately, this improvement after urethroplasty is significantly different between age groups, with less than 10 ml/s average change in those over 65 years old, probably affected by BPO and/or bladder dysfunction [586]. Another parameter to consider is the shape of the voiding curve, recording it as flat (obstructed) or bell-shaped [587]. An obstructive voiding curve demonstrated 93% sensitivity to predict recurrent strictures, while a combination of urinary symptoms and obstructive voiding curve achieved 99% sensitivity and 99% NPV [587].

11.3.2.2 Post-void residual ultrasound measure during follow-up after urethral surgery

Post-void residual US measure is significantly increased in patients with recurrent strictures compared with those without recurrences [582]. Unfortunately, PVR measurement is affected by abdominal ascites, bladder diverticula and/or poor bladder function [579], with some studies reporting inconsistent correlation with obstruction in the presence of BPO. Also US measures of PVR are user dependent, showing high interobserver variability. Combined with other tests – uroflowmetry, IPSS, and SUG – PVR achieves adequate predictive values [582], but currently there is no literature support for its solo use to assess urethral stricture recurrence [588].

11.3.2.3 Symptoms questionnaires during follow-up after urethral surgery

The IPSS questionnaire, despite being designed for BPO, showed significant improvement after successful urethroplasty and inverse significant correlation with Q_{max} [578, 589]. The mean improvement of IPSS is around -11 points (range -19 to -5) [586].

Table 11.2: Post-urethroplasty changes in IPSS values

Author	N	Mean pre-operative value	Mean post-operative value	Change	Significancy
Morey AF *et al*. 1998 [589]	50	26.9	4.4	NR	p < 0.0001
DeLong J *et al*. 2013 [586]	110	NR	NR	-11 (IQR -19 - -5)	p < 0.001
Maciejewski CC *et al*. 2017 [578]	94	18.7 (+/- 9)	5.8 (+/- 5)	NR	p < 0.0001

N = number of patients; NR = Not reported; IQR = Interquartile range.

Combination of IPSS and Q_{max} analysis was suggested to diagnose recurrences. Using an IPSS cut-off point of 10 points associated with Q_{max} > 15 ml/s would prevent further invasive studies in 34% of patients, while only 4.3% of strictures < 14 Fr would have been missed. Using an IPSS cut-off point of 15 points associated with Q_{max} >15 ml/s would prevent further invasive studies in 37% of cases, while 6% of strictures < 14 Fr would have been missed [590].

The Visual Prostate Symptom Score (VPSS) was also used to diagnose recurrent urethral strictures, offering a significantly shorter time to completion compared with IPSS, especially in cases of illiteracy or limited education. Visual Prostate Symptom Score showed a good correlation with IPSS, Q_{max} and urethral diameter. A combination of VPSS > 8 with Q_{max}< 15 ml/s had a NPV of 89% and a PPV of 87% for recurrent urethral strictures [591].

Post-micturition dribble, assessed by the specific question of the USS-PROM questionnaire, was present in 73% of patients pre-operatively and 40% after anterior urethroplasty, while only 6.3% was *de novo*. Incidence was not predicted by stricture location nor urethroplasty type [143].

*11.3.3 **Quality of life assessment, including disease specific questionnaires during follow-up after urethral surgery***

Urethral stricture affects QoL evaluated by EQ-5D-3L questionnaire. Pre-operative anxiety and depression was found in 29% of patients. *De novo* AD after urethroplasty is uncommon (10%), and has two predictors: decreased sexual function and poor reported image of overall health [592]. A more recommended approach is the assessment of the condition-related QoL [593]. The USS-PROM proved useful to assess outcomes in anterior urethroplasty patients [575]. Its use also received criticism, as some of the individual generic QoL questions do not improve after successful urethroplasty, as they are not condition-specific [594]. Currently, there is another version of PROM, being developed and validated by a North American collaborative group, including questions related to the sexual consequences of urethral stricture disease [154]. PROM questionnaires should be implemented in each visit to check for functional success, as they are able to show improvement over time.

The Core Lower Urinary Tract Symptom Score (CLSS) questionnaire was used to assess pre- and post-urethroplasty pain in the bladder, penis/urethra, and perineum/scrotum. Most of the parameters improved after urethroplasty, but up to 29% of patients reported worsening of perineal pain after surgery [595].

Sexual function should be evaluated by validated tools if not assessed in a - PROM. The international index on erectile function (IIEF), SHIM, O´Leary Brief Male Sexual Function Inventory (BMFSI), SLQQ (Sexual Life Quality Questionnaire), Male Sexual Health Questionnaire (MSHQ) have all been used after urethroplasties for evaluation of erectile and ejaculatory functions. Other non-validated tools were suggested such as the Post-Urethroplasty Sexual Questionnaire (PUSQ) [596] or specific questionnaires for genital appearance (length, curvature) or sensitivity [597].

Summary of evidence	LE
Retrograde urethrography and urethrocystoscopy are able to identify anatomical success after a urethroplasty.	2a
A significant gap was demonstrated between objective and subjective outcomes after urethroplasties. PROM questionnaires are specific tools to assess subjective outcomes and patient satisfaction after urethroplasty surgeries.	2a
Validated questionnaires proved useful to assess the consequences of urethral surgery on sexual function.	2a

Recommendations	Strength rating
Use cystoscopy or retrograde urethrography to assess anatomic success after urethroplasty surgery.	Weak
Use PROM questionnaires to assess subjective outcomes and patient satisfaction.	Strong
Use validated questionnaires to evaluate sexual function after urethral stricture surgeries.	Strong

11.4 Ideal follow-up interval after urethral surgery

The optimal follow-up strategy must allow for an objective determination of anatomic and functional outcomes to assess surgical success whilst avoiding excessive invasive testing that leads to unnecessary cost, discomfort, anxiety and risk [572].

After anterior urethroplasty, 21% of recurrences are clinically evident, and cystoscopically confirmed, after three months [598] and 96% after one year [581]. Early recurrences are more frequent in patients with LS and older age, in longer strictures and when skin grafts were used [598].

11.5 Length of follow-up after urethral surgery

The median time of recurrence after bulbar urethroplasty is approximately ten months [324]. In case series, between 55.4% [598] and 96% [581, 584] of all recurrences are detected during the first year of follow-up after urethral surgery. Twenty-three percent of bulbar stricture recurrences are detected during the second year of follow-up, and the percentage of recurrences decreases after the second year [322].

On the other hand, long-term follow-up studies highlighted the role of length of follow-up as a predictor for stricture recurrence after bulbar urethroplasty [322, 599]. Late recurrences – later than five years after urethroplasty – could be observed in up to 15% of cases [139, 322]. This should be considered mainly after augmentation urethroplasties, especially in case skin grafts were used [583]. Certainly, patients should be instructed to seek urological evaluation if they experience late recurrent symptoms [599].

11.6 Risk stratified proposals during follow-up after urethral surgery

Cost of follow-up after urethroplasty is higher in the first year after the procedure [600]. In a literature review it ranged between 205 to 1,784 US Dollars, with higher costs associated to posterior urethral repairs [600].

As the risk of recurrence and side effects are related to the type of stricture and urethroplasty, a different follow-up schedule was proposed and shown to be cost-effective in the USA, potentially saving up to 85% of costs after five years [573]:

- Urethroplasties with a low risk of recurrence (EPA urethroplasty without history of radiotherapy, hypospadias or LS features) could be safely followed up based on monitoring of symptoms, using self-administered IPSS questionnaire, every three months for one year, and annually thereafter.
- Urethroplasties with standard risk of recurrence (urethroplasty using grafts, flaps, and/or post-irradiation, hypospadias and/or LS patients) could combine IPSS questionnaire + flowmetry every three months for one year, and annually thereafter. Additionally, RUG at three and twelve months should be performed.

In this protocol, urethrocystoscopy is only performed if required [573]. Another suggested follow-up protocol includes urethrocystoscopy or RUG/VCUG at three months post-operatively, in order to rule out early failures, especially in case of graft use. If there is evidence of good anatomical outcome in these tests, flowmetry and questionnaire results at three months should be considered as the new baseline. Thereafter, follow-up could be safely and routinely performed with non-invasive tests (flowmetry – evaluating Q_{max} and the shape of curve – and questionnaires. Any deterioration should be further investigated with a urethrocystoscopy [588].

A recently suggested protocol also included assessment of LUTS, sexual function (erectile and ejaculatory), and lower urinary tract pain, that need to be compared with pre-operative findings which should include a PROM questionnaire [572]. Cystoscopy and flowmetry should be performed between three to six months post-operatively, and flowmetry findings should be considered as the new baseline for longitudinal follow-up. Future significant decline (25-30%) in Q_{max} or Q_{max}-(average flow rate) should trigger new cystoscopy to rule out anatomic recurrence, even in patients who are symptom-free [572]. A routine cystoscopy at twelve to fifteen months should be performed at the surgeon's discretion, based on risk assessment of three aspects: higher-risk patients, evidence of partial urethral narrowing at three month assessment, low-volume surgeons [572].

Summary of evidence	LE
The higher percentage of recurrences presents during the first twelve months, after urethoplasty surgery.	2a
Risk-adjusted follow-up protocols are cost-effective and safe for the patients.	3

Recommendations	Strength rating
Offer a routine follow-up of at least one year after urethroplasty.	Strong
Adopt a risk-adjusted follow-up protocol.	Weak

11.7 Follow-up protocol proposal after urethroplasty

*11.7.1 **Surgeries with low risk of recurrence***

- Anastomotic urethroplasties in the bulbar/(bulbo)membranous segment with no history of radiotherapy, hypospadias or balanitis xerotica obliterans (BXO)/LS features.

Table 11.3: Follow-up protocol for urethroplasty with low risk of recurrence

Surgery	3 months	12 months	24 months*
Uroflowmetry	+	+	+
PROM (incl. sexual function)	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+**	On indication	On indication

**Follow-up could be discontinued after two years, advising the patient to seek urological evaluation if symptoms worsen. Academic centres could increase the length of follow-up for research purposes.*
***The Panel suggests performing an anatomic assessment at three months.*

*11.7.2 **Surgical management options with standard risk of recurrence***

- Anastomotic urethroplasties in the bulbar segment with prior history of radiotherapy, hypospadias or BXO/LS features;
- Penile urethroplasties;
- Non-traumatic posterior urethroplasties;
- Graft or/and flap – substitution – urethroplasties.

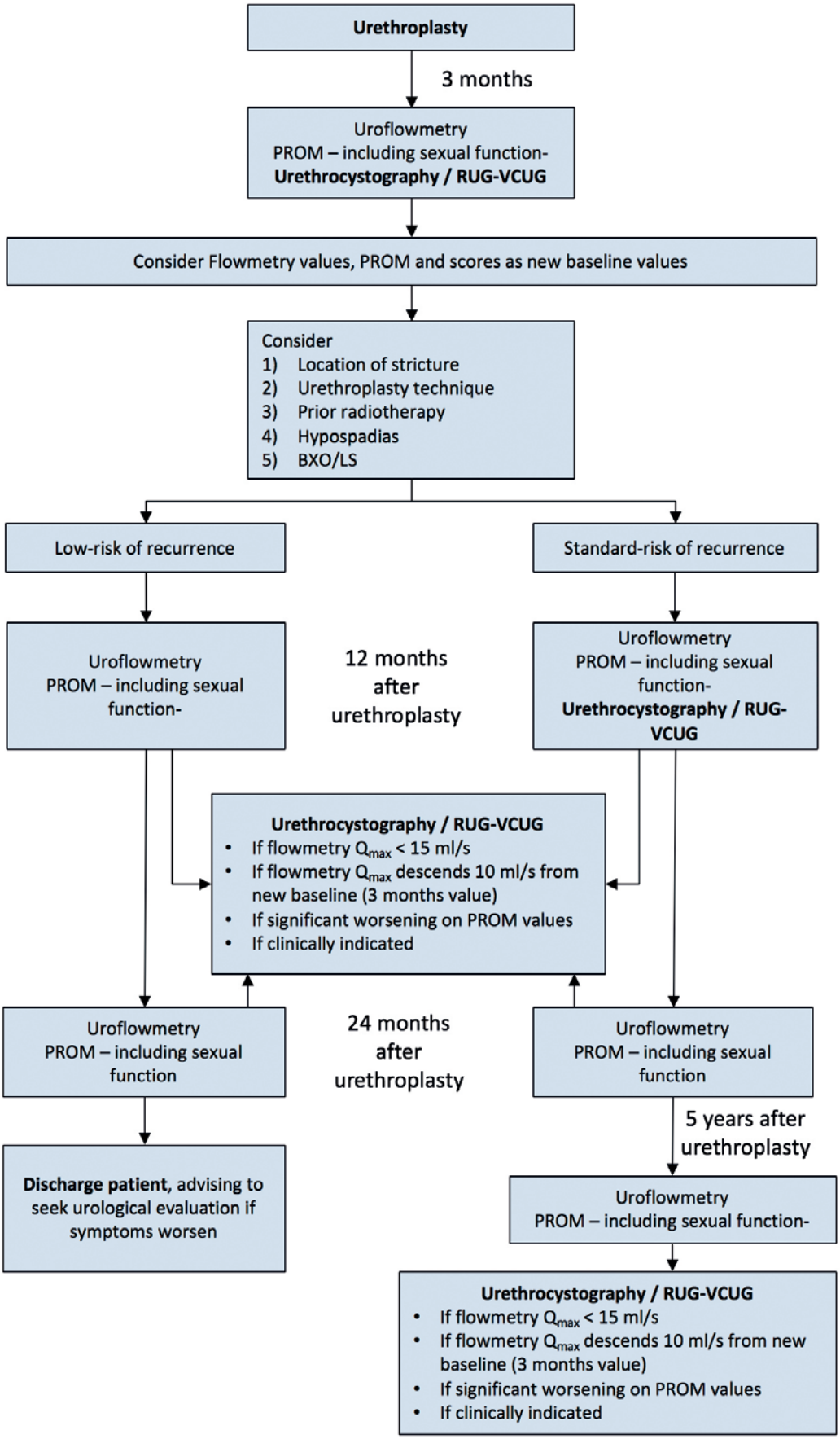
Table 11.4: Follow-up protocol for urethroplasty with standard risk of recurrence

Surgery	3 months	12 months	24 months	5 years *
Uroflowmetry	+	+	+	+
PROM (incl. sexual function)	+	+	+	+
Anatomic evaluation: (Urethrocystoscopy/ RUG-VCUG)	+	+	+	On indication

** Follow-up could be discontinued after five years, advising the patient to seek urological evaluation if symptoms worsen. A longer follow-up period should be considered after penile and subtitution urethroplasties. Academic centres could increase the length of follow-up for reseach purposes.*

Please see Figure 11.1 for further guidance.

Figure 11.1: Follow-up after urethroplasty



BXO = balanitis xerotica obliterans; LS = lichen sclerosus; PROM = patient reported outcome measure; Q_{max} = maximum flow rate; RUG = retrograde urethrography; VCUG = voiding cystourethrography.

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13. CONFLICT OF INTEREST

All members of the Urethral Strictures Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publicly accessible through the European Association of Urology website: http://www.uroweb.org/guidelines/. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

14. CITATION INFORMATION

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INTERNAL URETHROTOMY VERSUS DILATION AS TREATMENT FOR MALE URETHRAL STRICTURES: A PROSPECTIVE, RANDOMIZED COMPARISON

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ABSTRACT

Purpose: We compared the efficacy of dilation versus internal urethrotomy as initial outpatient treatment for male urethral stricture disease.

Materials and Methods: A total of 210 men with proved urethral strictures was randomized to undergo filiform dilation (106) or optical internal urethrotomy (104) with local anesthesia on an outpatient basis.

Results: Life table survival analysis showed no significant difference between the 2 treatments with regard to stricture recurrence. Hazard function analysis showed that the risk of stricture recurrence was greatest at 6 months, whereas the risk of failure after 12 months was slight. The recurrence rate at 12 months was approximately 40% for strictures shorter than 2 cm. and 80% for those longer than 4 cm., whereas the recurrence rate for strictures 2 to 4 cm. long increased from approximately 50% at 12 months to approximately 75% at 48 months. Cox regression analysis showed that for each 1 cm. increase in length of the stricture the risk of recurrence was increased by 1.22 (95% confidence interval 1.05 to 1.43).

Conclusions: There is no significant difference in efficacy between dilation and internal urethrotomy as initial treatment for strictures. Both methods become less effective with increasing stricture length. We recommend dilation or internal urethrotomy for strictures shorter than 2 cm., primary urethroplasty for those longer than 4 cm. and a trial of dilation or urethrotomy for those 2 to 4 cm. long.

KEY WORDS: urethral stricture, surgery, therapy, urethral obstruction

Urethral stricture is one of the oldest known urological diseases and remains a common problem with a high morbidity despite earlier predictions to the contrary.[1–4] The first known form of treatment for urethral stricture was dilation.[5] However, this method has never been regarded as curative, and internal urethrotomy, balloon dilation and urethral stents have replaced it as the first choice of treatment.[6,7] Urethroplasty is still regarded as the gold standard for treatment of urethral strictures but it requires surgical expertise, adequate operating room facilities and relatively long hospitalization, while the cost to the economy is further increased by the often prolonged absence from work.[8]

In many third world countries with limited medical resources male urethral stricture disease remains highly prevalent. Urethroplasty for all strictures is not feasible due to the lack of adequate operating room and hospital facilities. Urethral dilation can be performed on an outpatient basis with local anesthesia by an adequately experienced surgeon with relatively inexpensive equipment. Internal urethrotomy requires surgical expertise, the appropriate endoscopic equipment and operating room facilities.

The perception exists that internal urethrotomy is more effective than dilation but to our knowledge no prospective studies have been done comparing urethral dilation and optical internal urethrotomy as treatment for male urethral strictures. We determined prospectively the best initial treatment for stricture disease and the factors influencing the success of treatment.

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Editor's Note: **This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 336 and 337.**

MATERIALS AND METHODS

Male patients with proved urethral strictures were randomized to undergo dilation or internal urethrotomy with local anesthesia on an outpatient basis. Preoperative evaluation included a complete history and physical examination, urine culture and urethrography under x-ray fluoroscopy. The only study exclusion criterion was complete occlusion of the urethra on urethrography.

All procedures were performed on an outpatient basis by 1 surgeon (J. W. S.). Lidocaine jelly was instilled into the urethra and antibiotic prophylaxis was administered with intravenous injection of 80 mg. gentamicin. In patients randomized to undergo dilation a Phillips filiform leader was passed through the stricture under direct urethroscopic vision using a 19F rigid cystoscope, after which dilation to 24F was performed with serial filiform followers. In patients randomized to undergo internal urethrotomy a 5F whistle-tip ureteral catheter was passed under direct urethroscopic vision, after which optical internal Sachse urethrotomy was performed at the 12 o'clock position using a 21F urethrotome. In both groups of patients an 18F silicone Foley catheter was passed, the patient was discharged home and the catheter was removed 4 days later.

The patients were followed at 3, 6, 9, 12, 24, 36 and 48 months after the initial procedure. Retrograde urethrography was performed under fluoroscopic guidance and a transurethral 16F catheter was passed. If recurrent stricture was found the primary procedure was repeated. Urethroplasty was performed if there were more than 3 recurrent strictures within 1 year.

The life table method was used to estimate the survivor function for the 2 treatment methods. Survival time was regarded as the time to the first recurrent stricture. The log

rank test was used to compare the efficacy of the 2 treatments. Co-factors, such as etiology, clinical presentation, number, length and site of the stricture, complications during the procedure and previous stricture treatment, were evaluated with regard to their association with stricture-free survival using the Cox proportional hazards model with a discrete time scale. In all Cox analyses the treatment variable was included in the model. The cofactors were modeled in a univariate and simultaneous stepwise selection model.

RESULTS

Between January 1991 and January 1994, 210 consecutive men with proved urethral strictures were randomized to undergo dilation (106) or internal urethrotomy (104). There were no significant differences with regard to patient age, etiology of the stricture, clinical presentation, and number, length and site of the strictures between the 2 treatment groups (table 1). The incidence of complications and failure during performance of the procedure did not differ significantly between the 2 treatment groups (table 2), although the total number of patients with complications or failure was greater in the dilation group (34 or 32%) than in the internal urethrotomy group (24 or 23%). Subsequent to initial failure, most patients in both groups were treated with internal urethrotomy or urethroplasty rather than dilation. There was no significant difference between the 2 groups with regard to the availability and duration of followup (table 3).

Life table survival analysis showed no significant difference ($p = 0.22$) between the 2 treatments with regard to stricture recurrence (fig. 1). At 36 months the recurrence rate was 16% greater in the dilation than in the urethrotomy group, and at 48 months it was 10% greater in the dilation group but these differences were not statistically significant. Hazard function analysis showed that the risk of stricture recurrence was greatest at 6 months, whereas the risk of failure after 12 months was slight (fig. 2).

TABLE 1. *Patient and stricture characteristics*

	Dilation Group		Urethrotomy Group	
Mean pt. age (range)	49	(8–86)	50	(19–90)
No. etiology of stricture (%):				
Urethritis	56	(53)	52	(50)
External trauma	23	(22)	16	(15)
Iatrogenic trauma	11	(10)	18	(17)
Unknown	16	(15)	18	(17)
Mean mos. between etiological event and presentation (range)	226	(5–801)	225	(6–825)
No. previous stricture treatment (%):	31	(29)	37	(36)
Dilation	7		10	
Urethrotomy	21		26	
Urethroplasty	5		3	
No. clinical presentation (%):				
Symptoms only	54	(51)	62	(60)
Retention	41	(39)	27	(26)
Complications:	11	(10)	15	(14)
Paraurethral abscess	4		6	
Epididymo-orchitis	3		6	
Cystitis	1		0	
Pyelonephritis	0		1	
Renal failure	2		1	
Bladder stone	1		0	
Perineal fistula	0		1	
No. urine culture pos. (%)	14	(13)	8	(8)
Mean No. strictures (range)	1.35	(1–7)	1.28	(1–6)
No. with 1 stricture (%)	87	(82)	85	(82)
Mean cm. length of stricture (range)	2.37	(0.5–10.5)	2.23	(0.5–8)
No. site of stricture (%):				
Penile	30	(28)	21	(20)
Bulbar	56	(53)	70	(67)
Penile-bulbar	30	(28)	25	(24)
Membranous	4	(4)	1	(1)

TABLE 2. *Complications during procedure*

	No. Pts. (%)	
	Dilation Group	Urethrotomy Group
No problems	72 (68)	80 (77)
Complications	15 (14)	11 (11)
Failure	19 (18)	13 (13)
Cause of complications:		
Difficult (tight stricture)	9	7
Hemorrhage	3	4
False passage	1	1
Extravasation	0	2
Pain	0	4
Knotting of filiform leader	2	0
Breaking of filiform leader	1	0
Bending of filiform follower	1	0
Cause of failure:		
Hemorrhage	4	4
Extravasation	0	1
False passage	2	3
Breakage of filiform	2	0
Breakage of blade	0	1
Treatment after failure:		
Urethrotomy later	10	7
Dilation later	2	2
Suprapubic cystostomy	0	3
Urethroplasty	3	0

TABLE 3. *Followup*

Followup	Dilation Group	Urethrotomy Group
No. pts. (%):		
Available	74 (70)	77 (74)
Not available	32 (30)	27 (26)
Mean/median mos. (range)	15.4/12 (2–49)	14.4/7 (1–49)

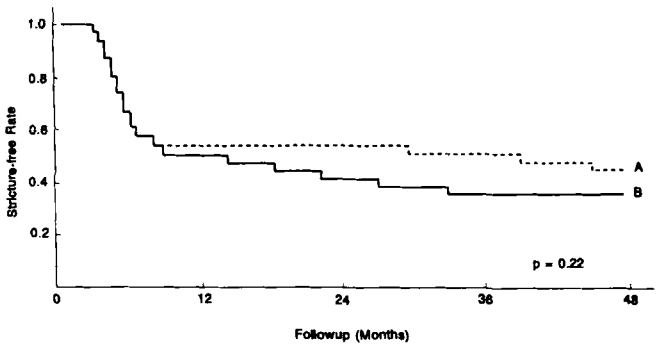

FIG. 1. Life table analysis of stricture recurrence after internal urethrotomy (*A*) or dilation (*B*).

The effect of several cofactors on stricture recurrence was analyzed including etiology (urethritis or trauma); clinical presentation (with or without complications); number, length and position of the strictures (penile, bulbar, penile-bulbar or membranous); complications during performance of the procedure, and previous stricture treatment. Cox regression analysis of treatment adjusted for each cofactor showed that only length of the stricture was significantly associated with stricture recurrence ($p = 0.001$). For each 1 cm. increase in length of the stricture the risk of recurrence was increased by 1.22 (95% confidence interval 1.05 to 1.43).

Life table analysis using various cutoff points for the length of the stricture showed that recurrence rates for less than 1 and less than 2 cm. were similar, whereas the differences for strictures less than 2, 2 to 4 and more than 4 cm. were statistically significant (fig. 3). The recurrence rate at 12 months was approximately 40% for strictures shorter than 2 cm. and 80% for those longer than 4 cm., whereas the recurrence rate for strictures 2 to 4 cm. long increased from approximately 50% at 12 months to 75% at 48 months.

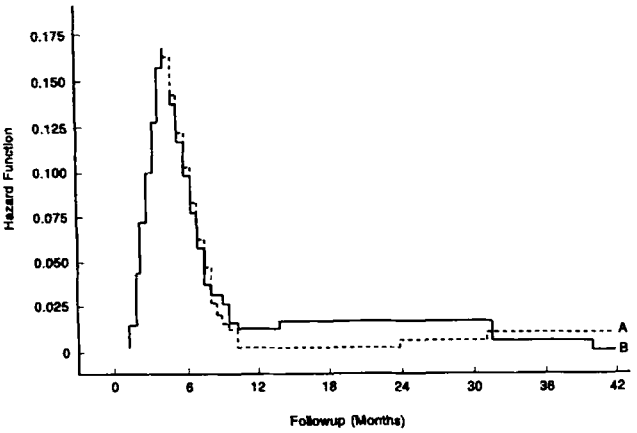

FIG. 2. Risk of first stricture recurrence after internal urethrotomy (*A*) or dilation (*B*).

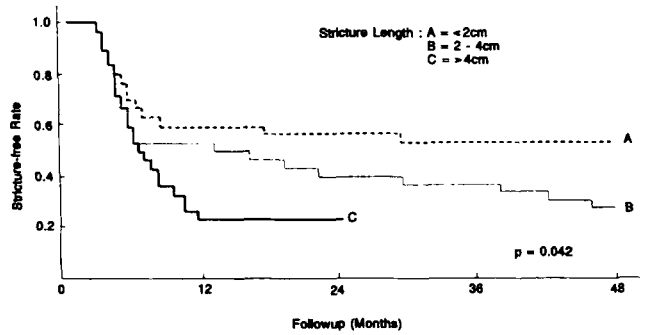

FIG. 3. Life table analysis of association between stricture length and recurrence after dilation or urethrotomy.

Cox regression analysis (univariate as well as with a stepwise procedure) showed that the treatment method was not significant with regard to stricture recurrence. Cofactors with marginal significance were clinical presentation with symptoms (risk ratio 1.73, 95% confidence interval 0.99 to 2.99, p = 0.052), penile location of the stricture (risk ratio 1.85, 95% confidence interval 0.94 to 3.67, p = 0.077) and complications encountered during performance of the procedure (risk ratio 1.72, 95% confidence interval 0.94 to 3.16, p = 0.08).

DISCUSSION

Male urethral strictures are still a common and challenging problem in urology. Although open urethroplasty remains the gold standard, it is time-consuming and requires expertise. The simplest and oldest form of treatment, dilation, has been discarded because it has never been regarded as curative. With introduction of internal urethrotomy initial reports showed good results but, more recently, lower cure rates have been reported.[9-14]

Our study showed no statistically significant difference in the success rate of urethral dilation compared to internal urethrotomy for initial treatment of urethral strictures. Although more complications and failures occurred in the dilation group, this difference was not statistically significant. Risk of stricture recurrence in our study was greatest for the first 6 months and decreased dramatically after 12 months, which supports the finding of Roosen of a 50% stricture recurrence rate during the first 6 months after internal urethrotomy.[15]

The only cofactor significantly associated with stricture recurrence in our study was stricture length, which is contrary to the study of Pitkamaki et al, who reported that stricture length did not affect the recurrence rate after optical urethrotomy.[16] In our study the recurrence rate at 12 months was approximately 40% for strictures shorter than 2 cm. and 80% for those longer than 4 cm., whereas the recurrence rate for strictures 2 to 4 cm. long increased from approximately 50% at 12 months to 75% at 48 months. In a retrospective study by Stormont et al patients with newly diagnosed bulbar strictures were treated with urethral dilation (67%), direct vision internal urethrotomy (26%) or suprapubic cystotomy (7%).[17] Their results support our study showing no difference in efficacy between the different treatment groups. They could not identify any specific patient or stricture characteristics predicting recurrence.[17]

Other reports showed that perioperative infection, previous treatment and periurethral scarring were associated with higher recurrence rates.[18-20] In our study several factors had no statistically significant effect on treatment results, including etiology (urethritis or trauma), clinical presentation (with or without complications), number or position of the strictures (penile, bulbar, penile-bulbar or membranous), complications during the procedure and previous stricture treatment. However, cofactors with marginal significance for stricture recurrence in our study included clinical presentation with complications, penile location of the stricture and complications encountered during the procedure.

CONCLUSIONS

We recommend urethral dilation for strictures shorter than 2 cm. Although the rate of complications or failure during dilation was 32% compared to 23% for internal urethrotomy, dilation does not require special endoscopic equipment or operating room facilities, the results are equivalent to those of internal urethrotomy and approximately 60% of our patients with strictures shorter than 2 cm. remained recurrence-free for up to 48 months after dilation. Optical internal urethrotomy was indicated when dilation was impossible due to complications during the procedure. Primary urethroplasty is recommended for strictures longer than 4 cm., since the recurrence rate after dilation or urethrotomy in our patients was approximately 80% at 12 months. In patients with strictures 2 to 4 cm. long a trial of dilation can be considered depending on the availability of resources and facilities, since approximately 50% of our patients were stricture-free at 12 months, although this rate decreased to approximately 25% at 48 months.

The statistical analysis was performed by Dr. C. J. Lombard, Centre for Epidemiological Research in Southern Africa at the Medical Research Council, Tygerberg, South Africa. Data were collected using computer software developed by Dr. F. J. Allen, Department of Urology, Tygerberg Hospital.

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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

American Urological Association (AUA) Guideline

MALE URETHRAL STRICTURE: AUA GUIDELINE

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PURPOSE

The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of urethral stricture.

METHODS

A systematic review of the literature using the Pubmed, Embase, and Cochrane databases (search dates 1/1/1990 to 12/1/2015) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of urethral stricture. The review yielded an evidence base of 250 articles after application of inclusion/exclusion criteria. These publications were used to create the guideline statements. If sufficient evidence existed, then the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty) and evidence-based statements of Strong, Moderate, or Conditional Recommendation based on risks and benefits were developed. Additional information is provided as Clinical Principles and Expert Opinions when insufficient evidence existed.

GUIDELINE STATEMENTS

Diagnosis/Initial Management

1. Clinicians should include urethral stricture in the differential diagnosis of men who present with decreased urinary stream, incomplete emptying, dysuria, urinary tract infection (UTI), and after rising post void residual. (Moderate Recommendation; Evidence Strength Grade C)
2. After performing a history, physical examination, and urinalysis, clinicians may use a combination of patient reported measures, uroflowmetry, and ultrasound post void residual assessment in the initial evaluation of suspected urethral stricture. (Clinical Principle)
3. Clinicians should use urethro-cystoscopy, retrograde urethrography, voiding cystourethrography, or ultrasound urethrography to make a diagnosis of urethral stricture. (Moderate Recommendation; Evidence Strength Grade C)
4. Clinicians planning non-urgent intervention for a known stricture should determine the length and location of the urethral stricture. (Expert Opinion)
5. Surgeons may utilize urethral endoscopic management (e.g. urethral dilation or direct visual internal urethrotomy [DVIU]) or immediate suprapubic

cystostomy for urgent management of urethral stricture, such as discovery of symptomatic urinary retention or need for catheterization prior to another surgical procedure. (Expert Opinion)

6. Surgeons may place a suprapubic (SP) cystostomy prior to definitive urethroplasty in patients dependent on an indwelling urethral catheter or intermittent self-dilation. (Expert Opinion)

Dilation/Internal Urethrotomy/Urethroplasty

7. Surgeons may offer urethral dilation, direct visual internal urethrotomy (DVIU), or urethroplasty for the initial treatment of a short (< 2 cm) bulbar urethral stricture. (Conditional Recommendation; Evidence Strength Grade C)
8. Surgeons may perform either dilation or direct visual internal urethrotomy (DVIU) when performing endoscopic treatment of a urethral stricture. (Conditional Recommendation; Evidence Strength Grade C)
9. Surgeons may safely remove the urethral catheter within 72 hours following uncomplicated dilation or direct visual internal urethrotomy (DVIU). (Conditional Recommendation; Evidence Strength Grade C)
10. In patients who are not candidates for urethroplasty, clinicians may recommend self-catheterization after direct visual internal urethrotomy (DVIU) to maintain urethral patency. (Conditional Recommendation; Evidence Strength Grade C)
11. Surgeons should offer urethroplasty, instead of repeated endoscopic management for recurrent anterior urethral strictures following failed dilation or direct visual internal urethrotomy (DVIU). (Moderate Recommendation; Evidence Strength Grade C)
12. Surgeons who do not perform urethroplasty should offer patients referral to surgeons with expertise. (Expert Opinion)

Anterior Urethral Reconstruction

13. Surgeons may initially treat meatal or fossa navicularis strictures with either dilation or meatotomy. (Clinical Principle)
14. Surgeons should offer urethroplasty to patients with recurrent meatal or fossa navicularis strictures. (Moderate Recommendation; Evidence Strength Grade C)
15. Surgeons should offer urethroplasty to patients with penile urethral strictures, given the expected high recurrence rates with endoscopic treatments. (Moderate Recommendation; Evidence Strength Grade C)
16. Surgeons should offer urethroplasty as the initial treatment for patients with long (≥2cm) bulbar urethral strictures, given the low success rate of direct visual internal urethrotomy (DVIU) or dilation. (Moderate Recommendation; Evidence Strength Grade C)
17. Surgeons may reconstruct long multi-segment strictures with one stage or multi-stage techniques using oral mucosal grafts, penile fasciocutaneous flaps or a combination of these techniques. (Moderate Recommendation; Evidence Strength Grade C)
18. Surgeons may offer perineal urethrostomy as a long-term treatment option to patients as an alternative to urethroplasty. (Conditional Recommendation; Evidence Strength Grade C)
19. Surgeons should use oral mucosa as the first choice when using grafts for urethroplasty. (Expert Opinion)
20. Surgeons should not perform substitution urethroplasty with allograft, xenograft, or synthetic materials except under experimental protocols. (Expert Opinion)
21. Surgeons should not perform a single-stage tubularized graft urethroplasty. (Expert Opinion)

22. Surgeons should not use hair-bearing skin for substitution urethroplasty. (Clinical Principle)

Pelvic Fracture Urethral Injury

23. Clinicians should use retrograde urethrography with voiding cystourethrogram and/or retrograde + antegrade cystoscopy for preoperative planning of delayed urethroplasty after pelvic fracture urethral injury (PFUI). (Moderate Recommendation; Evidence Strength Grade C)
24. Surgeons should perform delayed urethroplasty instead of delayed endoscopic procedures after urethral obstruction/obliteration due to pelvic fracture urethral injury (PFUI). (Expert Opinion)
25. Definitive urethral reconstruction for pelvic fracture urethral injury (PFUI) should be planned only after major injuries stabilize and patients can be safely positioned for urethroplasty. (Expert Opinion)

Bladder Neck Contracture/Vesicourethral Stenosis

26. Surgeons may perform a dilation, bladder neck incision or transurethral resection for bladder neck contracture after endoscopic prostate procedure. (Expert Opinion)
27. Surgeons may perform a dilation, vesicourethral incision, or transurethral resection for post-prostatectomy vesicourethral anastomotic stenosis. (Conditional Recommendation; Evidence Strength Grade C)
28. Surgeons may perform open reconstruction for recalcitrant stenosis of the bladder neck or post-prostatectomy vesicourethral anastomotic stenosis. (Conditional Recommendation; Evidence Strength Grade C)

Special Circumstances

29. In men who require chronic self-catheterization (e.g. neurogenic bladder), surgeons may offer urethroplasty as a treatment option for urethral stricture causing difficulty with intermittent self-catheterization. (Expert Opinion)
30. Clinicians may perform biopsy for suspected lichen sclerosus (LS), and must perform biopsy if urethral cancer is suspected. (Clinical Principle)
31. In lichen sclerosus (LS) proven urethral stricture, surgeons should not use genital skin for reconstruction. (Strong Recommendation; Evidence Strength Grade B)

Post-operative Follow-up

32. Clinicians should monitor urethral stricture patients to identify symptomatic recurrence following dilation, direct visual internal urethrotomy (DVIU) or urethroplasty. (Expert Opinion)

INTRODUCTION

Purpose

Urethral stricture is chronic fibrosis and narrowing of the urethral lumen caused by acute injury, inflammatory conditions, and iatrogenic interventions including urethral instrumentation or surgery and prostate cancer treatment. The symptoms of urethral stricture are non-specific and may overlap with other common conditions including lower urinary tract symptoms (LUTS) and urinary tract infections (UTI) to confound timely diagnosis. Urologists play a key role in the initial evaluation of urethral stricture and currently provide all accepted treatments. Thus, urologists must be familiar with the evaluation and diagnostic tests for urethral stricture as well as endoscopic and open surgical treatments. This guideline provides evidence guidance to clinicians and patients regarding how to recognize symptoms and signs of a urethral stricture/ stenosis, carry out appropriate testing to determine the location and severity of the stricture, and recommend the best options for treatment. The most effective approach for a particular patient is best determined by the individual clinician and patient in the context of that patient's history, values, and goals for treatment. As the science relevant to urethral stricture evolves and improves, the strategies presented here will be amended to remain consistent with the highest standards of clinical care.

Methodology

Systematic review. A systematic review was conducted to identify published articles relevant to the diagnosis and treatment of urethral stricture. Literature searches were performed on English-language publications using the Pubmed, Embase, and Cochrane databases from 1/1/1990 to 12/1/2015. Data from studies published after the literature search cut-off will be incorporated into the next version of this guideline. Preclinical studies (e.g., animal models), commentary, editorials, non-English language publications, and meeting abstracts were excluded. Additional exclusion criteria were as follows: studies of females; studies of stricture prevention; patients with epispadias, congenital strictures, and duplicated urethra; trauma already covered under trauma guidelines including diagnosis and management of acute pelvic fracture urethral injury (PFUI) or disruption (PFUD); urethral cancer not related to stricture; or voiding symptoms not related to stricture. Studies with less than 10 patients were generally excluded from further evaluation and thus data extraction given the unreliability of the statistical estimates and conclusions that could be derived from them. In rare instances, we have included studies with less than 10 patients or studies preceding the literature search date if no other evidence was identified. For certain key questions that had little or no evidence from comparative studies, we included case series with 50 or more patients. Review article references were checked to ensure inclusion of all possible relevant studies. Multiple reports on the same patient group were carefully examined to ensure inclusion of only non-redundant information. The systematic review yielded a total of 250 publications relevant to preparation of the guideline.

Quality of Individual Studies and Determination of Evidence Strength. The quality of individual studies that were either RCTs or CCTs was assessed using the Cochrane Risk of Bias tool.[1] Observational cohort studies with a comparison of interest were evaluated with the Drug Effectiveness Review Project instrument.[2] Conventional diagnostic cohort studies, diagnostic case-control studies, or diagnostic case series that presented data on diagnostic test characteristics were evaluated using the QUADAS 2 tool, which evaluates the quality of diagnostic accuracy studies.[3] Because there is no widely -agreed upon quality assessment tool for single cohort observational intervention studies, the quality of these studies was not assessed.

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only individual study quality but also consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the guideline. The AUA categorizes the strength of a body of evidence as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings); Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent

findings); or Grade C (RCTs with serious deficiencies of procedure, generalizability, or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[4]

AUA Nomenclature: Linking Statement Type to Evidence Strength. The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances but that better evidence *is likely to change confidence*. Body of evidence strength Grade C is only rarely used in support of a Strong Recommendation. Conditional Recommendations also can be supported by any body of evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

For some clinical issues, particularly diagnosis, there was little or no evidence from which to construct evidence-based statements. Where gaps in the evidence existed, the Panel provides guidance in the form of *Clinical Principles* or *Expert Opinion* with consensus achieved using a modified Delphi technique if differences of opinion emerged.[5] A *Clinical Principle* is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. *Expert Opinion* refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence.

Process. The Urethral Stricture Panel was created in 2013 by the American Urological Association Education and Research, Inc. (AUA). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Co-Chairs who in turn appointed the additional panel members with specific expertise in this area. The AUA conducted a thorough peer review process. The draft guidelines document was distributed to 90 peer reviewers. The panel reviewed and discussed all submitted comments and revised the draft as needed. Once finalized, the guideline was submitted for approval to the PGC and the AUA Science and Quality Council. Then it was submitted to the AUA Board of Directors for final approval. Funding of the panel was provided by the AUA; panel members received no remuneration for their work.

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength			
	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

Background

The urethra extends from the bladder neck, which is composed of smooth muscle circular fibers, to the meatus, with varying histological features and stromal support based on anatomical location. The components of the posterior urethra are lined with transitional epithelium, whereas the anterior urethra is lined with pseudostratified columnar epithelium that changes to stratified squamous epithelium in the fossa navicularis. The posterior urethra includes both the prostatic and membranous urethra. The prostatic urethra extends from the distal bladder neck to the distal end of the veru montanum. The distal external sphincter mechanism surrounds the membranous urethra and is comprised of both intrinsic smooth muscle and rhabdosphincter. The anterior urethra includes the bulbar urethra, penile urethra and fossa navicularis. This urethra is completely surrounded by the corpus spongiosum, which in the bulbar urethra is surrounded by the bulbocavernosus muscle. The fossa navicularis is located entirely within the glans penis.

Urethral stricture is the preferred term for any abnormal narrowing of the anterior urethra, which runs from the bulbar urethra to the meatus and is surrounded by the corpus spongiosum. Urethral strictures are associated with varying degrees of spongiofibrosis. Narrowing of the posterior urethra, which lacks surrounding spongiosum, is thus referred to as a "stenosis." Pelvic fracture urethral injury typically creates a distraction defect with resulting obstruction or obliteration.[6]

Urethral strictures or stenoses are treated endoscopically or with urethroplasty. Endoscopic management is performed by either urethral dilation or direct vision internal urethrotomy (DVIU). There are a multitude of different urethroplasty techniques that can be generally divided into tissue transfer involved procedures and non -tissue transfer involved procedures. Anastomotic urethroplasty does not involve tissue transfer and can be performed in both a transecting and non-transecting manner. Excision and primary anastomosis (EPA) urethroplasty involves transection and removal of the narrowed segment of urethra and corresponding spongiofibrosis with anastomosis of the two healthy ends of the urethra. Non-transecting anastomotic urethroplasty preserves the corpus spongiosum, thus allowing the strictured urethra to be excised and reanastomosed, or incised longitudinally through the narrowed segment of the urethra and closed in a Heineke-Mikulicz fashion.

Techniques that involve tissue transfer can be categorized into single stage and multi-stage procedures. In single stage procedures, the urethra is augmented in caliber by transferring tissue in the form of a graft or flap. Multi-stage procedures use a graft as a urethral substitute for future tubularization.

Epidemiology

Geographic setting, socioeconomic factors and access to healthcare can affect stricture etiology. In developed countries, the most common etiology of urethral stricture is idiopathic (41%) followed by iatrogenic (35%). Late failure of hypospadias surgery and stricture resultant from endoscopic manipulation (e.g. transurethral resection) are common iatrogenic reasons. In comparison, trauma (36%) is the most common cause in developing countries, reflecting higher rates of road traffic injuries, less developed trauma systems, inadequate roadway systems and conceivably socioeconomic factors leading to a higher prevalence of trauma-related strictures.[7-9]

Strictures in the bulbar urethra predominate over other anatomic locations; however, certain etiologies are closely associated with an anatomic segment of the urethra.[7] For example, strictures related to hypospadias - and lichen sclerosus (LS—previously termed balanitis xerotica obliterans) are generally located in the penile urethra, while traumatic strictures and stenoses tend to be located in the bulbar and posterior urethra.

Preoperative Assessment

Presentation

Patients with urethral stricture most commonly present with decreased urinary stream and incomplete bladder emptying but may also demonstrate UTI, epididymitis, rising post-void residual urine volume or decreased force of ejaculation. Additionally, patients may present with urinary spraying or dysuria.[10]

Patient Reported Outcomes Measures

Patient reported measures (PRMs) help elucidate the

presence and severity of patient symptoms and bother and thus may serve as an important component of urethral stricture diagnosis and management. While the American Urological Association Symptom Index (AUASI) includes items assessing decreased urinary stream and incomplete bladder emptying, it does not identify other symptoms seen in patients with a urethral stricture, such as urinary spraying and dysuria.[10] Therefore, there is a need for development of a standardized urethral stricture PRM that can be used to assess symptoms, degree of bother, and quality of life impact. A more disease specific standardized PRM will also allow for comparison of patient outcomes across research studies.

Diagnosis

All men being evaluated for lower urinary tract symptoms should have a complete history and physical examination and urinalysis at a minimum. Decreased urinary stream, incomplete emptying and other findings such as urinary tract infection should alert clinicians to include urethral stricture in the differential diagnosis. In the initial assessment of patients suspected of having a urethral stricture, a combination of PRMs to assess symptoms, uroflowmetry to determine severity of obstruction, and ultrasound post-void residual volume to identify urinary retention may be used. Patients with symptomatic urethral stricture typically have a reduced peak flow rate.[11,12] Confirmation of a urethral stricture diagnosis is made with urethroscopy, retrograde urethrography, or ultrasound urethrography. Urethroscopy readily identifies a urethral stricture, but does not delineate the location and length of strictures. Retrograde urethrography (RUG) with or without voiding cystourethrography (VCUG) allows for identification of stricture location in the urethra, length of the stricture, and degree of lumen narrowing.[13,14] All of these stricture characteristics are important for subsequent treatment planning. Ultrasound urethrography can be used to identify the location, length and severity of the stricture.[15] While ultrasound urethrography is a promising technique, further studies are needed to validate its value in clinical practice.

Preoperative assessment for definitive reconstruction should elicit details of the etiology, diagnostic information about length and location of the stricture, and prior treatments. In the case of pelvic fracture urethral injury, a detailed history should document all associated injuries and angiographic embolization of any pelvic vessels. The history should assess pre-operative erectile function and urinary continence. Physical examination should include an abdominal and genital exam, digital rectal exam, and assessment of lower extremity mobility for operative positioning.

Patient Selection

Patient selection and proper surgical procedure choice are paramount to maximize the chance of successful outcome in the treatment of urethral stricture. The main factors to consider in decision making include: stricture etiology, location, and severity; prior treatment; comorbidity; and patient preference. As with any operation, surgeons should consider a patient's goals, preferences, comorbidities and fitness for surgery prior to performing urethroplasty.[16]

Operative Considerations

Before proceeding with surgical management of a urethral stricture, the physician should provide an appropriate antibiotic to reduce surgical site infections. Preoperative urine cultures are recommended to guide antibiotic choice, and active urinary tract infections must be treated before urethral stricture intervention. Prophylactic antibiotic choice and duration should follow AUA Best Practice Policy Statement.[17] To avoid bacterial resistance, antibiotics should be discontinued after a single dose or within 24 hours. Antibiotics can be extended in the setting of an active urinary tract infection or if there is an existing indwelling catheter.[17] In the setting of endoscopic urethral stricture management, oral fluoroquinolones are more cost effective than intravenous cephalosporins leading the AUA Antimicrobial Prophylaxis panel to support their use.[17] Antimicrobial prophylaxis is recommended at the time of urethral catheter removal in patients with certain risk factors.[17]

Positioning of the extremities should be careful to avoid pressure on the calf muscles, peroneal nerve and ulnar nerve when using the lithotomy position. Use of sequential compression devices is recommended to reduce deep venous thromboembolism (VTE) and nerve compression injuries. Perioperative parenteral VTE

prophylaxis is a consideration in select circumstances for open reconstruction.

Postoperative Care

A urinary catheter should be placed following urethral stricture intervention to divert urine from the site of intervention and prevent urinary extravasation. Either urethral catheter or suprapubic cystostomy is a viable option; a urethral catheter is thought to be optimal as it may serve as a stent around which the site of urethra intervention can heal. The length of urinary catheterization is widely variable, with a shorter recommended time for endoscopic interventions than open urethral reconstruction.[18]

Urethrography or voiding cystography is typically performed two to three weeks following open urethral reconstruction to assess for complete urethral healing. Replacement of the urinary catheter is recommended in the setting of a persistent urethral leak to avoid tissue inflammation, urinoma, abscess, and/or urethrocutaneous fistula. A urethral leak will heal in almost all circumstances with a longer duration of catheter drainage.[19,20]

Complications

Erectile dysfunction, as measured by the International Index of Erectile Function (IIEF) may occur transiently after urethroplasty with resolution of nearly all reported symptoms approximately six months postoperatively.[21-25] Meta-analysis has demonstrated the risk of new onset erectile dysfunction following anterior urethroplasty to be ~1%.[26] Type of urethroplasty, specifically anastomotic urethroplasty, as a causative risk factor for sexual dysfunction remains unclear. Erectile function following urethroplasty for PFUI does not appear to significantly change as a result of surgery. Erectile dysfunction in this cohort may be related to the initial pelvic trauma rather that the subsequent urethral reconstruction.[27]

Ejaculatory dysfunction manifested as pooling of semen, decreased ejaculatory force, ejaculatory discomfort, and decreased semen volume has been reported by up to 21% of men following bulbar urethroplasty.[28] Urethroplasty technique may play a role in the occurrence of ejaculatory dysfunction but the exact etiology remains uncertain.[29-31] Conversely, some patients, as measured by the Men's Sexual Health Questionnaire (MSHQ), will notice an improvement in ejaculatory function following bulbar urethroplasty, particularly those with pre-operative ejaculatory dysfunction related to obstruction caused by the stricture.[28] Data on ejaculatory function in men undergoing penile urethroplasty or urethroplasty for PFUI is limited.

Follow Up

Successful treatment for urethral stricture (endoscopic or surgical) is most commonly defined as no further need for surgical intervention or instrumentation.[32-44] Some studies use the absence of postoperative or post-procedural patient reported obstructive voiding symptoms and/or peak uroflow > 15m/sec as a benchmark for successful treatment.[45-50] Additional measures of success that have been used alone or in combination include urethral patency assessed by urethro-cystoscopy, absence of recurrent stricture on urethrography, post-void residual urine <100mL, "unobstructed" flow curve shape on uroflowmetry, absence of urinary tract infection, ability to pass a urethral catheter, and patient reported improvement in lower urinary tract symptoms.[51-55] Consensus has not been reached on the optimal postoperative surveillance protocol to identify stricture recurrence following urethral stricture treatment.

GUIDELINE STATEMENTS

Diagnosis/Initial Management

1. **Clinicians should include urethral stricture in the differential diagnosis of men who present with decreased urinary stream, incomplete emptying, dysuria, urinary tract infection (UTI), and rising post void residual. (Moderate Recommendation; Evidence Strength Grade C)**

Differences in stricture characteristics (e.g. location, length, luminal diameter), duration of obstruction, and other factors create a heterogeneous combination of subjective complaints related to a symptomatic urethral stricture. Other urologic conditions such as benign prostate enlargement (with or without bladder outlet obstruction), bladder outlet obstruction, and abnormal detrusor function can present with similar subjective findings, making diagnosis challenging. Young men do

not commonly present with voiding urinary symptoms, therefore a urethral stricture should be considered in the differential diagnosis.

Common risk factors for developing a urethral stricture include a history of hypospadias surgery, urethral catheterization or instrumentation, traumatic injury, transurethral surgery, and prostate cancer treatment.[7,9,56] The stricture etiology will be idiopathic in many men. Among iatrogenic strictures, transurethral surgery is the most common etiology.[7,56] While inflammatory disorders are a less common etiology, LS-related urethral strictures are most troublesome among these stricture types. LS-related urethral strictures tend to be longer than other stricture etiologies, more commonly present in the penile urethra, and may have a higher association with urethral cancer.[7,9]

Men with urethral stricture most commonly report a weak urine stream and incomplete bladder emptying, although other symptoms may be urinary, erectile, and/or ejaculatory in nature.[10] Voiding symptoms not captured by the AUASI include urine spraying (13%) and dysuria (10%);[10] the former symptom is more common among patients with penile than bulbar urethral strictures. Recurrent urethral stricture causes the same general constellation of symptoms including weak stream, painful urination, and UTI.[57] Sexual dysfunction is present in a small minority of men with urethral stricture, with erectile dysfunction being more commonly reported than ejaculatory dysfunction.[10] Sexual dysfunction has been reported to be a more common presenting symptom among men with a history of hypospadias failure and LS.[10] A small subset of men with urethral stricture who are being evaluated for a different urological issue will not have urinary or sexual dysfunction complaints.[10]

2. After performing a history, physical examination, and urinalysis, clinicians may use a combination of patient reported measures, uroflowmetry, and ultrasound post void residual assessment in the initial evaluation of suspected urethral stricture. (Clinical Principle)

A number of self-report instruments, including the AUASI, have been used to evaluate men for lower urinary tract symptoms. Individual questions from these instruments may be used to detect symptoms consistent with stricture disease.

If symptoms and signs suggest the presence of a stricture, noninvasive measures such as uroflowmetry may then definitively delineate low flow, which is typically considered to be less than 12 mL per second.[11,12] Similarly, ultrasonographic post void residual measurement may detect poor bladder emptying. The presence of voiding symptoms as described above, in combination with reduced peak flow rate for age, place patients at higher probability for urethral stricture, therefore indicating definitive evaluation such as cystoscopy, retrograde urethrography, or ultrasound urethrography.

3. Clinicians should use urethro-cystoscopy, retrograde urethrography, voiding cystourethrography, or ultrasound urethography to make a diagnosis of urethral stricture. (Moderate Recommendation; Evidence Strength Grade C)

Endoscopy and/or radiological imaging of the urethra is essential for confirmation of the diagnosis, assessment of stricture severity (e.g. staging), and procedure selection. History, physical examination, and adjunctive measures described above in Statements One and Two cannot definitively confirm a urethral stricture. Urethroscopy identifies and localizes urethral stricture and allows evaluation of the distal caliber, but the length of the stricture and the urethra proximal to the urethral stricture cannot be assessed in most cases. When flexible cystoscopy does not allow visual assessment proximal to the urethral stricture, small caliber cystoscopy with a flexible ureteroscope or flexible hysteroscope can be useful adjuncts. MRI can provide important detail in select cases (i.e., PFUI, diverticulum, fistula, cancer).

Retrograde Urethrography

Retrograde urethrography (RUG), with or without voiding cystourethrography, remains the study of choice for delineation of stricture length, location, and severity.[13,14,58] However, the image quality and accuracy of RUG is operator-dependent; surgical planning should be based on high quality images

generated by experienced practitioners or the surgeon him/herself.[59]

The modestly invasive nature of RUG reflects the potential risks, including patient discomfort, urinary tract infection, hematuria, and contrast extravasation. UTI is rare and contrast extravasation is very rare in expert hands. Exposure to the contrast puts the patient at risk for a contrast reaction, should there be an allergy. The risk is very low in the absence of inadvertent extravasation, and may be mitigated by pre-medication with oral corticosteroids and histamine blockers. Complete or near complete occlusion of the urethra may make the assessment of the urethra proximal to the stricture difficult. In this instance, RUG may be combined with antegrade (voiding) cystourethrography or other methods to define the extent of the stricture.

Ultrasound urethrography

Ultrasound urethrography may serve to diagnose the presence of urethral stricture as well as describe the location, length, and severity of narrowing of strictures. It has a high sensitivity and specificity in the anterior urethra but shares the drawbacks of RUG, including patient discomfort and dependence on a skilled ultrasonographer.[15] Some advocate the use of urethral sonography (ultrasound urethrography) to define the extent of spongiofibrosis and absolute length of the urethral stricture,[60-73] although this is not strictly required and is not used by a majority of stricture experts.[74]

4. **Clinicians planning non-urgent intervention for a known stricture should determine the length and location of the urethral stricture. (Expert Opinion)**

Determination of urethral stricture length and location allows the patient and urologist to engage in an informed discussion about treatment options, perioperative expectations, and expected outcomes following urethral stricture therapy. In addition, preoperative planning permits operative and anesthetic planning.

5. **Surgeons may utilize urethral endoscopic management (e.g. urethral dilation or direct visual internal urethrotomy [DVIU]) or immediate suprapubic cystostomy for urgent management of urethral stricture, such as discovery of symptomatic urinary retention or need for catheterization prior to another surgical procedure. (Expert Opinion)**

When urethral strictures are identified at the time of catheter placement for another surgical procedure, assessment of the need for catheterization should be made. Urethral catheter placement may not be required for surgical procedures that are short in duration. If catheterization is deemed necessary, the primary consideration should be safe urinary drainage. Urethral strictures may be dilated in this setting to allow catheter insertion, and dilation over a guidewire is recommended to prevent false passage formation or rectal injury. Alternatively, internal urethrotomy may be performed, particularly if the stricture is too dense to be adequately dilated. Suprapubic cystotomy may also be performed to provide urinary drainage at the time of surgery if these initial maneuvers are unsuccessful, or when subsequent definitive treatment for urethral stricture is planned in the near future.

6. **Surgeons may place a suprapubic (SP) cystostomy prior to definitive urethroplasty in patients dependent on an indwelling urethral catheter or intermittent self-dilation. (Expert Opinion)**

Proper evaluation of a urethral stricture may require a period without urethral instrumentation to determine the true severity of the stricture including its degree of narrowing. Men with a urethral stricture who have been managed with either an indwelling urethral catheter or self-dilation should generally undergo suprapubic cystostomy placement prior to imaging. This allows the full length of the stricture to develop, and accurate determination of definitive treatment options. Although no specific studies have evaluated the efficacy of this approach, experts agree that a period of "urethral rest" between 4-12 weeks allows the stricture to mature prior to evaluation and management.[75] This is thought to maximize success by not underestimating the length of stricture and degree of spongiofibrosis. A similar period of observation is recommended before reassessing a stricture after failure or dilation or DVIU.

Dilation/Internal Urethrotomy/Urethroplasty

7. Surgeons may offer urethral dilation, direct visual internal urethrotomy (DVIU), or urethroplasty for the initial treatment of a short (< 2 cm) bulbar urethral stricture. (Conditional Recommendation; Evidence Strength Grade C)

Short bulbar urethral strictures may be treated by dilation, DVIU, or urethroplasty. Urethral dilation and DVIU have similar long-term outcomes in short strictures, with success ranging from 35-70%.[76-78] The success of endoscopic treatment depends on the location and length of the stricture, with the highest success rates found in those with bulbar strictures less than 1 cm.[79-81] Conversely, success rates for dilation or DVIU of strictures longer than 2cm are very low.[78,81]

Urethroplasty has a higher long-term success rate than endoscopic treatment, ranging from 80-95%. Urethroplasty may be offered as the initial treatment for a short bulbar urethral stricture, but the higher success rate of this treatment compared to endoscopic treatment must be weighed against the increased anesthesia requirement, cost, and higher morbidity of urethroplasty.

8. Surgeons may perform either dilation or direct visual internal urethrotomy (DVIU) when performing endoscopic treatment of a urethral stricture. (Conditional Recommendation; Evidence Strength Grade C)

Dilation and DVIU have similar success and complication rates and can be used interchangeably. Few studies exist that compare different methods of performing DVIU, but cold knife and laser incision of the stricture scar appear to have similar success rates and may be used interchangeably.[82,83] Other methods of incision may be used experimentally, such as PlasmaKinetic incision.[54] A small experimental study suggests that holmium: YAG laser urethrotomy may have higher success rates in iatrogenic strictures.[82]

Clinicians may endoscopically inject a urethral stricture at the time of DVIU to reduce risk of stricture recurrence. The few studies available showed a generally consistent lower stricture recurrence rate when steroids were added to DVIU, although the findings did not reach statistical significance and follow up was relatively short.[84,85] Mitomycin C injected at the time of DVIU has also been shown to reduce stricture recurrence rate, although data is limited regarding long term follow up.[86]

9. Surgeons may safely remove the urethral catheter within 72 hours following uncomplicated dilation or direct visual internal urethrotomy (DVIU). (Conditional Recommendation; Evidence Strength Grade C)

The reported length of catheterization after dilation or DVIU is highly variable in the literature, ranging from one to eight days.[78,81,82,87,-91] There is no evidence that leaving the catheter longer than 72 hours improves safety or outcome, and catheters may be removed after 24-72 hours. Catheters may be left in longer for patient convenience or if in the surgeon's judgment early removal will increase the risk of complications.

10. In patients who are not candidates for urethroplasty, clinicians may recommend self-catheterization after direct visual internal urethrotomy (DVIU) to maintain temporary urethral patency. (Conditional Recommendation; Evidence Strength Grade C)

Studies using varying self catheterization schedules after DVIU, ranging from daily to weekly, have demonstrated that stricture recurrence rates were significantly lower among patients performing self-catheterization (risk ratio 0.51, 95% CI 0.32 to 0.81, p = 0.004).[88,92-95] The optimal protocol for DVIU plus self-catheterization remains uncertain. However, data suggests that performing self-catheterization for greater than four months after DVIU reduced recurrence rates compared to performing self catheterization for less than three months.[88,92-97] Even though the risk of UTI does not appear to be increased in patients performing self catheterization after DVIU, the ability to continue with self-catheterization may be limited in some patients by manual dexterity or pain with catheterization.[88,96,98]

11. Surgeons should offer urethroplasty, instead of repeated endoscopic management for recurrent anterior urethral strictures following failed dilation or direct visual

internal urethrotomy (DVIU). (Moderate Recommendation; Evidence Strength Grade C)

Urethral strictures that have been previously treated with dilation or DVIU are unlikely to be successfully treated with another endoscopic procedure,[91] with failure rates of >80%.[99] Repeated endoscopic treatment may cause longer strictures, and may increase the complexity of subsequent urethroplasty.[100] In patients who are unable to undergo, or who prefer to avoid, urethroplasty, repeated endoscopic procedures, or intermittent self-catheterization may be considered as palliative measures.

12. Surgeons who do not perform urethroplasty should offer patients referral to surgeons with expertise. (Expert Opinion)

When evaluating a patient with a recurrent urethral stricture, a physician who does not perform urethroplasty should consider referral to a surgeon with experience in this technique due to the higher rate of successful treatment compared to repeat endoscopic management. The relationship between surgical volume and quality is an area for future investigation. There are cases series that suggest, as with many surgical procedures, that better outcomes following urethroplasty are associated with greater surgeon experience.[101,102]

Anterior Urethral Reconstruction

13. Surgeons may initially treat meatal or fossa navicularis strictures with either dilation or meatotomy. (Clinical Principle)

First time presentation of an uncomplicated urethral stricture confined to the meatus or fossa navicularis can be treated with simple dilation or meatotomy with or without guidewire placement, as long as it is not associated with previous hypospadias repair, prior failed endoscopic manipulation, previous urethroplasty, or LS.[39]

Strictures related to hypospadias and LS require unique treatment strategies.[103] However, in the setting of LS there is some evidence that extended meatotomy in conjunction with high-dose topical steroids may decrease the risk of recurrence as compared to meatotomy alone.[104] Additionally, no evidence exists on the optimal caliber of dilation or the need to implement a post dilation intermittent catheterization regimen to reduce stricture recurrence.

14. Surgeons should offer urethroplasty to patients with recurrent meatal or fossa navicularis strictures. (Moderate Recommendation; Evidence Strength Grade C)

Meatal and fossa navicularis strictures refractory to endoscopic procedures are unlikely to respond to further endoscopic treatments.[77,78,81,90,91,105,106] Furthermore, urethroplasty is the best option for completely obliterated strictures or strictures associated with hypospadias or LS. Some patients may opt for repeat endoscopic treatments or intermittent self-dilation in lieu of more definitive treatment such as urethroplasty. Similar to other types of stricture, exact delineation of length and etiology is important for guiding treatment.

Urologists have a variety of options at their disposal for the surgical treatment of meatal and fossa strictures, including meatoplasty, extended meatotomy, and several variations of urethroplasty. It is important to consider both aesthetic and functional outcomes when reconstructing strictures involving the glanular urethra. Simple reconfiguration of the meatus can be performed using a variety of techniques but is best suited to non-obliterated strictures confined to the meatus.[103] In this setting, there is an approximate 75% chance of success.[103] Meatotomy and extended meatotomy have also been employed with success rates up to 87%. [39,103]

Reconstruction of the fossa navicularis can be achieved using a variety of techniques and tissue sources without possible negative cosmetic and functional consequences of meatotomy. One-stage urethroplasty for recurrent meatal and fossa navicularis strictures has been reported with acceptable outcomes.[39,107-109]The most commonly used tissue sources are penile fasciocutaneous flaps and oral mucosal grafts. In the absence of LS, penile fasciocutaneous flaps have been used most commonly, with reported short-term success rates up to 94%.[39,103,109-111] Strictures related to LS are less likely to be reconstructed successfully using genital skin transfer, because LS is a condition of the genital

skin.[112] In these instances, the success of oral mucosal grafts has been reported between 83%-100%.[107,108,113]

In the setting of failed hypospadias surgery, no single technique can be recommended, although the absence of adjacent skin for transfer increases the likelihood of requiring a staged oral mucosa graft urethroplasty.[114-118]

15. Surgeons should offer urethroplasty to patients with penile urethral strictures, because of the expected high recurrence rates with endoscopic treatments. (Moderate Recommendation; Evidence Strength Grade C)

Strictures involving the penile urethra are more likely to be related to hypospadias, LS, or iatrogenic etiologies when compared to strictures of the bulbar urethra, and are thus unlikely to respond to dilation or urethrotomy, except in select cases of previously untreated, short strictures.[77,78,81,90,91] Given the low likelihood of success with endoscopic treatments, most patients with penile urethral strictures should be offered urethroplasty at the time of diagnosis, avoiding repeated endoscopic treatments. When compared to bulbar strictures, penile urethral strictures are more likely to require tissue transfer and/or a staged approach.[112,119]

When performing single stage urethroplasty, penile fasciocutaneous flaps and oral mucosal grafts have been used in differing configurations.[39,47,110,111,120-124] Success rates in penile urethroplasty for properly selected patients appear similar regardless of tissue and technique used.[122,125,126]

16. Surgeons should offer urethroplasty as the initial treatment for patients with long (≥2cm) bulbar urethral strictures, given the low success rate of direct visual internal urethrotomy (DVIU) or dilation. (Moderate Recommendation; Evidence Strength Grade C)

Longer strictures are less responsive to endoscopic treatment, with success rates of only 20% for strictures longer than 4cm in the bulbar urethra.[76] The success rate for buccal mucosa graft urethroplasty for strictures of this length is greater than 80%.[41,127,128]

Given the low efficacy of endoscopic treatment, urethroplasty should be offered to patients with long urethral strictures. Urethroplasty may be performed using a variety of techniques based on the experience of the surgeon, most often through substitution or augmentation of the narrowed segment of the urethra.

17. Surgeons may reconstruct long multi-segment strictures with one stage or multi-stage techniques using oral mucosal grafts, penile fasciocutaneous flaps or a combination of these techniques. (Moderate Recommendation; Evidence Strength Grade C)

Multi-segment strictures (frequently referred to as panurethral strictures) are most commonly defined as strictures over 10 cm in length spanning long segments of both the penile and bulbar urethra. These strictures are particularly complex to treat surgically.[35] Several treatment options exist including long-term endoscopic management, urethroplasty, or perineal urethrostomy. Clinicians should be aware that panurethral strictures are very unlikely to be treated successfully with endoscopic means, which offer only temporary relief of obstruction.[77,78,81,90,91,105,106] However, urethroplasty in these instances is also more complicated, time-consuming, and have a higher failure rate as compared to urethroplasty for less complicated strictures.[35,129,130] Thus, some patients may choose repeat endoscopic treatments, with or without a self-dilation protocol, or a perineal urethrostomy, in order to avoid complex urethral reconstructive surgery.

Reconstruction of panurethral strictures should be addressed with all of the tools in the reconstructive armamentarium including fasciocutaneous flaps, oral mucosal grafts, or other ancillary tissue sources, and may require a combination of these techniques.[35,121,131] These labor intensive and technically challenging surgeries are best performed at established high volume reconstructive centers. Several tissue sources have been reported including oral mucosal grafts, various skin grafts, and genital fasciocutaneous flaps.[35,121,131] Regardless of technique and combinations, success rates appear similar in all of these small series. Superior efficacy of "double graft" procedures has not yet been demonstrated and these techniques are

typically applied to select instances of urethral obliteration.[19,44,47,52,113,132,133] Staged procedures may offer a conservative approach suited to the most complex strictures such as those related to failed hypospadias surgery.[114-118]

18. Surgeons may offer perineal urethrostomy as a long term treatment option to patients as an alternative to urethroplasty. (Conditional Recommendation; Evidence Strength Grade C)

Perineal urethrostomy can be used as a staged or permanent option for patients with anterior urethral strictures in order to establish unobstructed voiding and improve quality of life. Reasons to perform perineal urethrostomy include recurrent or primary complex anterior stricture, advanced age, medical co-morbidities precluding extended operative time, extensive LS, numerous failed attempts at urethroplasty, and patient choice.[39,134,135] Patients undergoing perineal urethrostomy have reported high quality of life, although surgical revision may be necessary to maintain patency over long term follow up.[134,135] Successful treatment with perineal urethrostomy has been reported in both traumatic and LS strictures.[134,135] There are no data demonstrating that a specific surgical technique is associated with a higher patient quality of life or long term patency rate.

19. Surgeons should use oral mucosa as the first choice when using grafts for urethroplasty. (Expert Opinion)

Oral mucosa is the preferred graft for substitution urethroplasty. Patient satisfaction is higher for oral mucosa due to less post-void dribbling and penile skin problems.[45,136]

Oral mucosa may be harvested from the inner cheeks, which provide the largest graft area, the undersurface of the tongue, or the inner lower lip. Harvest of buccal mucosa from the inner cheek results in fewer complications and better outcomes as compared to a lower lip donor site.[137] A randomized controlled trial comparing buccal and lingual donor sites demonstrated that minor morbidity lasted longer following lingual graft harvest,[46] while other cohort studies have exhibited inconsistent findings.[51,138] None reported any major complications.

When harvesting buccal mucosa from the inner cheek, the donor site may safely be left open to heal by secondary intention or closed primarily.[139] Ultimately the decision to close the donor site primarily or leave it open is at the discretion of the surgeon.

20. Surgeons should not perform substitution urethroplasty with allograft, xenograft, or synthetic materials except under experimental protocols. (Expert Opinion)

Use of non-autologous grafts may be indicated in the patient who has failed a prior urethroplasty and has no tissue available for reoperative substitution urethroplasty. However, experience to date is limited and the long term success rates are unknown.[37,140-143] Such patients should be considered for referral to a center involved in clinical trials using allograft, xenograft, engineered or synthetic materials.

21. Surgeons should not perform a single-stage tubularized graft urethroplasty. (Expert Opinion)

Tubularized urethroplasty consists of a technique in which a graft or flap is rolled into a tube over a catheter to completely replace a segment of urethra. This approach, when attempted in a single stage, has a high risk of restenosis and should be avoided. When no alternative exists, a tubularized flap can be performed with results that are inferior to onlay flaps.[144,145] Currently, available alternatives include combined tissue transfer (e.g. a dorsal buccal graft combined with a ventral skin flap in a single stage), combined dorsal and ventral grafts (e.g. a dorsal graft in the technique of Asopa and a ventral onlay graft), or staged urethroplasty with local skin flaps or oral mucosa grafts.

22. Surgeons should not use hair-bearing skin for substitution urethroplasty. (Clinical Principle)

The use of hair-bearing skin for substitution urethroplasty may result in urethral calculi, recurrent urinary tract infection and a restricted urinary stream due to hair obstructing the lumen, and therefore should be avoided except in rare cases where no alternative exists.[146] Intraurethral hair should be suspected in

patients who report these symptoms and have a history of prior tubularized urethroplasty or surgery for proximal hypospadias, in which scrotal skin may have been incorporated into the repair and demonstrate later hair growth.

Pelvic Fracture Urethral Injury

23. Clinicians should use retrograde urethrography with voiding cystourethrogram and/or retrograde + antegrade cystoscopy for preoperative planning of delayed urethroplasty after pelvic fracture urethral injury (PFUI). (Moderate Recommendation; Evidence Strength Grade C)

Pre-operative evaluation of the distraction defect after PFUI should include retrograde urethrography, voiding cystourethrography (VCUG) and/or retrograde urethroscopy. The VCUG may include a static cystogram to determine the competency of the bladder neck mechanism and the level of the bladder neck in relation to the symphysis pubis. Other adjunctive studies may include antegrade cystoscopy (with or without fluoroscopy) and pelvic CT or MRI to assess the proximal extent of the injury, degree of malalignment of the urethra, and length of the defect.

24. Surgeons should perform delayed urethroplasty instead of delayed endoscopic procedures after urethral obstruction/ obliteration due to pelvic fracture urethral injury (PFUI). (Expert Opinion)

The acute treatment of PFUI includes endoscopic primary catheter realignment or insertion of a SP tube. The resulting distraction defect, stenosis or obliteration should be managed with delayed perineal anastomotic urethroplasty. Repeated endoscopic maneuvers including intermittent catheterization should be avoided because they are not successful in the majority of PFUI, increase patient morbidity, and may delay the time to anastomotic reconstruction. Clinicians should avoid blind "cut to the light" procedures in the obliterated PFUI since they are rarely successful in long term follow up.

Anastomotic reconstruction is performed through a perineal approach. Excision of the scar tissue and wide spatulation of the anastomosis is required. Several methods to gain urethral length and reduce tension can be employed when necessary including mobilization of the bulbar urethra, crural separation, inferior pubectomy and supracrural rerouting, but in most cases the latter two maneuvers are not required. In rare cases, trans abdominal or transpubic techniques may be required. In order to potentially decrease the potential for vascular compromise to the urethra, a bulbar artery sparing approach has been described. No comparative study has yet shown any definitive benefit. Clinicians should refer patients to appropriate tertiary care centers for reconstruction when necessary.

25. Definitive urethral reconstruction for pelvic fracture urethral injury (PFUI) should be planned only after major injuries stabilize and patients can be safely positioned for urethroplasty. (Expert Opinion)

The timing of urethral reconstruction in PFUI is highly dependent on patient factors. No optimal time to perform urethral reconstruction has been established, with studies reporting a wide range of times from six weeks to four years. Reconstruction should occur when patient factors allow the surgery to be performed (usually within three to six months after the trauma). Patient positioning in the lithotomy (standard, high, or exaggerated) may be limited until orthopedic and lower extremity soft tissues injuries have resolved.

Bladder Neck Contracture/Vesicourethral Stenosis

26. Surgeons may perform a dilation, bladder neck incision or transurethral resection for bladder neck contracture after endoscopic prostate procedure. (Expert Opinion)

Treatment of bladder neck contractures following endoscopic prostate procedures can be performed with either a bladder neck incision or bladder neck resection depending on surgeon preference, with comparable outcomes expected. Repeat endoscopic treatment may be necessary for successful outcomes. No studies exist that compare the different treatment strategies for bladder neck contractures after endoscopic prostate procedures.

27. Surgeons may perform a dilation,

vesicourethral incision, or transurethral resection for post-prostatectomy vesicourethral anastomotic stenosis. (Conditional Recommendation; Evidence Strength Grade C)

Treatment of first time vesicourethral anastomotic stenosis is successful in about 50-80% of cases, with all techniques having similar success rates.[147-151] Success appears to be lower in cases with prior pelvic radiation; however, prospective cohort studies including radiated and nonradiated patients are lacking. Repeat endoscopic treatment may be necessary for successful treatment. There is conflicting data about the utility of Mitomycin-C for the treatment of recurrent vesicourethral stenosis, with further study necessary to validate its use.[152,153] Patients should be made aware of the risk of incontinence after any of these procedures.

28. **Surgeons may perform open reconstruction for recalcitrant stenosis of the bladder neck or post-prostatectomy vesicourethral anastomotic stenosis. (Conditional Recommendation; Evidence Strength Grade C)**

The treatment of recalcitrant vesicourethral anastomotic stenosis must be tailored to the preferences of the patient, taking into consideration prior radiotherapy and the degree of urinary incontinence. Urethral reconstruction is challenging and may cause significant urinary incontinence requiring subsequent artificial urinary sphincter implantation, but offers success rates of approximately 66-80%.[154,155] Success rates are lower after radiation. For the patient who does not desire urethroplasty, repeat urethral dilation, incision or resection of the stenosis is appropriate. Intermittent self-dilation with a catheter may be used to prolong the time between operative interventions. Suprapubic diversion is an alternative.

Special Circumstances

29. **In men who require chronic self-catheterization (e.g. neurogenic bladder), surgeons may offer urethroplasty as a treatment option for urethral stricture causing difficulty with intermittent self-catheterization. (Expert Opinion)**

In men with neurogenic bladder urethral pathology may include stricture, diverticulum, fistula, and erosion. Bladder function must be considered prior to urethroplasty as significant underlying detrusor dysfunction it may alter the course of treatment. It is unclear if anterior urethroplasty in this setting has higher rates of complications, stricture recurrence or reoperation when compared to men with anterior urethral stricture and intact bladder function.[156,157] There is some evidence to suggest that urethral reconstruction, if offered at an early stage in men with stricture and neurogenic bladder, can achieve outcomes comparable to men without neurogenic bladder.[157] It is not definitively known if resumption of intermittent catheterization following anterior urethroplasty impacts the risk of stricture recurrence.

30. **Clinicians may perform biopsy for suspected lichen sclerosus (LS), and must perform biopsy if urethral cancer is suspected. (Clinical Principle)**

The external manifestations of LS in males can range in severity from mild to aggressive. It is most commonly found in the genital region and may be associated with urethral strictures.[158-160] LS may mimic many other skin diseases: therefore, biopsy is the best method for definitive diagnosis. The rate of squamous cell carcinoma in male patients with LS has been reported to be 2-8.6% thus further indicating the need for biopsy in selected cases both to confirm the diagnosis as well as to exclude malignant or premalignant changes.[160-163]

31. **In lichen sclerosus (LS) proven urethral stricture, surgeons should not use genital skin for reconstruction. (Strong Recommendation; Evidence Strength Grade B)**

Goals of management of LS should be to alleviate symptoms, prevent and treat urethral stricture disease and prevent and detect malignant transformation.[159]

Treatment of genital skin LS reduces symptoms, such as skin itching and bleeding, and may serve to prevent meatus stenosis and progression to extensive stricture of the penile urethra. Current therapies rely heavily on topical moderate- to high-potency steroid creams, such

as clobetasol or mometasone creams. Calcineurin inhibitors such as tacrolimus have been shown to cause regression in external skin manifestations.[159]

Reconstruction of anterior urethral strictures associated with LS should proceed according to principles outlined previously, with the caveat that the use of genital skin flaps and grafts should be avoided due to very high long-term failure rates.[112,138,164,165]

Post-operative Follow-up

32. Clinicians should monitor urethral stricture patients to identify symptomatic recurrence following dilation, direct visual internal urethrotomy (DVIU) or urethroplasty. (Expert Opinion)

Urethral stricture recurrence following endoscopic treatment or urethroplasty can occur at any time in the postoperative period, and, because of this, a specific regimen for postoperative follow-up cannot be reliably determined. The surgeon may consider more frequent follow-up intervals in men at an increased risk for stricture recurrence including those with prior failed treatment (multiple endoscopic procedures or previous urethroplasty), tobacco use, diabetes, increasing stricture length, strictures related to LS, hypospadias, or a repair involving a flap or graft. [101,102,122,129,130, 165-173]

Surgeons can use a number of diagnostic tests to detect or screen for stricture recurrence following open or endoscopic treatment (see guideline statements 1 and 2); however the use of, or combination of, urethrocystoscopy, urethral ultrasound, or RUG appears to provide the most definitive confirmation of stricture recurrence.[60-67,174,175] No specific urethral lumen diameter, determined endoscopically or radiographically, has been shown to be diagnostic of a stricture recurrence.

Although stents are not currently recommended for the treatment of urethral stricture. Patients treated with a urethral stent after dilation or internal urethrotomy should be monitored for recurrent stricture and complications. Recurrent strictures have been reported in new urethral regions outside of the stent placement in addition to within the stent treated region.[176-178] Patients with completely obstructed stents may require open urethroplasty and removal of the stent.[178] Other stent complications include stent-induced hematuria, urethral pain, urinary incontinence, and chronic urinary tract infection.[99,176-180] Complications can occur at any time point after stent placement, so long term monitoring with cystoscopy or urethral imaging, is advised. Stents do not need to be prophylactically removed and should be followed conservatively unless associated with significant urethral or voiding symptoms.

RESEARCH NEEDS AND FUTURE DIRECTIONS

Much of the literature on the topic urethral strictures consists of single surgeon or single institution case series with inconsistent definitions of disease process, success of treatment, and follow up. These inconsistencies resulted in difficulty in comparison between studies. These inadequacies in the literature means there is ample opportunities for future research. To improve the quality of research, the Panel recommends the following:

- Research terms should be standardized to allow comparison between centers—the International Consultation on Urological Diseases[6] nomenclature should be used. For example, the term "urethral stricture" should be applied to a narrowing of the anterior urethra that restrict the flow of urine.

- In studies of the treatment of urethral strictures, multiple criteria for success should be reported. When data is available, studies should report success based several criteria: patient reported outcome measures, symptoms, uroflowmetry, radiography, cystoscopy, and need for subsequent procedures. Reporting success based on multiple criteria would facilitate comparison between multiple studies.

- The duration and type of follow up should be reported in all studies of urethral stricture treatment, follow up based on time of last clinic visit, telephone contact, or absence of known treatment for recurrence. Time-to-event analysis (Kaplan-Meier) should be reported.

- Multi-institutional collaboration should be formed to evaluate management of uncommon diagnoses

such as pelvic fracture urethral injury, hypospadias, panurethral strictures, and LS.

- Multi-centered randomized clinical trials, pragmatic trials, or registries should be created for evaluation of techniques, such as injection of antiproliferative agents during DVIU, dorsal versus ventral onlay buccal mucosa graft urethroplasty, and skin flap versus oral mucosa graft urethroplasty.
- Multiple measures have been used to determine and report success after treatment for urethral stricture. Currently there is no universally accepted definition of success following treatment for urethral stricture. Multi-center randomized trials are necessary to standardize follow-up protocols to accurately and efficiently define successful treatment, and enable comparative effectiveness research across centers.

Urethral stricture remains a subject of active investigation. The Panel suggests the following issues in future investigations:

- Both basic science and epidemiological research into the etiology of urethral strictures.
- Prevention of traumatic strictures through educational efforts on proper technique of catheter insertion.
- Studies on the effectiveness of early diagnosis and treatment of LS toward prevention of disease progression and urethral stricture formation.
- Basic science and animal studies using novel graft materials for urethral reconstruction—stem cells, tissue-engineered scaffolds, etc.
- Long term follow up for adults in patients who have been treated as children, such as urethral stricture in adults after hypospadias repair.
- Further evaluation of alternative sources of autologous graft material.
- The efficacy of injection of anti-proliferative or other pharmacological agents at time of endoscopic incision for urethral stricture and bladder neck contracture.
- The relationship between of urethroplasty and erectile dysfunction.
- Role of urethral transection in urethroplasty regarding morbidity and outcomes.
- The optimal timing and duration of perioperative antibiotics given at the time of urethrotomy and urethroplasty.
- Determination of the ideal tissue for substitution urethroplasty.

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LIST OF ABBREVIATIONS

AUSAI	**American Urological Association Symptom Index**
CCT	**Controlled clinical trials**
DVIU	**Direct visual internal urethrotomy**
EPA	**Excision and primary anastomosis**
IIEF	**International Index of Erectile Function**
LS	**Lichen Sclerosis**
LUTS	**Lower urinary tract symptoms**
MSHQ	**Men's Sexual Health Questionnaire**
PFUD	**Pelvic fracture urethral disruption**
PFUI	**Pelvic fracture urethral injury**
PRM	**Patient reported measures**
RCT	**Randomized controlled trial**
RUG	**Retrograde urethrography**
SP	**Suprapubic**
UTI	**Urinary tract infection**
VCUG	**Voiding cystourethrography**
VTE	**Deep venous thromboembolism**

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DISCLAIMER

This document was written by the Male Urethral Stricture Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2015. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the panel included specialists in urology with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of male urethral strictures.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (‘off label‘) that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

Richtlinie zur Erprobung gemäß § 137e Absatz 1 SGB V:
Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Organisationen, die eine erste Einschätzung abgegeben haben [Langfassung (Abkürzung)]	**Literatur beigefügt [ja/nein]**
Langfassung (Abkürzung)	
Deutschen Gesellschaft für Urologie e.V. (**DGU**)	nein
Urotronic Inc.	ja

Population	
In die Erprobungsstudie einzuschließen sind erwachsene Männer mit symptomatischer kurzstreckiger (≤ 2 cm) Rezidivstriktur der anterioren Harnröhre. Frage des G-BA: Ist dies die aus Ihrer Sicht treffende Beschreibung der Studienpopulation? Wenn nicht, wie sollte die Studienpopulation definiert werden? Sollten Subpopulationen gebildet werden? (z.B. entsprechend der Genese der Harnröhrenstrikturen?	
Überlegungen der Geschäftsstelle aufgrund eingegangener Einschätzungen	
Aktuelle Gebrauchsanweisung erweiterte Anwendung auf <3cm Strikturlänge Erste Daten zur ROBUST III Studie zeigen keine Unterschiede in Ergebnissen bei unter oder über 2 cm Strikturlänge	
§ 3 Population (BE)	**(TrGr)**
[1]In die Erprobungsstudie einzuschließen sind Patientinnen und Patienten - mit …, - die …, - die …. [2]<ggf. Vorgabe, was ansonsten von der UWI festgelegt werden soll>. [3]Die weiteren Ein- und Ausschlusskriterien <(z. B. Alter, Komorbiditäten)> sind so festzulegen, dass eine Übertragbarkeit der Ergebnisse auf die Zielpopulation gemäß Satz 1 ermöglicht wird.	Die Studienpopulation baut auf der in der Informationsübermittlung nach § 137h Absatz 1 SGB V durch das Krankenhaus definierten Patientenpopulation auf. In die Erprobungsstudie einzuschließen sind demnach Patientinnen und Patienten mit …. <Konkretisierung/Begründung für Ein- bzw. Ausschlusskriterien>. Bei der Studienplanung sollten weitere Ein- oder Ausschlusskriterien, <ggf. Beispielnennungen> festgelegt werden. Dabei ist darauf zu achten, dass die Übertragbarkeit der Ergebnisse auf die Zielpopulation (gemäß § 3 Satz 1) nicht gefährdet wird.
Eingegangene Einschätzungen	
Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen	
DGU	Max. 2cm lange Rezidivstrikturen der anterioren Harnröhre sind die korrekte Studienpopulation. Bezüglich Subpopulationen sollte die Ätiologie „traumatisch vs. iatrogen“ (z. B. Katheterisierung, endoskopischer Eingriff) ebenso erfasst werden wie „Striktur geht nahtlos in den Sphinkter über“ oder „ist vom Sphinkter externus entfernt“. Die Subpopulationen müssen jedoch bei der Randomisierung keine Berücksichtigung finden.

Population	
Urotronic Inc.	Gemäß aktueller Gebrauchsanweisung vom Februar 2021 wird der Optilume medikamentenbeschichtete Ballonkatheter (DCB) für die Behandlung von Männern ≥ 18 Jahren mit störenden Harnwegssymptomen bei Rezidivstrikturen der anterioren Harnröhre verwendet. Er dient zur Verwendung als Dilatationsballon für Einzel-, Tandem- oder diffuse Harnröhrenstrikturen mit einer Länge von **≤3 cm** oder als Ergänzungstherapie mit anderen Dilatationsprodukten und/oder -verfahren.[1] Die Studienpopulation sollte diesen Kriterien, also der aktuellen Zweckbestimmung, folgen und wäre somit im Einklang mit den vorliegenden Studienprotokollen der ROBUST-Studienserien, insbesondere der Studien I, II und III[2]. Urotronic möchte an dieser Stelle auf die neue, im April 2021 veröffentlichte Leitlinie der European Association of Urology hinweisen. Unter 6.2.1.3.5 auf Seite 28 findet sich die „strong recommendation", penile Harnröhrenstrikturen nicht mittels Urethrotomia interna zu behandeln.[3] Urotronic schlägt vor, dieser Empfehlung zu folgen und eine penile Lokalisierung der Striktur als Ausschlusskriterium aufzunehmen. Diese Einschränkung spiegelt weitestgehend die diesbezüglichen Patientencharakteristika in der ROBUST-Studienserie wider, die zu 100% bulbäre Strikturen in ROBUST I und II und zu lediglich 10,1% penile Strikturen in ROBUST III umfasste.[4]

Intervention
Im Rahmen der Studienplanung durch eine UWI soll unter Einbezug klinischer Expertise konkretisiert werden, ob und ggf. mit welchem Verfahren bei stark stenotischen Strikturen unmittelbar vor der Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter eine Prädilatation der Striktur erfolgen soll. Frage des G-BA:

[1] Siehe Gebrauchsanweisung

[2] Informationen zu den Studien ROBUST I und II sind der übermittelten Information im Rahmen des §137h-Verfahrens zu entnehmen. Das Protokoll der ROBUST III Studie ist dem Fragebogen beigefügt.

[3] Lumen, N., Campos-Juanatey, F., Dimitropoulos, K., Greenwell, T., Martins, F. E., Osman, N., . . . Verla, W. (2021). EAU Guidelines on Urethral Stricture. Retrieved from https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urethral-Strictures1-2021.pdf

[4] Übersicht ROBUST-Studien: LA1093rA Optilume® DCB Clinical Program summary - Siehe Übersicht auf Seite 4.

Intervention	
1. Verfahren zur Prädilatation stellen die Urethrotomia interna, die Dilatation mit unbeschichteten Ballonkathetern und die Aufbougierung mit Kathetern zunehmender Größe dar. Im deutschen Versorgungskontext kommt in erster Linie die Urethrotomia interna für die Prädilatation zum Einsatz. Stimmen Sie mit der Überlegung des G-BA überein, dass im Rahmen der Studienplanung durch eine UWI festgelegt werden sollte, ob und ggf. mit welchem Verfahren eine Prädilatation von stark stenotischen Strikturen erfolgen soll? Falls nein, welche Vorgaben zur Prädilatation sollten Ihrer Meinung nach definiert werden? Die Prüfintervention ist die Behandlung mit einem medikamentenbeschichteten Ballondilatationskatheter. Frage des G-BA: 2. Stimmen Sie mit der Überlegung des G-BA zur Intervention überein? Falls nein, wie würden Sie die Intervention definieren?	
Überlegungen der Geschäftsstelle	
ROBUST-III: Urethrotomia intern unter Sicht (4%) oder Ballonkatheter (91%) oder beides (5%) als Verfahren zur Prädilatation	
§ 4 Intervention und Vergleichsintervention (BE)	**(TrGr)**
(1) [1]Die Prüfintervention besteht in Beschreibung Intervention.	Für das für die Prüfintervention eingesetzte Medizinprodukt muss Verkehrsfähigkeit vorliegen und die Studienpopulation von der Zweckbestimmung umfasst sein. <Ggf. weitere Ausführungen zur Intervention>
Eingegangene Einschätzungen	
Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen	
DGU	Zu 1.: Als Verfahren zur Prädilatation sollte standardisiert die Urethrotomia interna bis in das Schleimhautniveau angegeben werden, um eine einheitliche „Prädilatation“ zu erreichen und gleichzeitig die genaue Länge der Enge noch einmal endoskopisch ermitteln zu können. Zu 2.: ja
Urotronic Inc.	Zu 1.: Das Produkt hat erst im September 2020 die CE-Zertifizierung erhalten. Anschließend stand die Covid-19 Situation einer schnellen Einführung in Markt entgegen. Daher ist es zu früh, von einem Standardvorgehen zur Prädilatation im Kontext der gegenständlichen Methode im deutschen Versorgungskontext zu sprechen.

Intervention	
	Im Gegensatz zu dem Vorgehen in den USA, ist die Verwendung unbeschichteter Ballons zur Dilatation von Harnröhrenstrikturen in Deutschland nicht als Standard etabliert. Daher ist zu erwarten, dass die Prädilatation, falls notwendig, überwiegend durch eine Urethrotomia interna, bei Nähe zum Harnröhrensphinkter als Aufbougierung durchgeführt werden wird. Aus diesem Grund schlagen wir vor, die Wahl des Verfahrens zur Prädilatation dem Ermessen der behandelnden Urologen zu überlassen. Eine Subgruppenanalyse des Interventionsarms der ROBUST-III-RCT[5] auf Basis der Resultate nach 6 Monaten ergab, dass das gewählte Prädilationsverfahren keinen Einfluss auf die Rate an Patienten, die frei von Strikturen waren, hatte. Auch diese Beobachtung spricht dafür, den behandelnden Studienzentren keine Vorgaben zu machen und die Wahl des Vorgehens dem Ermessen der Studienärzte zu überlassen. Zu 2.: Wir stimmen der Überlegung des G-BA zur Intervention uneingeschränkt zu.

Vergleichsintervention (Kontrolle)
Die Vergleichsintervention ist die Urethrotomia interna. Frage des G-BA: Stimmen Sie mit der Überlegung des G-BA zur Vergleichsintervention überein? Falls nein, wie würden Sie die Vergleichsintervention definieren? 1. Sollten andere/weitere Vergleichsinterventionen berücksichtigt werden? 2. Inwieweit sollten Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichstherapie als möglicherweise hierfür relevante Faktoren berücksichtigt werden?
Überlegungen der Geschäftsstelle
ROBUST-III: Urethrotomia interna (25%), unbeschichtete Ballon (56%), starrer Stab (16%), Stab + unbeschichteter Ballon (2%) Hinweis auf ein RCT im Informationsübermittlungsformular, dass Vergleichsinterventionen zu gleichen Ergebnissen führen

[5] Siehe Dokument: Subgruppenanalyse Prädilatationsverfahren: t11-2_primary_subgroup_dilation_pool_ITT.pdf

Vergleichsintervention (Kontrolle)	
§ 4 Intervention und Vergleichsintervention (BE)	**(TrGr)**
(2)[1]<Die Vergleichsintervention ist Beschreibung Vergleichsintervention.	Die Vergleichsintervention ist die <Vergleichsintervention>. <Ausführungen zur Vergleichsintervention, z.B. Bezugnahme auf Leitlinienempfehlungen>
Eingegangene Einschätzungen	
Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen	
DGU	Zu 1.: s. oben, d.h. die Urethrotomia interna ist die sinnvollste Vergleichsintervention. Zu 2.: s. oben, d.h. die Genese traumatisch vs. instrumentell (DK, Katheterisierung, endoskopischer Eingriff) sollte ebenso dokumentiert werden wie die Lage der Striktur zum Sphinkter. Darüber hinaus sollte die Anzahl der Rezidive sowie die Strikturlänge dokumentiert werden, ohne dass dies bei der Randomisierung berücksichtigt werden muss.
Urotronic Inc.	Wir stimmen mit der Überlegung der G-BA zur Vergleichstherapie überein. Aus der Sicht von Urotronic ist es nicht notwendig, dass Genese, Rezidivsituation und Strikturlänge der Harnröhrenstriktur bei der Wahl der Vergleichsintervention eine Rolle spielen. So zeigt beispielsweise die aktuelle Auswertung der ROBUST III-Studie konsistente Resultate bzgl. der Outcomes unabhängig davon, ob die Strikturen < 2 cm oder $\geq$ 2 cm (Einschlusskriterium war eine Länge von $\leq$ 3m) waren, bzw. ob < oder $\geq$ 5 vorherige Dilatationsverfahren durchgeführt worden waren[6].

[6] ROBUST III 3 Abstract_ICS 2021, eingereicht.

Primärer Endpunkt

Der primäre Endpunkt ist der Anteil an Patienten, die

- nach 12 Monaten eine Verbesserung im IPSS-Score im Vergleich zum Ausgangswert aufweisen (Verbesserung um mindestens sechs Punkte [>15%der Skalenspannweite])

und

- sich innerhalb dieses Zeitraums keiner klinisch-indizierten Reintervention aufgrund des Wiederauftretens der Striktur einschließlich entsprechender Symptomatik unterziehen müssen (Strikturfreiheit).

Frage des G-BA:

Stimmen Sie mit der Überlegung des G-BA zum primären Endpunkt und der vorgeschlagenen Responseschwelle überein? Falls nein, was ist aus Ihrer Sicht ein angemessener primärer Endpunkt für die Erprobungsstudie und welche validierten Erhebungsinstrumente gibt es nach Ihrer Kenntnis für diesen von Ihnen vorgeschlagenen Endpunkt?

Bitte beschreiben Sie bezüglich der von Ihnen vorgeschlagenen Erhebungsinstrumente die minimale klinische Differenz zur Beurteilung des Behandlungsergebnisses und belegen Sie Ihre Aussagen nach Möglichkeit mit geeigneten Studien.

Überlegungen der Geschäftsstelle

ROBUST-III Studie: Strikturfreiheit (primärer Endpunkt) nach 6 Monaten, IPSS (sekundärer Endpunkt) nach 12 Monaten, 5 Jahre Follow Up; Responder definiert als >50 % Verbesserung ggü. Baseline

§ 5	**Endpunkte (BE)**	**(TrGr)**
1)	[1]Der primäre Endpunkt ist ….	<Begründung der Wahl des primären Endpunkts> Zur Erfassung des primären Endpunkts ist nach Kenntnisstand des G-BA insbesondere <Benennung eines validierten Erhebungsinstruments und ggf. der MID> geeignet.

Eingegangene Einschätzungen

Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen

DGU	12 Monate sind ein guter Endpunkt, unbedingt sollte dieser jedoch nach 24 Monaten noch einmal wiederholt werden.

Primärer Endpunkt	
	Die IPSS-Score-Verbesserung um mindestens 6 Punkte ist ein sinnvolles Maß, sollte jedoch nicht das alleinige Maß sein, da der IPSS-Score rein subjektive Verbesserungen misst und die Angaben somit zwangsläufig intra- und interindividuelle Schwankungen aufweisen. Unbedingt sollte die Uroflowmetrie präoperativ sowie nach 12 und 24 Monaten herangezogen werden zusammen mit der sonographischen Restharnbestimmung. Für die Beurteilung relevante Messergebnisse bei diesen beiden Erhebungs-instrumenten leiten sich aus deren Definition ab: Klinisch relevanter Restharn liegt dann vor, wenn mehr als 10% des Miktionsvolumens im Anschluss an die Miktion in der Blase verbleiben oder einfacher, wenn der Restharn höher als 100ml beträgt. Insofern sollte der Restharn nach der Intervention < als 10% des Miktionsvolumens oder <100ml absolut betragen. Bezüglich der Uroflowmetrie würde ich die Parameter „max. Flussgeschwindigkeit in ml/s“ sowie „Flusszeit“ prä- und postoperativ messen und die Differenzen dann als Studienergebnis ausweisen. Im Vorhinein anzugeben, welche Verbesserung beispielsweise der max. Flussgeschwindigkeit signifikant ist oder nicht, ist schwierig bis unmöglich, da unter anderem von der präoperativen Situation und auch von psychovegetativen Einflüssen abhängig. So wäre beispielsweise der Anstieg der max. Flussgeschwindigkeit von 3 auf 8ml/s eine Verbesserung um über 100%, wäre klinisch jedoch immer noch als hoch obstruktiv zu werten, wohingegen eine Verbesserung von 10 auf 15ml/s klinisch eine deutliche Verbesserung darstellt, obwohl die Verbesserung nur 50% beträgt.
Urotronic Inc.	Urotronic stimmt dem Endpunkt, der eine Kombination von Symptomverbesserung und Freiheit von klinisch indizierten Reinterventionen vorsieht, zu. Urotronic möchte darauf hinweisen, dass bei dem IPSS-Score die minimale klinisch relevante Differenz vom Ausgangswert abhängen kann (Barry et al J Urol 1995)[7], ist sich allerdings der Tatsache bewusst, dass sich diese Publikation auf die gutartige Vergrößerung der Prostata und deren Symptomatik bezieht. Ein klinisch bedeutsamer Schwellenwert hängt also vom Ausgangswert des IPSS ab. Urotronic schlägt deshalb vor, einen Schwellenwert von ≥30% Verbesserung im Vergleich zum Ausgangswert zu wählen, der auch von der United States Food and Drug Administration für Studien mit Produkten zur Behandlung der BPH

[7] Barry, M. J., Williford, W. O., Chang, Y., Machi, M., Jones, K. M., Walker-Corkery, E., & Lepor, H. (1995). Benign Prostatic Hyperplasia Specific Health Status Measures in Clinical Research: How Much Change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is Perceptible to Patients? The Journal of Urology, 154(5), 1770-1774. doi:10.1016/s0022-5347(01)66780-6

Primärer Endpunkt	
	empfohlen wird[8]. Dieser Schwellenwert basiert auf der Arbeit von Roehrborn und Kollegen aus dem Jahr 2012, die die Beziehung von Symptomverbesserung gemäß IPSS und Patientenzufriedenheit ermittelt haben.[9]

Sekundäre Endpunkte
Als sekundäre Endpunkte sind (unter anderem) zu erheben: • Morbidität (z. B. klinisch-indizierte Reinterventionen, Wiederauftreten der Striktursymptomatik, wiederkehrende Harnwegsinfekte), • gesundheitsbezogene Lebensqualität, • unerwünschte Ereignisse. Frage des G-BA: Stimmen Sie mit der Überlegung des G-BA zu den sekundären Endpunkten überein? Welche validierten Erhebungsinstrumente zu diesen Endpunkten halten Sie für geeignet? Sollten Ihrer Meinung nach weitere bzw. andere sekundäre Endpunkte ergänzend in der Erprobungsstudie untersucht werden? In diesem Fall benennen Sie bitte die entsprechenden validierten Erhebungsinstrumente.
Überlegungen der Geschäftsstelle
ROBUST-III: IPSS-Score, Zeit bis zum Therapieversagen (Re-Interventionen?), UE

§ 5	**Endpunkte (BE)**	**(TrGr)**
(2)	[1]Als sekundäre Endpunkte sind insbesondere zu erfassen:	…

[8] FDA-Dokument *Select Updates for Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/select-updates-guidance-non-clinical-and-clinical-investigation-devices-used-treatment-benign

[9] Roehrborn CG, Wilson TH, Black LK. Quantifying the contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia: 4-year data from the CombAT trial. J Urol. 2012 May;187(5):1732-8. doi: 10.1016/j.juro.2011.12.083. Epub 2012 Mar 15. PMID: 22425127.

Sekundäre Endpunkte	
- …, - …, - … . [2]Die Operationalisierung der Endpunkte sowie die Erhebung und die Operationalisierung weiterer Endpunkte sind jeweils zu begründen. (3) Sofern vorhanden, sind für alle Endpunkte validierte Erhebungsinstrumente zu verwenden.	Die gewählten sekundären Endpunkte ergänzen den primären Endpunkt durch international übliche Parameter und dienen zur weiteren Beurteilung möglicher Effekte. Die Operationalisierung der einzelnen Endpunkte obliegt der unabhängigen wissenschaftlichen Institution, die diese jeweils zu begründen hat. Grundsätzlich sind, wo immer möglich, validierte Instrumente zur Erhebung der Endpunkte einzusetzen. Von besonderer Bedeutung ist dies bei subjektiven Endpunkten, d. h. solchen, die auf Befragung von Studienteilnehmenden, an der Behandlung beteiligten Personen oder Dritten beruhen. Für die Erhebung des [Endpunkt X] sind, sofern möglich, krankheitsspezifische validierte Instrumente einzusetzen. [ggf. beispielhafte Benennung validierter Erhebungsinstrumente für sekundäre Endpunkte, die in Betracht kommen können.]
Eingegangene Einschätzungen	
Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen	
DGU	Ein sekundärer Endpunkt, wie schon angegeben, wäre nach 24 Monaten, dann gleiche Messinstrumente wie nach 12 Monaten. Zu registrieren sind unerwünschte Ereignisse wie Harnverhalt, Harnwegsinfekte, Reinterventionen, wobei bezüglich letzteren die Latenzzeiten zwischen einer konventionellen Sachse-Urethrotomie und einer Sachse-Urethrotomie mit Ballondilatation bis zu einer Reintervention verglichen werden können.
Urotronic Inc.	Urotronic hält die Erhebung mehrerer sekundärer Endpunkte für geeignet: Sicherheit: • Häufigkeit der berichteten Arten von unerwünschten Ereignissen (z. B. Harnwegsinfektion, Hämaturie, Harnsymptome, akuter Harnverhalt)

Sekundäre Endpunkte	
	• Häufigkeit von Wiederholungseingriffen, einschließlich intermittierendem Katheterismus und Wiederholung der Dilatation/Urethrotomie oder Durchführung einer Urethroplastik. Wirksamheit • Verwendung eines Patient Reported Outcome Measure, der speziell für Harnröhrenstrikturen entwickelt wurde.[10] Dieser Fragebogen ist auch in deutscher Sprache validiert.[11] • Berichterstattung über Symptom-Scores (IPSS, PROM) im Zeitverlauf, mit der Maßgabe, dass bei Patienten mit einer Reintervention der studierten Striktur keine weitere Symptombeurteilung erfolgt oder der schlechteste vorherige Wert zugewiesen wird, um das klinische Versagen der ersten Intervention zu reflektieren.

Studientyp und Beobachtungszeitraum
Die Erprobungsstudie ist als randomisierte, kontrollierte Studie (RCT) multizentrisch durchzuführen. Frage des G-BA: 1. Stimmen Sie mit der Überlegung des G-BA zum Studientyp überein? Falls nein, welche Vorgaben zum Studientyp sollten definiert werden? Die Randomisierung sollte im Verhältnis 1:1 erfolgen. 2. Stimmen Sie mit der Überlegung des G-BA zur Randomisierung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. Dieser Vorgabe? Die Studienteilnehmer und die weiterbehandelnden Personen sowie die Endpunkterheber sollen verblindet sein.

[10] Jackson, M. J., Sciberras, J., Mangera, A., Brett, A., Watkin, N., N'Dow J, M., . . . Mundy, A. R. (2011). Defining a patient-reported outcome measure for urethral

[11] Kluth, L. A., Dahlem, R., Becker, A., Schmid, M., Soave, A., Rosenbaum, C., . . . Ahyai, S. A. (2016). Psychometric validation of a German language version of a PROM for urethral stricture surgery and preliminary testing of supplementary ED and UI constructs. World J Urol, 34(3), 369-375. doi: 1007/s00345-015-1610-8

Studientyp und Beobachtungszeitraum	
3. Stimmen Sie mit der Überlegung des G-BA zur Verblindung überein? Falls nein, welche Einwände oder Vorschläge haben Sie gegen diese Vorgaben? Die patientenindividuelle Nachbeobachtungszeit soll 12 Monate betragen. 4. Eine Nachbeobachtungszeit von 12 Monaten (nach der Intervention) wird als angemessen angesehen, da bei Patienten mit Rezidivstrikturen das Auftreten eines erneuten Rezidivs nach einer Urethrotomia interna oft bereits innerhalb dieses Zeitraums erfolgt. Stimmen Sie mit dieser Überlegung überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. Dieser Vorgabe?	
Überlegungen der Geschäftsstelle	
ROBUST-III: Studienteilnehmer verblindet, Cross-over nach 6 Monaten (66%), Entblindung, wenn zuvor Symptome im Kontrollarm auftraten; 5 Jahre Follow-Up	
§ 6 Studientyp und Beobachtungszeitraum (Vorlage für BE)	**(TrGr)**
(1) [1]Die Erprobungsstudie ist als <Studiendesign: z. B. randomisierte, kontrollierte Studie (RCT)> zu konzipieren und durchzuführen. [2]Die Studie soll multizentrisch durchgeführt werden. <[3]Aussagen zum Cross-over-Design, inkl. Dauer der Eingewöhnungs- bzw. Trainings- und der Auswaschphase>. (2) [1]<Die patientenindividuelle Nachbeobachtungszeit / Der Beobachtungszeitraum> soll mindestens <Dauer> umfassen. [2]<Ggf. generische Angabe des Beobachtungszeitraums, z. B.: Der Beobachtungszeitraum ist so zu bestimmen, dass die Gewinnung hinreichender Informationen zu Effekten der Intervention sichergestellt ist; ein Zeitraum von weniger als <Dauer> ist hierfür ungeeignet>. (3) <Aussage zur Verblindung, z. B.: Die Studienteilnehmerinnen und Studienteilnehmer / weiterbehandelnden Personen / Per-	**Zu Absatz 1** In Satz 1 ist geregelt, dass die Erprobungsstudie als eine randomisierte, kontrollierte Studie (RCT) zu konzipieren und durchzuführen ist, da dieser Studientyp ein ausreichend sicheres Erkenntnisniveau für eine spätere Systementscheidung bietet. In Satz 2 wird festgelegt, dass die Studie multizentrisch durchgeführt werden soll. Die Aussagekraft multizentrischer Studien ist im Allgemeinen höher als bei monozentrischen Studien. Das liegt vornehmlich daran, dass der Einfluss lokaler Besonderheiten auf das Ergebnis reduziert wird. Zudem können schneller höhere Patientenzahlen rekrutiert werden. Weitere Konkretisierungen des Designs sollen von der UWI vorgenommen werden; dazu gehört insbesondere <Benennung von Beispielen, die insbesondere durch die UWI konkretisiert werden sollen, was ist gegeneinander abzuwägen>. **Zu Absatz 2**

Studientyp und Beobachtungszeitraum	
sonen, die die Endpunkte erheben / die Personen, die die Endpunkte auswerten>, sollen gegen die Intervention verblindet sein.>	Dieser Absatz regelt, dass eine ausreichend lange <patientenindividuelle Nachbeobachtungszeit / Beobachtungszeit> für die Studie eingeplant werden soll, um hinreichende Informationen zu den Effekten der Intervention zu erhalten. Nach Einschätzung des G-BA ist dies jedenfalls nicht bei einer <patientenindividuelle Nachbeobachtungszeit / Beobachtungszeit> von weniger als <Anzahl> <Wochen / Monate> der Fall. Bei der Festlegung des Beobachtungszeitraums sollte auch die Dauer <z.B. der Eingewöhnungszeit, der Auswaschphasen> berücksichtigt werden. **Zu Absatz 3** Die Studie ist mit angemessenen Maßnahmen zur Verblindung zu konzipieren und durchzuführen. Die <Studienteilnehmerinnen und Studienteilnehmer / weiterbehandelnden Personen / Personen, die die Endpunkte erheben,> sollen nicht über die Gruppenzugehörigkeit informiert sein. Auch bei denjenigen Personen, die die Endpunkte auswerten, soll eine vollständige Verblindung gewährleistet werden, um mögliche Verzerrungen des Studienergebnisses, die aufgrund der Kenntnis der Gruppenzugehörigkeit entstehen können, zu vermeiden. Die Verblindung soll bis zum Ende der Studie aufrechterhalten werden.
Eingegangene Einschätzungen	
Wenn Einschätzungen zu konkret gestellter Frage, dann hier Frage einfügen	
DGU	Zu 1.: ja Zu 2.: ja Zu 3.: Die Studienteilnehmer sollten verblindet sein, für die weiterbehandelnden Personen sowie die Endpunkterheber ist dies jedoch nicht notwendig. Zu 4.: s.o.

Studientyp und Beobachtungszeitraum	
Urotronic Inc.	Zu 1.: Zustimmung Zu 2: Zustimmung Zu 3.: Wir stimmen zu, dass Patienten, behandelnde Ärzte und die Erhebung der Endpunkte so weit wie möglich verblindet werden sollten. Urotronic ist sich jedoch auch bewusst, dass diese Anforderung erheblichen zusätzlichen Aufwand für die Kliniken, die Patienten in die Studie einbringen, nach sich zieht. Zu 4.: Urotronic ist der Meinung, dass der primäre Endpunkt nach 12 Monaten erhoben werden sollte, jedoch sollte auch eine längerfristige Nachbeobachtung (z.B. 3 Jahre) in Betracht gezogen werden, um die Dauerhaftigkeit der Ergebnisse besser bewerten zu können.

Erfassung und Dokumentation bestimmter Parameter	
Die Art und Anzahl weiterer therapeutischer Interventionen mit Bezug zur Grunderkrankung oder mit möglichen Einfluss auf die zu erfassenden Endpunkte sollten dokumentiert werden. Frage des G-BA: Stimmen Sie mit der Überlegung des G-BA überein? Falls nein, welche Einwände oder Vorschläge haben Sie bzgl. dieser Vorgabe?	
Überlegungen der Geschäftsstelle	
Überlegungen, Diskussionspunkte, Fragen	
Eingegangene Einschätzungen	
DGU	Ja
Urotronic Inc.	Urotronic stimmt zu, dass die Häufigkeit und die Art vorheriger Interventionen mit Bezug auf die in der Studie untersuchte Harnröhrenstriktur erhoben werden sollte.

Erfassung und Dokumentation bestimmter Parameter	
	Urotronic empfiehlt außerdem, weitere wichtige Informationen zur Krankengeschichte zu erfassen, wie z. B. die Ätiologie der Strikturentwicklung, die Vorgeschichte anderer urologischer Erkrankungen (z. B. Krebserkrankungen, BPH, Kontrakturen des Blasenhalses, überaktive Blase, Inkontinenz usw.)

Ergänzende Fragen	
Wie viele Studienzentren in Deutschland kämen für die Studie in Frage?	
DGU	Mindestens 20.
Urotronic Inc.	Laut NUB-Aufstellung des InEK haben 85 Kliniken die NUB-Anfrage „Medikamentebeschichteter Ballonkatheter bei symptomatischer Harnröhrenstriktur“ eingereicht. Diese kommen also grundsätzlich als Studienzentren in Frage. Laut Weiße Liste (www.weisse-liste.de) behandelten im Jahr 2019 39 Kliniken in Deutschland 60 oder mehr Patienten mit einer Hauptdiagnose der Gruppe N35, also einer Harnröhrenverengung. Insgesamt behandelten 539 Kliniken Patienten mit dieser Indikation. Hinzu kommen deutschlandweit 3.411 Fälle mit der Hauptdiagnose N99.1 Harnröhrenstriktur nach medizinischen Maßnahmen. Die Fallzahlen der 4-Steller der Diagnosecodes sind der weißen Liste jedoch nicht zu entnehmen,
Wie viele Studienzentren sollten initiiert werden, um die Studie in angemessener Zeit abzuschließen?	
DGU	Mindestens 10.
Urotronic Inc.	Um eine Effektgröße von 15% detektieren können, wäre eine Stichprobengröße von etwa 350 Probanden notwendig. Um diese Anzahl in einem überschaubaren Zeitraum rekrutieren zu können, würde Urotronic empfehlen, ca. 35 Zentren mit jeweils 10 Patienten in die Studie einzubeziehen. Wird die durchschnittliche Anzahl von Probanden je Studienzentrum aus der ROBUST III-Studie zugrunde gelegt (5,77), wären 61 Studienzentren notwendig, um die oben genannte Anzahl an Probanden zu rekrutieren. Urotronic möchte an dieser Stelle darauf hinweisen, dass die NUB-Anfrage zu der neuen Methode überraschend den Status 2 erhalten hat. Kliniken können also kein zusätzliches Budget für die Methode verhandeln, und können die Methode im Rahmen des DRG-Systems nicht wirtschaftlich erbringen. Diese Situation könnte der Rekrutierung einer höheren Anzahl an Probanden je Zentrum im Weg stehen.

Ergänzende Fragen	
Welche Maßnahmen wären erforderlich, um eine zügige Rekrutierung zu gewährleisten?	
DGU	Es sollte ein Studienleiter bestimmt werden, der wiederum direkt verschiedene Klinikleiter anspricht. Da sich die Klinikleiter der größeren deutschen urologischen Kliniken gut kennen und sich in aller Regel gerne gegenseitig bei wissenschaftlichen Fragestellungen unterstützen, wäre damit die entscheidende Voraussetzung gegeben.
Urotronic Inc.	Es wäre erforderlich solche Zentren in die Studie einzubeziehen, die eine hohe Anzahl von Patienten mit Harnröhrenstriktur behandeln bzw. die eine relevante Anzahl an Urethrotomien durchführen.
Ergänzende Fragen	
Gibt es aus Ihrer Sicht Aspekte zu berücksichtigen, welche die geplante Studiendurchführung erschweren könnten? (Beispielsweise geplante oder laufende Studien mit Rekrutierung derselben Patientengruppen im Indikationsgebiet der Erprobungsstudie)	
DGU	Geplante laufende Studien überregionaler Art dürfte es im Moment nicht geben. Da bisher zur Sachse-Urethrotomie sowie zur offenen Urethraplastik keine sinnvollen etablierten Alternativen existieren, dürfte die Studiendurchführung nicht durch andere Studien erschwert werden.
Urotronic Inc.	Patienten könnten aufgrund ihrer rezidivierenden Erkrankung der Randomisierung kritisch gegenüberstehen, nachdem sie sich zuvor einer oder mehreren Urethrotomien unterzogen haben. Dies kann dazu führen, dass die Patienten eher versuchen, eine Behandlung mit der gegenständlichen Methode außerhalb der Studie zu erhalten, oder dass sie sich für die invasivere, aufwändigere plastische Rekonstruktion der Harnröhre entscheiden. Urotronic weist auch an dieser Stelle darauf hin, dass die NUB-Anfrage zu der neuen Methode überraschend mit dem Status 2 beschieden wurde. Kliniken können also kein zusätzliches Budget für die Methode verhandeln, und können daher die Methode im Rahmen des DRG-Systems nicht wirtschaftlich erbringen. Diese Situation kann die geplante Studiendurchführung erschweren.
Welche Anforderungen, insbesondere hinsichtlich der personellen, technischen und räumlichen Ausstattung, sind aus Ihrer Sicht zur Erbringung der Methode im Rahmen einer Studie zu stellen? Bitte berücksichtigen Sie hierbei auch mögliche periprozedurale Risiken ihrer Anwendung.	
DGU	Für die Studie sind keinerlei besondere Anforderungen erforderlich. Jede urologische Klinik hat einen Röntgen-Arbeitsplatz mit Durchleuchtungsmöglichkeit, so dass die Studie in jeder urologischen Klinik sofort begonnen werden kann.

Ergänzende Fragen	
Urotronic Inc.	Die Anforderungen der Prozedur sind vergleichbar mit denen der Urethrotomia interna.
Ergänzende Fragen	
Wird bei den genannten Eckpunkten die Versorgsungsrealität in Hinblick auf die Durchführbarkeit der Erprobung und der Leistungserbringung angemessen berücksichtigt?	
DGU	Siehe oben
Urotronic Inc.	Insgesamt berücksichtigen die genannten Eckpunkte aus Sicht von Urotronic die Versorgungsrealität in angemessener Weise.
Überlegungen des G-BA zur näherungsweisen Fallzahlschätzung	
Für die Fallzahl ist die Größe des nachzuweisenden Effekts maßgeblich. Diese wiederum hängt maßgeblich von der Operationalisierung des primären Endpunkts (hier: IPSS Score und Strikturfreiheit) ab. Unter Annahme einer Effektstärke von beispielsweise 15 % (80 % der Teilnehmer erreichen den primären Endpunkt in der Interventionsgruppe, 65 % in der Kontrollgruppe), abgeleitet aus den Ergebnissen der Studien ROBUST-I1 und ROBUST-II2 sowie aus Daten zur Strikturfreiheit nach 12 Monaten in Abhängigkeit der Anzahl vorheriger Interventionen3, ergibt sich als grobe Approximation eine Fallzahl in der Kategorie einer mittleren Studie (100 bis < 500).	
DGU	Eine Studie mit mehr als 100 auswertbaren Teilnehmern erscheint mir unrealistisch. In Deutschland ist es zunehmend schwierig, manchmal fast unmöglich, prospektiv randomisierte Studien durchzuführen – insbesondere, wenn wie im vorliegenden Fall der Patient eine Überlegenheit der Dilatation zusätzlich zur Sichturethrotomie vermuten könnte. Insofern erscheinen mir 100 Patienten sowohl von der Realisierungsmöglichkeit als auch inhaltlich ausreichend.
Urotronic Inc.	Urotronic erwartet eine Erfolgsrate zwischen 70% und 80% für Optilume und zwischen 55% und 65% für die Urethrotomie je nach Charakteristik der Patientenpopulation. Daraus leitet sich ebenfalls eine Studiengröße in der mittleren Kategorie ab.

Schätzung der Overheadkosten und der Dauer der Erprobungsstudie (Beispiel)	
Für Studien mit mittlerer Fallzahl (hier: 400 Studienteilnehmer als Kalkulationsgrundlage) und mittlerem Aufwand lässt sich ein studienspezifischer Aufwand in Höhe von etwa 5500 € je Teilnehmer beziffern. Auf der Basis dieser Annahmen lassen sich geschätzte Studienkosten von 2,2 Millionen € berechnen.	
DGU	Dies hängt stark vom vorgesehenen Studienhonorar ab. Die minimalen Kosten bei 100 Teilnehmern wären die Kosten des Ballons für 50 Teilnehmer, die zusätzlichen Kosten richten sich dann in erster Linie nach dem Honorar.
Urotronic Inc.	Urotronic stimmt der Kalkulation der Kosten für den studien-spezifischen Aufwand im Rahmen der obigen Annahmen zu den Fallzahlschätzungen zu.

Literaturlisten

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Gemeinsamer Bundesausschuss

Beschlussentwurf

des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung gemäß § 137e SGB V: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Vom T. Monat JJJJ

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am T. Monat JJJJ folgende Richtlinie zur Erprobung der Methode „Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen“ beschlossen.

I. Die Richtlinie zur Erprobung wird wie folgt gefasst:

„Richtlinie des Gemeinsamen Bundesausschusses zur Erprobung des Medikamentenbeschichteten Ballondilatationskatheters zur transurethralen Behandlung von Harnröhrenstrikturen

§ 1 Zielsetzung

[1]Um den Gemeinsamen Bundesausschuss (G-BA) in die Lage zu versetzen, eine abschließende Bewertung des Nutzens des Medikamentenbeschichteten Ballondilatationskatheters zur transurethralen Behandlung von Harnröhrenstrikturen durchzuführen, sollen im Wege der Erprobung die hierfür nach den §§ 135 und 137c des Fünften Buches Sozialgesetzbuch (SGB V) in Verbindung mit den Vorgaben der Verfahrensordnung des G-BA (VerfO) notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode gewonnen werden. [2]Die für die Beantwortung dieser Frage in ihrer Konkretisierung nach § 2 notwendige Studie soll durch eine unabhängige wissenschaftliche Institution (UWI) nach Maßgabe dieser Richtlinie entworfen, durchgeführt und ausgewertet werden. [3]Die Ausgestaltung des Studiendesigns ist – soweit nicht im Folgenden näher bestimmt – von der UWI auf der Basis des Standes der wissenschaftlichen Erkenntnisse vorzunehmen und zu begründen. [4]Bei der Erstellung des Studienprotokolls ist das Wirtschaftlichkeitsprinzip zu beachten.

§ 2 Fragestellung

[1]Die Erprobung soll der Beantwortung der Frage dienen, ob bei erwachsenen Männern mit symptomatischer

DKG/KBV/PatV	GKV-SV
kurzstreckiger	*keine Aufnahme*

Rezidivstriktur der anterioren Harnröhre

DKG/KBV/PatV	GKV-SV
keine Aufnahme	von bis zu 2 cm Länge

die Behandlung mittels eines medikamentenbeschichteten Ballondilatationskatheters im Vergleich zur Urethrotomia interna hinsichtlich des primären Endpunktes bestehend aus dem International Prostate Symptom Score (IPSS) und der Strikturfreiheitsrate überlegen ist**.**

§ 3 Population

[1]In die Erprobungsstudie einzuschließen sind erwachsene Männer mit symptomatischer

DKG/KBV/PatV	GKV-SV
kurzstreckiger	*keine Aufnahme*

Rezidivstriktur der anterioren Harnröhre

DKG/KBV/PatV	GKV-SV
keine Aufnahme	von bis zu 2 cm Länge.

[2]Die weiteren Ein- und Ausschlusskriterien (z. B. Lokalisation der anterioren Harnröhrenstriktur,

DKG/KBV/PatV	GKV-SV
Länge der Harnröhrenstriktur	*keine Aufnahme*

) sind so festzulegen, dass eine Übertragbarkeit der Ergebnisse auf die Zielpopulation gemäß Satz 1 ermöglicht wird.

§ 4 Intervention und Vergleichsintervention

(1) [1]Die Prüfintervention besteht in der transurethralen Dilatation der Harnröhre im Bereich der Harnröhrenstriktur mittels eines Ballondilatationskatheters, welcher mit einem zellproliferations- und migrationshemmenden Medikament beschichtet ist. [2]Die UWI legt das Nähere zur Notwendigkeit und Art der Prädilatation fest.

(2) Die Vergleichsintervention ist die Urethrotomia interna.

§ 5 Endpunkte

(1) [1]Der primäre Endpunkt ist der Anteil an Patienten, die

- nach 12 Monaten eine klinisch relevante Verbesserung im IPSS-Score im Vergleich zum Ausgangswert aufweisen und
- sich innerhalb dieses Zeitraums keiner klinisch indizierten Reintervention aufgrund des Wiederauftretens der Striktur einschließlich entsprechender Symptomatik unterziehen müssen (Strikturfreiheit).

(2) [1]Als sekundäre Endpunkte sind insbesondere zu erfassen:

- harnwegsbezogene Morbidität,

- gesundheitsbezogene Lebensqualität (mittels eines krankheitsspezifischen, validierten Instruments zu messen),
- unerwünschte Ereignisse.

[2]Die Operationalisierung der Endpunkte sowie die Erhebung und die Operationalisierung weiterer Endpunkte sind jeweils zu begründen.

(3) Sofern vorhanden, sind für alle Endpunkte validierte Erhebungsinstrumente zu verwenden.

§ 6 Studientyp und Beobachtungszeitraum

(1) [1]Die Erprobungsstudie ist als randomisierte, kontrollierte Studie (RCT) zu konzipieren und durchzuführen. [2]Die Studie soll multizentrisch durchgeführt werden.

(2) Die Nachbeobachtungszeit beginnend ab Intervention soll mindestens 12 Monate umfassen.

(3) Die Studienteilnehmer und die weiterbehandelnden Personen sowie die Personen, die die Endpunkte erheben, und die Personen, die die Endpunkte auswerten, sollen gegen die Intervention verblindet sein.

(4) Bei Studieneinschluss sind die Ausgangswerte der in § 5 genannten Endpunktparameter und die Charakteristika der Patientenpopulation zu erfassen.

§ 7 Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung

Es ist in jedem Studienzentrum sicherzustellen, dass die Behandlung gemäß dem Studienprotokoll unter Berücksichtigung aller erforderlichen, anerkannten, nach ethischen und wissenschaftlichen Gesichtspunkten aufgestellten Regeln für die Durchführung von klinischen Studien erfolgt.

§ 8 Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung

(1) Im Auftrag an die unabhängige wissenschaftliche Institution ist diese – unabhängig davon, ob die Erprobung durch den G-BA oder Hersteller oder Unternehmen durchgeführt wird – insbesondere zu verpflichten,

a) ein Studienprotokoll zu erstellen und dieses sowie gegebenenfalls die Amendments unverzüglich nach Fertigstellung an den G-BA zur weitergehenden Information zu übersenden,

b) die Konformität des Studienprotokolls mit den Vorgaben der Erprobungs-Richtlinie und bei Abweichungen gegenüber diesen Vorgaben eine Begründung bei Übersendung des Studienprotokolls darzulegen,

c) die Studie in einem einschlägigen, von der World Health Organization akkreditierten Register klinischer Studien zu registrieren und den Eintrag regelmäßig zu aktualisieren und den G-BA hierüber zu informieren,

d) zur Durchführung der Erprobung nach den Anforderungen der Richtlinie und nach Maßgabe des Auftrags, einschließlich der datenschutzkonformen Erhebung, Speicherung und Nutzung der Daten und der Einholung von erforderlichen Genehmigungen,

e) Bericht zu erstatten an den G-BA bei Abweichungen von den Vorgaben in der Erprobungs-Richtlinie,

f) zur Auswahl der Leistungserbringer, Festsetzung und Auszahlung der angemessenen Aufwandsentschädigung an diese,

g) zur Auswertung der Studie,

h) unverzüglich nach Abschluss der Studie den Studienbericht, der entsprechend der International Council for Harmonisation (ICH)-E3-Richtlinie zu erstellen ist, zusammen mit dem statistischen Analyseplan an den G-BA zu übermitteln,

i) dem G-BA das Recht einzuräumen, ihm auf seine Kosten eine nachträgliche Datenauswertung zur Verfügung zu stellen und

j) dem G-BA das Recht zur Veröffentlichung zumindest der Synopse des Studienberichts sowie weitergehender für seine Entscheidung relevanter Informationen aus dem Studienbericht und aus den nachträglichen Datenauswertungen einzuräumen.

(2) [1]Wird die Studie vom G-BA durchgeführt, ist die UWI in diesem Fall zu verpflichten, an den G-BA zu festgelegten Meilensteinen Bericht zu erstatten. [2]Außerdem ist die UWI in Ergänzung der Verpflichtung nach Absatz 1 Buchstabe j zu beauftragen, dass sie die Studienergebnisse spätestens 3 Monate nach Abnahme des Studienberichts durch den G-BA zur Veröffentlichung in einer Fachzeitschrift mit wissenschaftlichem Begutachtungsprozess einreicht und dem G-BA das Recht einräumt, im Anschluss an deren Veröffentlichung oder nach Ablauf eines Jahres nach Einreichung der Studienergebnisse den Studienbericht zu veröffentlichen. [3]Die UWI arbeitet vertrauensvoll mit der mit dem Projektmanagement beauftragten Stelle zusammen und hat dieser die zur Ausübung ihrer Aufgabe erforderlichen Informationen und Unterlagen zur Verfügung zu stellen.

(3) [1]Wird die Studie durch Medizinproduktehersteller oder Unternehmen durchgeführt, sind diese verpflichtet, die Anforderungen dieser Richtlinie an die Durchführung und Auswertung der Erprobung zu beachten. [2]Um sicherzustellen, dass eine durchgeführte Studie den Anforderungen dieser Richtlinie entspricht und geeignet ist, die notwendigen Erkenntnisse des Nutzens der Methode zu gewinnen, haben die durchführenden Medizinproduktehersteller und Unternehmen dem G-BA das Studienkonzept zur Prüfung vorzulegen und zu erklären, dass der Vertrag mit der UWI den Anforderungen nach Absatz 1 entspricht und eine Einflussnahme durch den Sponsor auf das Ergebnis der Studie vertraglich ausgeschlossen ist. [3]Bei positivem Ergebnis der Überprüfung bescheinigt der G-BA die Konformität des vorgelegten Studienkonzepts mit den Anforderungen dieser Richtlinie und dass damit die im Rahmen der Erprobung erbrachten Leistungen von der GKV übernommen werden; andernfalls teilt er die bestehenden Defizite mit.“

II. Die Richtlinie tritt am Tag nach der Veröffentlichung im Bundesanzeiger in Kraft.

Die Tragenden Gründe zu diesem Beschluss werden auf den Internetseiten des G-BA unter www.g-ba.de veröffentlicht.

Berlin, den T. Monat JJJJ

Gemeinsamer Bundesausschuss
gemäß § 91 SGB V
Der Vorsitzende

Prof. Hecken

Gemeinsamer Bundesausschuss

Tragende Gründe

zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung gemäß § 137e SGB V: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Vom T. Monat JJJJ

Inhalt

1. Rechtsgrundlage

Stellt der Gemeinsame Bundesausschuss (G-BA) in einer Bewertung nach § 137h Absatz 1 Satz 4 des Fünften Buches Sozialgesetzbuch (SGB V) fest, dass für die zu bewertende Methode weder der Nutzen noch die Schädlichkeit oder die Unwirksamkeit als belegt anzusehen ist (§ 137h Absatz 1 Satz 4 Nummer 3 SGB V), entscheidet er innerhalb von sechs Monaten nach dem Beschluss nach § 137h Absatz 1 Nummer 3 SGB V über eine Richtlinie zur Erprobung nach § 137e SGB V, um die notwendigen Erkenntnisse für die Bewertung des Nutzens der Methode zu gewinnen.

Der G-BA regelt in der Richtlinie nach § 137e Absatz 1 Satz 1 SGB V die in die Erprobung einbezogenen Indikationen und die sächlichen, personellen und sonstigen Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung. Er legt zudem Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung fest (§ 137e Absatz 2 Satz 1 und 2 SGB V).

Falls bereits Studien laufen oder geplant sind, die Erkenntnisse für eine abschließende Nutzenbewertung liefern können, kann der G-BA gemäß 2. Kapitel § 37 Absatz 4 Satz 7 der Verfahrensordnung des G-BA (VerfO) das Beratungsverfahren über eine Richtlinie zur Erprobung aussetzen. Für den Aussetzungsbeschluss gilt nach 2. Kapitel § 37 Absatz 4 Satz 8 VerfO das Stellungnahmerecht nach § 92 Absatz 7d SGB V.

2. Eckpunkte der Entscheidung

2.1 Hintergrund

Der G-BA hat im Rahmen einer Bewertung nach § 137h Absatz 1 Satz 4 SGB V mit Beschluss vom 1. April 2021 festgestellt, dass für die Methode des Medikamentenbeschichteten Ballondilatationskatheters zur transurethralen Behandlung von Harnröhrenstrikturen weder der Nutzen noch die Schädlichkeit oder die Unwirksamkeit der Methode als belegt anzusehen ist[1], und das Beratungsverfahren über eine Richtlinie zur Erprobung nach § 137e SGB V der vorgenannten Methode eingeleitet. Zuvor hatte sich der G-BA versichert, dass keine weiteren abgeschlossenen oder laufenden Studien vorlagen, die grundsätzlich geeignet wären, derzeit oder in naher Zukunft einen Nachweis des Nutzens dieser Methode zu liefern.

2.2 Zu § 1 Zielsetzung

Die in Satz 1 formulierte Zielsetzung dieser Erp-RL verdeutlicht, dass die entsprechend der Vorgaben dieser Erp-RL zu konzipierende Erprobungsstudie geeignet sein muss, die in § 2 konkretisierte Fragestellung beantworten zu können. Damit wird dem G-BA eine Bewertung des Nutzens dieser Methode auf einem für eine spätere Richtlinienentscheidung ausreichend sicheren Erkenntnisniveau erlaubt.

[1] https://www.g-ba.de/bewertungsverfahren/verfahren-137h/36

Mit Satz 2 wird vorgeschrieben, dass eine unabhängige wissenschaftliche Institution (UWI) mit der Planung, Durchführung und Auswertung einer Studie beauftragt werden soll, die den Vorgaben dieser Erp-RL entspricht.

Die UWI wird mit Satz 3 verpflichtet, aus Gründen der Objektivierbarkeit und Nachvollziehbarkeit sämtliche Festlegungen der Parameter des Studiendesigns nach wissenschaftlichen Kriterien zu treffen; damit wird sichergestellt, dass die Zielsetzung nach § 1 Satz 1 erreicht werden kann.

Das Wirtschaftlichkeitsprinzip ist gemäß § 1 Satz 4 bereits bei der Erstellung des Studienprotokolls zu beachten, da sich die späteren Studienkosten unmittelbar oder mittelbar aus den im Studienprotokoll spezifizierten Eckdaten und Parametern (z. B. der benötigten Patientenzahl, der Studiendauer, der Anzahl der Studienzentren, der Studienvisiten und der Qualitätssicherung) ergeben. Darüber hinaus ist gemäß 2. Kapitel § 25 Absatz 3 Spiegelstrich 3 VerfO neben der fachlichen Eignung sowie der Geeignetheit des Angebots der angebotene Preis der wissenschaftlichen Begleitung und Auswertung ein Kriterium für die Beauftragung der UWI.

2.3 Zu § 2 Fragestellung

Mit der hier definierten Fragestellung adressiert der G-BA die am 1. April 2021 im Rahmen der Bewertung nach § 137h Absatz 1 Satz 4 SGB V festgestellte Erkenntnislücke.

2.4 Zu § 3 Population

Die Studienpopulation baut auf der in der Informationsübermittlung nach § 137h Absatz 1 SGB V durch das Krankenhaus definierten Patientenpopulation auf. In die Erprobungsstudie einzuschließen sind demnach erwachsene Männer mit symptomatischer

DKG/KBV/PatV	**GKV-SV**
kurzstreckiger	*keine Aufnahme*

DKG/KBV/PatV	**GKV-SV**
keine Aufnahme	bis zu 2 cm langer

Rezidivstriktur der anterioren Harnröhre. Bei der Studienplanung sollten weitere Ein- oder Ausschlusskriterien, wie z. B. die Lokalisation der anterioren Harnröhrenstriktur (bulbär, penil, glandulär)

DKG/KBV/PatV	**GKV-SV**
und die Strikturlänge	*keine Aufnahme*

durch die UWI festgelegt werden. Dabei ist gemäß Satz 2 darauf zu achten, dass die Übertragbarkeit der Ergebnisse auf die Zielpopulation gemäß Satz 1 nicht gefährdet wird.

2.5 Zu § 4 Intervention und Vergleichsintervention

Zu Absatz 1

Für das eingesetzte Medizinprodukt im Prüfinterventionsarm muss Verkehrsfähigkeit vorliegen und die Studienpopulation von der Zweckbestimmung umfasst sein. Bei stark stenotischen Strikturen stellen die Urethrotomia interna, die Dilatation mit unbeschichteten Ballondilatationskathetern und die Aufbougierung mit Kathetern zunehmender Größe mögliche Verfahren zur Prädilatation vor Durchführung der Prüfintervention dar. Ob eine Prädilatation erfolgen soll und welches Verfahren dafür anzuwenden ist, wird von der UWI festgelegt. Dabei kann es der Ärztin oder dem Arzt entweder freigestellt werden, im Rahmen der Behandlung individuell zu entscheiden, ob und ggf. mit welchem Verfahren eine Prädilatation der Striktur erfolgen soll, oder die UWI legt entsprechend dem aktuellen Stand der Wissenschaft ein einheitliches Vorgehen fest.

Zu Absatz 2

Die Vergleichsintervention ist die Urethrotomia interna. Gemäß internationaler Leitlinien[2,3] sollen in der Rezidivsituation offen-chirurgische Verfahren aufgrund höherer Erfolgsraten angeboten werden.

Auf Basis der durch das informationsübermittelnde Krankenhaus angeführten Zahlen der DRG-Statistik kommt der G-BA jedoch zu dem Schluss, dass aufgrund einer höheren Einsatzhäufigkeit die Urethrotomia interna im deutschen Versorgungskontext, vermutlich aufgrund der Patientenpräferenz, als Versorgungsstandard zu betrachten ist.

2.6 Zu § 5 Endpunkte

Zu Absatz 1

Als primärer Endpunkt der Studie wird die Kombination aus der klinisch relevanten Verbesserung im IPSS-Score im Vergleich zum Ausgangswert sowie der Strikturfreiheit über einen Zeitraum von 12 Monaten erhoben. Der IPSS-Score stellt ein geeignetes Erhebungsinstrument dar, um als patientenrelevanter Endpunkt die Verbesserung der Harnröhrenstriktur-bedingten Symptomatik, wie beispielsweise die Verbesserung von Miktionsbeschwerden subjektiv erfassen zu können. Die Festlegung einer klinisch relevanten Verbesserung im IPSS-Score soll unter Zugrundelegung einer Verbesserung um mindestens sechs Punkte [≥15% der Skalenspannweite] im Vergleich zum Ausgangswert erfolgen. Die Strikturfreiheit nach Intervention, definiert als fehlende Erforderlichkeit von weiteren klinisch indizierten Reinterventionen aufgrund erneut auftretender Rezidivstrikturen innerhalb von 12 Monaten, stellt eine weitere patientenrelevante Verbesserung dar. Anhand der bisher vorliegenden Daten (ROBUST I und II Studien) ist erwartbar, dass eine aussagekräftige Anzahl der Patienten eine solchermaßen definierte Strikturfreiheit nach 1 Jahr erzielen kann.

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[2] **Wessells H, Angermeier KW, Elliott S et al**. Male Urethral Stricture: American Urological Association Guideline. J Urol 2017; 197(1): 182-190. https://dx.doi.org/10.1016/j.juro.2016.07.087.

[3] **Chapple C, Andrich D, Atala A et al**. SIU/ICUD Consultation on Urethral Strictures: The management of anterior urethral stricture disease using substitution urethroplasty. Urology 2014; 83(3 Suppl): S31-47. https://dx.doi.org/10.1016/j.urology.2013.09.012.

Zu Absatz 2 und 3

Die gewählten sekundären Endpunkte ergänzen den primären Endpunkt durch international übliche Parameter und dienen zur weiteren Beurteilung möglicher Effekte. Als geeignete Parameter für den sekundären Endpunkt harnwegsbezogene Morbidität können beispielsweise klinisch indizierte Reinterventionen, Wiederauftreten der Striktursymptomatik, wiederkehrende Harnwegsinfekte und akuter Harnverhalt in Betracht kommen.

Die Operationalisierung der einzelnen Endpunkte obliegt der UWI, die diese jeweils zu begründen hat. Grundsätzlich sind, wo immer möglich, validierte Instrumente zur Erhebung der Endpunkte einzusetzen. Von besonderer Bedeutung ist dies bei subjektiven Endpunkten, d. h. solchen, die auf Befragung von Studienteilnehmenden, an der Behandlung beteiligten Personen oder Dritten beruhen.

Für die Erhebung der Lebensqualität sind, sofern möglich, krankheitsspezifische validierte Instrumente einzusetzen.

2.7 Zu § 6 Studientyp und Beobachtungszeitraum

Zu Absatz 1

In Satz 1 ist geregelt, dass die Erprobungsstudie als eine randomisierte, kontrollierte Studie (RCT) zu konzipieren und durchzuführen ist, da jedenfalls dieser Studientyp ein ausreichend sicheres Erkenntnisniveau für eine spätere Systementscheidung bietet. In Satz 2 wird festgelegt, dass die Studie multizentrisch durchgeführt werden soll. Die Aussagekraft multizentrischer Studien ist im Allgemeinen höher als bei monozentrischen Studien. Das liegt vornehmlich daran, dass der Einfluss lokaler Besonderheiten auf das Ergebnis reduziert wird. Zudem können schneller höhere Patientenzahlen rekrutiert werden.

Weitere Konkretisierungen des Designs sollen von der UWI vorgenommen werden.

Zu Absatz 2

Eine über die Erfassung des primären Endpunktes (12 Monate nach Intervention) hinausgehende Beobachtung kann erfolgen. Dieser Absatz regelt, dass eine ausreichend lange Nachbeobachtungszeit für die Studie eingeplant werden soll, um hinreichende Informationen zu den Effekten der Intervention zu erhalten.

Zu Absatz 3

Die Studie ist mit angemessenen Maßnahmen zur Verblindung zu konzipieren und durchzuführen. Die Studienteilnehmer und weiterbehandelnden Personen sowie Personen, die die Endpunkte erheben, sollen nicht über die Gruppenzugehörigkeit informiert sein. Auch bei denjenigen Personen, die die Endpunkte auswerten, soll eine vollständige Verblindung gewährleistet werden, um mögliche Verzerrungen des Studienergebnisses, die aufgrund der Kenntnis der Gruppenzugehörigkeit entstehen können, zu vermeiden. Die Verblindung soll bis zum Ende der Studie aufrechterhalten werden.

Zu Absatz 4

Zur Darstellung der Interventionseffekte und zur Interpretation patientenindividueller Unterschiede sind entsprechend den Vorgaben der Gute Klinische Praxis (Good Clinical

Practice) die Ausgangswerte der unter § 5 genannten Endpunktparameter und die Charakteristika der Patientenpopulation (z. B. Genese der Harnröhrenstriktur, Lage der Striktur zum Sphinkter, Anzahl der Rezidive, Strikturlänge, Vorliegen anderer urologischer (Vor-)Erkrankungen) zu erfassen.

2.8 Zu § 7 Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung

Bei der Durchführung von Erprobungsstudien des G-BA mit Medizinprodukten soll die Gute Klinische Praxis gemäß ISO 14155 (Klinische Prüfung von Medizinprodukten an Menschen - Gute Klinische Praxis) angewendet werden.

Die Gute Klinische Praxis ist ein internationaler ethischer und wissenschaftlicher Standard für Planung, Durchführung, Dokumentation und Berichterstattung von klinischen Studien am Menschen. Die Einhaltung dieses Standards schafft öffentliches Vertrauen, dass die Rechte, die Sicherheit und das Wohl der Prüfungsteilnehmerinnen und -teilnehmer gemäß der Deklaration von Helsinki geschützt werden und die bei der klinischen Studie erhobenen Daten glaubhaft sind.

2.9 Zu § 8 Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung

Zu Absatz 1

Absatz 1 beschreibt die notwendigen Inhalte des Auftrags an die UWI. Die in Absatz 1 aufgeführten Auftragsinhalte gelten sowohl für die durch Hersteller oder Unternehmen als auch durch den G-BA beauftragte wissenschaftliche Begleitung und Auswertung der Erprobung. Nur bei Vorliegen eines den Anforderungen dieses Absatzes genügenden Vertrages mit der UWI ist die Erprobung als konform mit der Erprobungs-Richtlinie anzusehen und kann damit als Erprobung im Sinne des § 137e SGB V gewertet und im Leis-tungsanteil von der Gesetzlichen Krankenversicherung (GKV) finanziert werden.

Nach Buchstabe a) soll die Übersendung des Studienprotokolls und der Amendments die rasche Abklärung von Zweifelsfragen ermöglichen; eine Gesamtprüfung auf Konformität des Studienprotokolls mit den Vorgaben der Erprobungs-Richtlinie wird vom G-BA nicht von Amts wegen vorgenommen.

In Buchstabe b) wird die UWI verpflichtet, die Konformität des Studienprotokolls mit den Vorgaben der Erprobungs-Richtlinie gegenüber dem G-BA zur weitergehenden Information mit Übersendung des Studienprotokolls darzulegen. Zeitgleich hat die UWI Abweichungen von den Vorgaben zu begründen. Dies eröffnet nicht die Möglichkeit, von der Erprobungs-Richtlinie abzuweichen.

Nach Buchstabe c) ist die Studie in einem einschlägigen, von der World Health Organization (WHO) akkreditierten Register klinischer Studien zu registrieren und der Eintrag regelmäßig zu aktualisieren. Der G-BA ist hierüber zu informieren. Zu den akkreditierten Registern zählen derzeit insbesondere das Deutsche Register Klinischer Studien (DRKS) und das ClinicalTrials.gov; eine vollständige Übersicht findet sich auf der Homepage der WHO (https://www.who.int/clinical-trials-registry-platform/network/data-providers). Durch die

Registrierung wird der weltweite Überblick über laufende Studien unterstützt, der für die Transparenz der Studiendurchführung und auch für den G-BA insbesondere bei Methodenbewertungen wichtig ist.

Nach Buchstabe e) ist vorgesehen, dass Abweichungen von den Vorgaben der Erprobungs-Richtlinie im Laufe der Erprobung durch die UWI dem G-BA mitzuteilen sind.

Nach den Buchstaben f) und g) ist die UWI verpflichtet, die Leistungserbringer auszuwählen, die angemessene Aufwandsentschädigung festzusetzen und an diese auszuzahlen sowie die Studie auszuwerten.

Nach Buchstabe h) ist nach Abschluss der Studie der Studienbericht zusammen mit dem statistischen Analyseplan an den G-BA ohne schuldhaftes Zögern zu übermitteln. Es wird zwingend vorgegeben, dass dieser entsprechend der International Council for Harmonisation (ICH)-E3-Richtlinie zu erstellen ist.

Gemäß Buchstabe i) ist dem G-BA die Möglichkeit einzuräumen, auf eigene Kosten Datenauswertungen bei der UWI durchführen zu lassen. Die Datenhoheit verbleibt bei den durch Unternehmen und Hersteller durchgeführten Erprobungen grundsätzlich bei diesen Sponsoren. Da jedoch gesichert sein muss, dass die Bewertung der Studie durch den G-BA dadurch nicht beeinträchtigt wird, muss er die durch den Studienbericht nicht eindeutig beantworteten relevanten Fragen aufklären können.

Synopse im Sinne des Buchstaben j) meint eine der ICH-E3-Leitlinie Annex I entsprechende Übersicht zu den wesentlichen Eckdaten und Ergebnissen der Studie. Durch die in Buchstabe j) vorgesehene Regelung sichert der G-BA die Verwertbarkeit der Erprobungsstudie, weil die Qualität der Studie sowie Einzelfragen unter Umständen nur mit den angeforderten Daten oder deren spezifischer Auswertung geprüft werden können. Der G-BA geht davon aus, dass die Studienergebnisse zeitnah nach der Übermittlung des Studienberichts an den G-BA zur Veröffentlichung in einer referenzierten Fachzeitschrift eingereicht werden.

Zu Absatz 2

Absatz 2 legt erweiterte Verpflichtungen für die UWI fest, die gelten, wenn die Beauftragung der UWI durch den G-BA erfolgt:

Die UWI hat über die vereinbarten Meilensteine dem G-BA gegenüber Bericht zu erstatten. Über Absatz 1 Buchstabe j) hinausgehend, hat der G-BA im Auftrag mit der UWI festzulegen, dass diese die Studienergebnisse spätestens 3 Monate nach Abnahme des Studienberichts zur Veröffentlichung in einer Fachzeitschrift mit wissenschaftlichem Begutachtungsprozess einreicht. Sie hat dem G-BA im Anschluss an deren Veröffentlichung oder nach Ablauf eines Jahres nach Einreichung der Studienergebnisse das Recht zur Veröffentlichung des Studienberichts einzuräumen. Satz 3 legt fest, dass die UWI vertrauensvoll mit der mit dem Projektmanagement beauftragten Stelle zusammenzuarbeiten und dieser die zur Ausübung ihrer Aufgabe erforderlichen Informationen und Unterlagen zur Verfügung zu stellen hat. Die Verpflichtung ist ebenso im Vertrag mit der UWI zu regeln.

Zu Absatz 3

Absatz 3 stellt klar, dass die beteiligten Hersteller und Unternehmen sämtliche Anforderungen der Erprobungs-Richtlinie zu beachten haben, damit ihre Studie als Erprobung im Sinne des § 137e SGB V gewertet und im Leistungsanteil von der GKV finanziert wird.

Die Regelungen sehen vor, dass Medizinprodukthersteller und Unternehmen gehalten sind, in Abstimmung mit dem G-BA sicherzustellen, dass die Vorgaben nach § 137e Absatz 2 Satz 2 SGB V beachtet werden. Dem G-BA ist daher nach Absatz 3 Satz 2 das Studienkonzept und eine Erklärung, dass der Vertrag mit der UWI den Anforderungen nach Absatz 1 entspricht und eine Einflussnahme durch den Sponsor auf das Ergebnis der Studie vertraglich ausgeschlossen ist, vor Beauftragung einer UWI in deutscher Sprache vorzulegen. Damit erfolgt nicht erst nach Studienabschluss eine Prüfung der Konformität von Inhalt der Erprobungs-Richtlinie und Studiendurchführung und die Finanzierung im Leistungsanteil von der GKV wird bestätigt. Der G-BA bescheinigt nach positivem Prüfergebnis die Konformität. Weisen die vorgelegten Unterlagen hingegen noch Defizite auf, weil die Studie ausweislich der vorgelegten Unterlagen den Anforderungen der Richtlinie nach § 137e Absatz 1 Satz 1 SGB V nicht entspricht oder nicht geeignet ist, die notwendigen Erkenntnisse des Nutzens der Methode zu gewinnen, wird dies dem vorlegenden Unternehmen oder Hersteller mitgeteilt, das beziehungsweise der daraufhin die verbesserten Unterlagen erneut zur Prüfung einreichen kann.

3. Würdigung der Stellungnahmen

Wird nach dem Stellungnahmeverfahren ergänzt.

4. Bürokratiekostenermittlung

Durch den vorgesehenen Beschluss entstehen keine neuen bzw. geänderten Informationspflichten für Leistungserbringer im Sinne von Anlage II zum 1. Kapitel VerfO und dementsprechend keine Bürokratiekosten.

5. Schätzung der Studienkosten entsprechend 2. Kapitel § 22 Absatz 2 Satz 4 VerfO

Für die Fallzahl ist die Größe des nachzuweisenden Effekts maßgeblich. Diese hängt maßgeblich von der Operationalisierung des primären Endpunkts (hier: IPSS Score und Strikturfreiheit) ab.

Unter Annahme einer Effektstärke von beispielsweise 15 % (80 % der Teilnehmer erreichen den primären Endpunkt in der Interventionsgruppe, 65 % in der Kontrollgruppe), abgeleitet aus den Ergebnissen der Studien ROBUST- I[4] und ROBUST-II[5] sowie aus Daten zur Strikturfreiheit nach 12 Monaten in Abhängigkeit der Anzahl vorheriger Interventionen[6], ergibt sich als grobe Approximation eine Fallzahl von 400 Studienteilnehmern.

Eine konkrete Fallzahlkalkulation kann erst im Rahmen der genauen Studienplanung erfolgen.

Im Ergebnis von Informationen der Koordinierungszentren für Klinische Studien, dem Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen sowie dem DLR Projektträger (Projektmanagement für Erprobungen des G-BA) schätzt der G-BA die Kosten pro Teilnehmer

4 Urotronic. ROBUST I Pilot Study (ROBUST) [online]. 2020 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03014726.

5 Urotronic. Re-establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease (ROBUST-II) [online]. 2019 [Zugriff: 17.12.2020]. URL: https://clinicaltrials.gov/ct2/show/NCT03270384.

6 Heyns CF, Steenkamp JW, De Kock ML et al. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol 1998; 160(2): 356-358. https://dx.doi.org/10.1016/s0022-5347(01)62894-5.

auf Basis der Studiengröße und des studienbezogenen Mehraufwands (s. nachstehende Tabelle).

Studiengröße (n)	studienbezogener Mehraufwand		
	gering	Normal	hoch
klein (< 100)	8.000 €	10.000 €	12.000 €
mittel (100 bis < 500)	4.000 €	5.500 €	7.000 €
groß (≥ 500)	2.000 €	3.000 €	4.000 €

Entsprechend der o. g. Fallzahlschätzung handelt es sich um eine mittelgroße Studie (100 bis < 500). Der studienbezogene Mehraufwand wird als normal (hier etwa 5.500 € je Studienteilnehmer) eingeschätzt. Auf der Basis dieser Annahmen lassen sich geschätzte Studienkosten von 2,2 Millionen € berechnen.

6. Verfahrensablauf

Datum	**Gremium**	**Beratungsgegenstand/ Verfahrensschritt**
01.04.2021	Plenum	Einleitung des Beratungsverfahrens zur Erprobungs-Richtlinie gemäß § 137e SGB V
06.04.2021		Ankündigung des Beratungsverfahrens im Bundesanzeiger zur strukturierten Einholung von ersten Einschätzungen (gemäß 2. Kapitel § 6 VerfO) sowie zur Ermittlung weiterer betroffener Medizinprodukthersteller
08.07.2021	UA MB	Einleitung des Stellungnahmeverfahrens
TT.MM.JJJJ	*UA MB*	*Mündliche Anhörung*
TT.MM.JJJJ	*UA MB*	*Würdigung der Stellungnahmen und abschließende Beratung der Beschlussempfehlung*
	Plenum	*Abschließende Beratung und Beschlussfassung*
		Nichtbeanstandung i.R. d. Prüfung nach § 94 Abs. 1 SGB V des Bundesministeriums für Gesundheit
		Veröffentlichung im Bundesanzeiger
		Inkrafttreten

7. Fazit

Der Gemeinsame Bundesausschuss beschließt die Richtlinie zur Erprobung eines Medikamentenbeschichteten Ballondilatationskatheters zur transurethralen Behandlung von Harnröhrenstrikturen.

Berlin, den T. Monat JJJJ

Gemeinsamer Bundesausschuss
gemäß § 91 SGB V
Der Vorsitzende

Prof. Hecken

Stellungnahme zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung:

Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Stellungnahme der Deutschen Gesellschaft für Urologie, e.V.
Stellungnahme des Mandatsträger Prof. Dr. Tilman Kälble, Fulda

Zu § 1 Zielsetzung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k.

Zu § 2 Fragestellung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k.

Zu § 3 Population	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	Max. 2cm lange Rezidivstrikturen der anterioren Harnröhre sind die korrekte Studienpopulation. Bezüglich Subpopulationen sollte die Ätiologie „traumatisch vs. iatrogen“ (z. B. Katheterisierung, endoskopischer Eingriff) ebenso erfasst werden wie „Striktur geht nahtlos in den Sphinkter über“ oder „ist vom Sphinkter externus entfernt“. Die Subpopulationen müssen jedoch bei der Randomisierung keine Berücksichtigung finden.

Zu § 4 Intervention und Vergleichsintervention	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k. Zusatz: Als Verfahren zur Prädilatation sollte standardisiert die Urethrotomia interna bis in das Schleimhautniveau angegeben werden, um eine einheitliche „Prädilatation“ zu erreichen und gleichzeitig die genaue Länge der Enge noch einmal endoskopisch ermitteln zu können.

Zu § 5 Endpunkte	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	12 Monate sind ein guter Endpunkt, unbedingt sollte dieser jedoch nach 24 Punkten noch einmal wiederholt werden. Die IPSS-Score-Verbesserung um mind. 6 Punkte ist ein sinnvolles Maß, sollte jedoch nicht das alleinige Maß sein, da der IPSS-Score rein subjektive Verbesserungen misst und die Angaben somit zwangsläufig intra- und interindividuelle Schwankungen aufweisen. Unbedingt sollte die Uroflowmetrie präoperativ sowie nach 12 und 24 Monaten herangezogen werden zusammen mit der sonographischen Restharnbestimmung. Für die Beurteilung relevante Messergebnisse bei diesen beiden Erhebungsinstrumenten leiten sich aus deren Definition ab: Klinisch relevanter Restharn liegt dann vor, wenn mehr als 10% des Miktionsvolumens im Anschluss an die Miktion in der Blase verbleiben oder einfacher, wenn der Restharn höher als 100ml beträgt. Insofern sollte der Restharn nach der Intervention < als 10% des Miktionsvolumens oder <100ml absolut betragen. Bezüglich der Uroflowmetrie würde ich die Parameter „max. Flussgeschwindigkeit in ml/s“ sowie „Flusszeit“ prä- und postoperativ messen und die Differenzen dann als Studienergebnis ausweisen. Im Vorhinein anzugeben, welche Verbesserung, beispielsweise der max. Flussgeschwindigkeit, signifikant ist oder nicht, ist schwierig bis unmöglich, da sie unter anderem von der präoperativen Situation und auch von psychovegetativen Einflüssen abhängig ist. So wäre beispielsweise der Anstieg der max. Flussgeschwindigkeit von 3 auf 8ml/s eine Verbesserung um über 100%, wäre klinisch jedoch immer noch als hoch obstruktiv zu werten, wohingegen eine Verbesserung von 10 auf 15ml/s klinisch eine deutliche Verbesserung darstellt, obwohl die Verbesserung nur 50% beträgt.

Zu § 6 Studientyp und Beobachtungszeitraum	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k. Zusatz: Sollte der G-BA auf der Notwendigkeit einer Erprobungsstudie insistieren, so ist die Begründung §6 Abschnitt 1 bis 4 so korrekt bezüglich der Durchführung einer randomisiert kontrollierten Studie. Es ist meines Erachtens allerdings unbedingt zu überlegen, ob solch eine randomisierte Studie vor dem Hintergrund mittlerweile existierender wissenschaftlicher Daten überhaupt notwendig ist: Schließlich liegen 3-Jahresdaten aus der ROBUST-I-Studie vor (Virasoro et al, European Urology 2021; 79:555). Die Erfolgsrate der Methode Optilume-Katheter bei bulbären Rezidivstrikturen nach drei Jahren wurde mit bei 67 % und die Reinterventionsfreiheit mit 77 % bestimmt. Auch wurden dieses Jahr beim Europäischen Urologenkongress 6-Monatsdaten der ROBUST-III-Studie vorgelegt, in die 127 Patienten mit einer 2:1-Randomisierung prospektiv randomisiert eingeschlossen wurden. Beim Vergleich Optilume-Katheter versus der Standardtherapie war die Strikturfreiheitsrate nach sechs Monaten mit 76 % versus 27 % bei der Standardtherapie signifikant ($p < 0,001$) besser. Zudem war im Vergleichsarm die Reinterventionsrate signifikant höher. Es wäre vor dem Hintergrund dieser Ergebnisse dringend zu überlegen, ob nicht 1- bis 2-Jahresdaten der ROBUST-III-Studie abgewartet werden sollten und man auf die Kosten und den Aufwand einer weiteren randomisierten Studie verzichten kann. Schließlich legen die 3-Jahresdaten der ROBUST-I-Studie und die bisherigen Daten der ROBUST-III-Studie die Wirksamkeit des Optilume-Katheters nahe.

Zu § 7 Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k.

Zu § 8 Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Bitte nutzen Sie nach Möglichkeit für inhaltlich voneinander abgrenzbare Aspekte Ihrer Stellungnahme jeweils gesonderte Tabellenzeilen und fügen bei Bedarf weitere Tabellenzeilen hinzu. Vielen Dank.	o.k.

Voraussichtliche Teilnahme an der mündlichen Anhörung

Deutsche Gesellschaft für Urologie e.V., vertreten durch Prof. Dr. med. T. Kälble, Fulda		
Die Anhörung findet voraussichtlich am 26. August 2021 statt		
Teilnahmeoptionen	**Einladung**	**Ihre Rückmeldung zur Teilnahme**
Wir nehmen teil.	**Eine gesonderte Einladung wird Ihnen zugesandt**	
Wir können derzeit nicht sagen, ob wir an der Anhörung teilnehmen.	**Eine gesonderte Einladung wird Ihnen zugesandt**	
Wir nehmen nicht teil. Auch bei Terminänderungen für diese Anhörung möchten wir nicht teilnehmen.	**Sie werden nicht zur Anhörung eingeladen.**	**Wir nehmen nicht teil.**

Stellungnahme zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung:

Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Urotronic Inc. als Hersteller des für die Methode maßgeblichen Medizinprodukts *Optilume Drug-coated urology balloon catheter* Urotronic Inc. 2495 Xenium Lane North Plymouth, MN 55441 USA USA Kalms Consulting GmbH ist bevollmächtigt, Urotronic im Rahmen des Verfahrens nach §137h SGB V zu vertreten. Diese Vollmacht umfasst laut Nachricht des Gemeinsamen Bundesausschusses vom 13. April 2021 auch das Folgeverfahren.
05.08.2021

Zu § 1 Zielsetzung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Der Erfolg einer Erprobungsstudie hängt davon ab, dass eine ausreichende Zahl von Krankenhäusern an der Studie teilnimmt. Die zu untersuchende Methode hat nennenswert höhere Sachkosten als die Vergleichsmethode. Aus unserer Sicht ist die zu untersuchende Methode bisher im DRG-System nicht sachgerecht vergütet. Dennoch hat das InEK zuletzt einen NUB-Status 2 erteilt, so dass ein NUB-Entgelt nicht verhandelt werden kann. Wir würden es im Blick auf die zu erwartenden Anfragen für das Jahr 2022 begrüßen, wenn der G-BA mit Bezug auf die Erprobungsstudie das InEK nochmals auf diese Problematik aufmerksam machen könnte.	Im Rahmen des NUB-Verfahrens 2021 wurden dem InEK Daten übermittelt, gemäß denen die Kosten des Verfahrens die Kostenerstattung im aG-DRG-System um 81,5% bzw. zirka 1.600 Euro je Fall übersteigt. Es ist nicht zu erwarten, das Kliniken bereit sind, Fälle für eine Studie zu rekrutieren, wenn sie je Fall ca. 1.600 Euro Verlust zu erwarten haben. Daher stellt der aktuelle NUB-Status 2 ein wichtiges Rekrutierungshindernis für Erprobungsstudie dar.
Der Gemeinsame Bundesausschuss formuliert in Satz 4 der Zielsetzung, dass bei der Erstellung des Studienprotokolls ist das Wirtschaftlichkeitsprinzip zu beachten. Dem stimmt Urotronic selbstverständlich zu und schlägt vor, Satz 4 um einen Hinweis zu ergänzen, dass im Sinne des Wirtschaftlichkeitsprinzips ein adaptives Studiendesign erwogen werden sollte.	Der Option eines adaptiven Studiendesigns kommt im Zusammenhang mit der Behandlung von Rezidivharnröhrenstrikturen mittels Harnröhren-DCB besondere Bedeutung zu, weil die Charakteristik der Patientenpopulation im Hinblick auf die Anzahl vorheriger Behandlungen der Striktur maßgeblichen Einfluss auf das Auftreten erneuter Rezidive hat (Heyns, 1998). Je höher die mittlere Anzahl an vorherigen Eingriffen an einer Striktur ist, desto eher sind Rezidive zu erwarten und desto größer ist der zwischen den Studiengruppen zu erwartende Unterschied. Vorhersagen über die bezüglich der Anzahl an vorherigen Eingriffen zu erwartende Studienpopulation sind schwer zu treffen, da im

Zu § 1 Zielsetzung	
Stellungnahme / Änderungsvorschlag	**Begründung**
	Voraus nicht abschätzbar ist, wie einzelne Leistungserbringer, die an einer Erprobung teilnehmen werden, mit der vom G-BA in den Tragenden Gründen unter *2.5 zu §4 Intervention und Vergleichsintervention zu Absatz 2* geschilderten Situation umgehen werden. Der G-BA führt an dieser Stelle aus: „Die Vergleichsintervention ist die Urethrotomia interna. Gemäß internationaler Leitlinien sollen in der Rezidivsituation offen-chirurgische Verfahren aufgrund höherer Erfolgsraten angeboten werden. Auf Basis der durch das informationsübermittelnde Krankenhaus angeführten Zahlen der DRG-Statistik kommt der G-BA jedoch zu dem Schluss, dass aufgrund einer höheren Einsatzhäufigkeit die Urethrotomia interna im deutschen Versorgungs-kontext, vermutlich aufgrund der Patientenpräferenz, als Versorgungsstandard zu betrachten ist." Aufgrund des Einflusses der Studienpopulation auf die Rezidivrate und aufgrund der schwer vorhersehbaren Rekrutierung von Patienten in Bezug auf die Anzahl vorheriger Striktureingriffe durch die verschiedenen Leistungserbringer hält Urotronic es für besonders wichtig, auf die Option eines adaptiven Studiendesigns hinzuweisen. Ein adaptives Studiendesign bietet die Option, die Erprobung schneller abschließen zu können, und folgt somit dem Wirtschaftlichkeitsprinzip. Hinzu kommt, dass in dem Fall, dass die Erprobungsstudie die Resultate der Robust-III RCT bestätigt, die Methode schneller als Teil der Regelversorgung verankert werden kann.

Zu § 2 Fragestellung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic schließt sich dem Vorschlag von DKG, KBV und PatV an.	Die Begründung ist der Begründung zum § 3 Population zu entnehmen.
Im Dokument "Tragende Gründe" wird ausgeführt, dass der G-BA mit der in § 2 des Beschlussentwurfs definierten Fragestellung die am 1. April 2021 im Rahmen der Bewertung nach § 137h Absatz 1 Satz 4 SGB V festgestellte Erkenntnislücke adressiert. Urotronic möchte an dieser Stelle erneut herausstellen, dass aus der Sicht von Urotronic die Resultate der Robust-III Studie, einer prospektiven RCT, die dem G-BA bereits zur Verfügung gestellt wurden, und die in Kürze publiziert	Bei der mit dem Ziel der FDA-Zulassung durchgeführten ROBUST III-Studie handelt es sich um eine hochwertige RCT. Dies möchten wir im Folgenden kurz ausführen. • Die Randomisierung erfolgte stratifiziert durch permutierte Blöcke innerhalb eines Studienzentrums unter Verwendung eines elektronischen Datener-fassungssystems (EDC). Sie erfolgte unmittelbar vor Beginn des Behandlungs-/Kontrollverfahrens randomi-siert. Damit sind die adäquate Erzeugung der Randomisierungssequenz und die Verdeckung der Gruppenzuteilung gewährleistet. • Die Studienteilnehmer waren bis zur Erhebung des primären Studienendpunktes verblindet.

Zu § 2 Fragestellung	
Stellungnahme / Änderungsvorschlag	**Begründung**
werden, geeignet sind, die Erkenntnislücke zu schließen.	• Urotronic ist bewusst, dass die Nachuntersuchungen nicht verblindet waren. o Der primäre Endpunkt „Strikturfreiheit“ als ungehinderte Passage eines 16F Zystoskops ist jedoch ein objektives Kriterium, was das Verzerrungspotenzial begrenzt. o Bei dem IPSS handelt es sich um einen patientenberichteten Endpunkt. Ein erhöhtes Verzerrungspotenzial ist für diesen Endpunkt nur durch den Patienten zu erwarten, der jedoch verblindet ist. o Ebenso geht Urotronic davon aus, dass der Bedarf für eine Reintervention unabhängig von der Verblindung des Nachuntersuchers ist. • Urotronic ist sich der Tatsache bewusst, dass die Definition des Behandlungsverfahrens in der Kontrollgruppe (Ballondilatation, Urethrotomia interna oder Bougierung nach Ermessen des Behandlers) dazu führt, dass diese nicht genau dem Standardvorgehen im deutschen Gesundheitswesen (Urethrotomia interna) entspricht. Aufgrund der wegweisenden Publikation von Steenkamp, 1997, geht man jedoch davon aus, dass sich die Wirksamkeit und die Rezidivraten von Ballondilatation, Urethrotomia interna oder Bougierung bei der Behandlung von Strikturen nicht wesentlich unterscheiden. Diese Studie von Steenkamp ist nach wie vor wichtig für die aktuell gültigen Leitlinien, in denen Empfehlungen bezüglich Urethrotomia interna und Dilatationsverfahren ohne Unterscheidung zwischen den Verfahren ausgesprochen werden (Leitlinien der EAU, SIU und AUA). Aus diesem Grund ist Urotronic davon überzeugt, dass die Resultate der ROBUST III-Studie trotz der Vergleichsintervention, die scheinbar nicht dem Standardvorgehen in Deutschland entspricht, als Grundlage für eine Nutzenbewertung herangezogen werden können. Mittlerweile wurden erste Resultate der ROBUST-III Studie im Rahmen des Kongresses der EAU vorgestellt und ein publizierter Abstract liegt vor (Virasoro, 2021). Die Anzahl an vorherigen Strikturbehandlungen lag im Mittel 3,6, Die mittlere Strikturlänge betrug bei 1,7 cm. Die Resultate der 6-Monats Nachbeobachtung liegen vollständig vor, die 12-Monatsdaten sind noch nicht vollständig. Der Primäre Endpunkt „Strikturfreiheit nach 6 Monaten“ wurde gemäß publiziertem Abstract in der Interventionsgruppe in 76% der Patienten im Vergleich zu 27% in der Kontrollgruppe erreicht ($p<0,001$). Die Ergebnisse waren in Subgruppen mit ≥5 versus <5 vorherigen Strikturbehandlungen und für Längen <2cm versus ≥2cm konsistent. Die Resultate für *den Endpunkt Freiheit von einer erneuten Intervention waren in der Interventionsgruppe signifikant höher.*

Zu § 2 Fragestellung	
Stellungnahme / Änderungsvorschlag	**Begründung**
	Dem G-BA liegt der Studienbericht vom 27. April, 2021 vor, dem bislang noch nicht veröffentlichte Resultate zu weiteren patientenrelevanten Endpunkten zu entnehmen ist: • Time to treatment failure at 6 months • Änderung des mittleren IPSS über die Zeit • IPSS Responder Rate mit Responderschwellen von ≥ 50% bzw. ≥ 30% Verbesserung im Vergleich zum Ausgangswert. • IPSS-QoL
Darüber hinaus weist Urotronic an dieser Stelle auf die in Großbritannien in Zusammenarbeit mit dem National Institute for Health Research (NIHR) geplante Studie „Adjunctive Local Drug Treatment at the Time of Endoscopic Surgery for Recurrent Bulbar Urethral Stricture in Men (ReBUS)“ hin. Auch die Resultate dieser Studie werden aus Sicht von Urotronic geeignet sein, die nach § 137h Absatz 1 Satz 4 SGB V festgestellte Erkenntnislücke zu adressieren.	Bei der ReBUS-Studie handelt es sich um eine prospektive, multizentrische RCT, in die Männer mit einer Rezidivharnröhrenstriktur von bis zu 3 cm Länge eingeschlossen sind. Der primäre Endpunkt umfasst: Strikturrezidive auf der Grundlage der von den Patienten selbst gemachten Angaben und des klinischen Nachweises eines Wiederauftretens nach 24 Monaten. Drei Studiengruppen werden verglichen: • Die alleinige endoskopische Urethrotomia interna • Die endoskopische Urethrotomia interna mit lokaler Injektion von Mitomycin C • Ballondilatation mit dem Paclitaxel beschichteten DCB. Detailliertere Informationen zur ReBUS-Studie bzgl. Ein- und Ausschlusskriterien, Operationalisierung der Endpunkte, Stichprobengröße und Operationalisierung der Endpunkte sind den angefügten Dokumenten zu entnehmen (ReBUS-study; ReBUS-study endpoint assessment). Die Bestätigung der Finanzierung der Studie durch das NIHR wird Urotronic dem G-BA in Kürze zur Verfügung stellen.

Zu § 3 Population	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic schließt sich dem Vorschlag von DKG, KBV und PatV an, der die abschließende Definition der Studienpopulation gemäß Vorgaben der Erprobungsrichtlinie in die Hände der UWI legt.	In den Tragenden Gründen wird Folgendes ausgeführt: „Die Studienpopulation baut auf der in der Informationsübermittlung nach § 137h Absatz 1 SGB V durch das Krankenhaus definierten Patientenpopulation auf.“ Aus 2.3. der Beschreibung des Anwendungsgebiets in der Informationsübermittlung ergibt sich nicht notwendigerweise eine Begrenzung der Länge der Harnröhre auf 2 cm. Zum Zeitpunkt der Informationsübermittlung nach §137h entsprach die Begrenzung der Länge der Striktur dem aktuellen Zulassungsstatus des maßgeblichen Medizinprodukts. Im Februar 2021 erfolgte auf der Basis der Resultate der Robust-II-Studie eine Erweiterung der Indikation auf ein Strikturlänge von bis zu 3 cm. Die aktualisierte Gebrauchsinformation hat der G-BA mit Schreiben vom 5. Mai 2021 erhalten. Dieser Erweiterung der Indikation des maßgeblichen Medizinprodukts trägt auch die

Zu § 3 Population	
Stellungnahme / Änderungsvorschlag	**Begründung**
	Forschungsgruppe in England Rechnung, die in Kooperation mit NIHR die randomisierte ReBUS-Studie plant (Adjunctive Local Drug Treatment at the Time of Endoscopic Surgery for Recurrent Bulbar Urethral Stricture in Men), die aus Sicht von Urotronic geeignet sein wird, die Frage nach dem Nutzen der Methode zu beantworten. Aus diesen Gründen befürworten wir den Vorschlag von DKG, KBV und PatV, die Entscheidung über die Patientenpopulation im Rahmen der Vorgaben der Erprobungsrichtlinie in die Hände der UWI zu legen.

Zu § 4 Intervention und Vergleichsintervention	
Stellungnahme / Änderungsvorschlag	**Begründung**
Wir begrüßen ausdrücklich, dass die Festlegung des näheren Vorgehens zur Notwendigkeit und Art der Prädilatation in die Hände der UWI gelegt wird. Im Dokument tragende Gründe wird ausgeführt, dass es der Ärztin oder dem Arzt entweder freigestellt werden kann, im Rahmen der Behandlung individuell zu entscheiden, ob und ggf. mit welchem Verfahren eine Prädilatation der Striktur erfolgen soll, oder die UWI legt entsprechend dem aktuellen Stand der Wissenschaft ein einheitliches Vorgehen fest. Wir möchten an dieser Stelle ergänzend darauf hinweisen, dass die individuelle Entscheidung über das Vorgehen bezüglich der Prädilatationsmethode bei der Anwendung des Harnröhren-DCB durch die Ärztin oder den Arzt dem aktuellen Stand der Wissenschaft entspricht.	Die Studienprotokolle der Studien ROBUST-I, -II und -III haben jeweils eine individuelle Entscheidung über die Notwenigkeit zur Prädilatation sowie das Prädilatations-verfahren durch den behandelnden Arzt oder Ärztin vorgesehen. Aus der Literatur geht hervor, dass die verschiedenen Dilatationsmethoden (Aufbougierung mit Katheter, Ballondilatation, Urethrotomia interna) zu ähnlichen Ergebnissen führen (Steenkamp, 1997, MacDiarmid, 2000, Santucci, 2010), was auch in der ROBUST-III-Studie bestätigt wurde. Resultate einer Subgruppenanalyse zum primären Endpunkt der Robust-III Studie nach der Prädilatations- bzw. Dilatationsmethode finden Sie unten. Primärer Endpunkt war die Strikturfreiheit nach 6 Monaten. Eine Striktur galt als beseitigt, wenn ein flexibles 16F-Zystoskop oder ein 14F-Gummikatheter durch die Striktur geführt werden konnte. Es gab keinen signifikanten Unterschied bei den Ergebnissen für den primären Endpunkt zwischen den Dilatationsmethoden für den Kontrollarm (p=0,45), und die Ergebnisse begünstigten den Optilume DCB unabhängig von der Prädilatations- oder Dilatationsmethode.

Dilatations Methode	Kontrolle (N=48)	Optilume (N=79)	Differenz (95% CI)[1]
Urethrotomia interna[3]	2/12 (16,7%)	5/6 (83,3%)	66,7% (15,2%, 95,7%)
Aufbougierung mit Katheter	1/7 (14.3%)	-	-
Unbeschichteter Ballonkatheter	8/22 (36,4%)	45/61 (73,8%)	37.4% (13,2%, 59,3%)

Zu § 4 Intervention und Vergleichsintervention	
Stellungnahme / Änderungsvorschlag	**Begründung**
	Test innerhalb der Gruppe [2] | p=0,45 | p>0,99 | [1]Confidence intervals for the difference between groups estimated using the exact approach [2]Test for differences within each arm by Fisher's Exact test [3] Diese Reihe umfasst Patienten, die die Urethrotomia interna als Prozedur in der Kontrollgruppe oder als Prädilationsverfahren vor der Intervention erhalten hatten.

Zu § 5 Endpunkte	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic stimmt der Festlegung des primären Endpunkts, der eine Kombination von klinische signifikanter Symptomverbesserung und Freiheit von klinisch indizierten Reinterventionen vorsieht, zu.	
In dem Dokument „Tragende Gründe" fordert der G-BA als Responderkriterium eine IPSS-Differenz von >15 % der Skala, was einer Verbesserung von mindestens 6 Punkten auf dem IPSS-Fragebogen entspricht (max. Score 36). Urotronic möchte darauf hinweisen, dass die minimale klinisch relevante Differenz für den IPSS-Score vom Ausgangswert abhängen kann (Barry et al. 1995), ist sich aber bewusst, dass sich diese Publikation auf eine gutartige Vergrößerung der Prostata und deren Symptomatik bezieht. Ein klinisch sinnvoller Schwellenwert hängt also vom IPSS-Ausgangswert ab. Urotronic schlägt daher vor, anstelle eines festen Wertes einen Schwellenwert von >30% Verbesserung gegenüber dem Ausgangswert zu wählen. Dieser Schwellenwert entspricht auch dem von der US-amerikanischen Food and Drug Administration empfohlenen Schwellenwert für Studien zu Produkten für die Behandlung von BPH. Dieser Schwellenwert basiert auf der Arbeit von Roehrborn und Kollegen aus dem Jahr 2012, die den Zusammenhang zwischen der Symptomverbesserung nach IPSS und der Patientenzufriedenheit ermittelt haben.	Urotronic ist der Ansicht, dass ein relativer Schwellenwert für klinische Verbesserung eine bessere Aussage über das gesamte Spektrum an Patienten erwarten lässt, als ein fester Wert, da die Patientenzufriedenheit je nach Schweregrad der anfänglichen Symptomwerte beeinflusst werden kann. Urotronic räumt ein, dass die meisten Arbeiten zur Festlegung der Schwellenwerte für eine Verbesserung auf Patienten mit symptomatischer BPH beruhen. Deren Symptomatik ist jedoch der von Harnröhrenstrikturen (Blasenauslassobstruktion, die zu Symptomen des unteren Harntrakts (LUTS) führt) so ähnlich, dass die Ergebnisse im Allgemeinen übertragbar sein dürften.

Zu § 6 Studientyp und Beobachtungszeitraum	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic ist generell mit dem vorgeschlagenen Studientyp und dem Beobachtungszeitraum einverstanden.	

Zu § 7 Anforderungen an die Qualität der Leistungserbringung im Rahmen der Erprobung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic stimmt den Anforderungen zu.	

Zu § 8 Anforderungen an die Durchführung, die wissenschaftliche Begleitung und die Auswertung der Erprobung	
Stellungnahme / Änderungsvorschlag	**Begründung**
Urotronic stimmt den Anforderungen zu.	

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ReBUS-study

ReBUS-study endpoint assessment

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Voraussichtliche Teilnahme an der mündlichen Anhörung

Bitte klicken Sie hier und geben dann den Namen der stellungnehmenden Organisation ein.		
Die Anhörung findet voraussichtlich am 26. August 2021 statt		
Teilnahmeoptionen	**Einladung**	**Ihre Rückmeldung zur Teilnahme**
Wir nehmen teil.	**Eine gesonderte Einladung wird Ihnen zugesandt**	**Bitte klicken Sie hier und geben dann "Wir nehmen teil." ein**
Wir können derzeit nicht sagen, ob wir an der Anhörung teilnehmen.	**Eine gesonderte Einladung wird Ihnen zugesandt**	**Bitte klicken Sie hier und geben dann "Wir nehmen teil." ein**
Wir nehmen nicht teil. Auch bei Terminänderungen für diese Anhörung möchten wir nicht teilnehmen.	**Sie werden nicht zur Anhörung eingeladen.**	**Bitte klicken Sie hier und geben dann "Wir nehmen nicht teil." ein**

UKE HAMBURG
Klinik und Poliklinik für Urologie

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UP
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Unabhängige Stellungnahme zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung gemäß § 137 e SGB V: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Sehr geehrte Damen und Herren,

beiliegend erhalten Sie unsere unabhängige Stellungnahme zur Kenntnisnahme.

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Gemeinsamer Bundesausschuss

Unabhängige Stellungnahme zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Richtlinie zur Erprobung gemäß § 137 e SGB V:

Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen

Im Folgenden dürfen wir die Möglichkeit nutzen eine unabhängige Stellungnahme zu o.g. Beschlussentwurf des gemeinsamen Bundesausschusses vorzulegen. Hintergrund dieser Stellungnahme ist die Einbindung als NUB-Antrag-stellende Klinik als anerkanntes klinisches und wissenschaftliches Zentrum der rekonstruktiven Urologie in Deutschland.

Der G-BA fordert zum Nachweis der Überlegenheit des medikamentenbeschichteten Ballondilatationskatheters (Optilume™) eine randomisierte kontrollierte Studie mit Einschluss von ca. 400 Männern mit kurzstreckiger (≤2 cm) Rezidivstriktur der anterioren Harnröhre.

Nach kritischer Prüfung der vorhandenen Evidenzlage und vor dem Hintergrund der aktuell vorgestellten und publizierten Interimsanalysen der ROBUST-III-Studie -die bislang in dem G-BA Beschlussentwurf, soweit beurteilbar, nicht berücksichtigt wurden- halten wir die Durchführung der Erprobung in der geforderten Form und Umfang für nicht sinnvoll, nicht notwendig und realistisch auch nicht durchführbar.

Begründungen:

(1) Es existiert für die Urethrotomia interna nach Sachse/Sichturethrotomie in der Rezidivsituation eine breite Evidenzlage bezüglich der zu erwartenden Erfolgsraten.[1] In diesem Rahmen existiert seit letztem Jahr Level-1-Evidenz aus der randomisiert-kontrollierten „OPEN"-Studie. In dieser wurden 220 Patienten mit Rezidivstriktur randomisiert in Urethrotomia interna (n=112) versus Urethroplastik (n=108).[2] Nach 24 Monaten erlitten 35% der Patienten, die per Urethrotomie behandelt wurden ein Rezidiv und 26% mussten sich einer Reintervention unterziehen.[2] Diese Daten bestätigen die Ergebnisse zahlreicher retrospektiver Serien.

(2) Aus der ROBUST-I-Studie existieren mittlerweile 3-Jahres-Follow-up-Daten von 43 Patienten, die bei bulbärer Rezidivstriktur (≤2 cm) und bis zu vier vorherigen endoskopischen Therapien mit dem Optilume™ Ballondilatationskatheter behandelt wurden. Die Erfolgsrate nach 3 Jahren lag bei 67%. Die Reinterventionsfreiheit nach 3 Jahren lag bei 77%.[3]

(3) Mit den Daten aus der ROBUST-III-Studie liegen nun auch direkte Vergleichsdaten aus einer randomisiert-kontrollierten Studie vor. Insgesamt wurden 127 Patienten in einer multizentrischen Studie eingeschlossen, die Randomisierung erfolgte in die Therapiearme Optilume™-Ballondilatationskatheter (n=79) gegen die Standardtherapie (Bougierung, klassische Ballondilatation oder Urethrotomie; n=48). Auch wenn noch keine Langzeitdaten vorliegen, so liegen Ergebnisse nach vollständigem 6 Monate Follow-up vor. Die Strikturfreiheit nach 6 Monaten lag bei 76% (Optilume™) versus 27% (Standardtherapie; p<0.001). Zudem war die Reinterventionsfreiheit im Optilume™-Arm im Vergleich zum Standardarm signifikant höher, dies auch über die bisher vorhandenen 1-Jahres-Daten.[4]

Mit den aktuellen Interimsdaten aus ROBUST-III liegen Ergebnisse einer prospektiven, randomisierten, multizentrischen Studie vor, die soweit ersichtlich bisher bei der Beurteilung des G-BA nicht berücksichtigt wurden. Das Studiendesign deckt sich hierbei in weiten Teilen mit der geforderten Erprobungsstudie. Die von GBA vorgeschlagene Populationsgröße von 400 Männern halten wir für eine randomisiert-kontrollierte Studie bei Harnröhrenstrikturen für unrealistisch. Die wenigen vorliegenden randomisierten Daten aus der Harnröhrenchirurgie rekrutierten selten mehr als 120 Patienten.[2] In endoskopisch vergleichenden Studien i.d.R. < 100 Probanden. In ROBUST-III wurden 127 Patienten rekrutiert, was damit eine im Vergleich hohe und nach unserem Kenntnisstand die bis dato größte prospektiv randomisierte Kohorte darstellt.

Wir danken für die Möglichkeit zur Stellungnahme und hoffen die Diskussion des Beschlusses aus klinisch-wissenschaftlicher Perspektive ergänzen zu können.

Mit freundlichen Grüßen

Prof. Dr. med. Margit Fisch	Dr. med. Phillip Marks	PD Dr. med. Malte Vetterlein
- Klinikdirektorin -	- Oberarzt -	- Facharzt -

Literaturangaben

[1] Lumen N, Campos-Juanatey F, Greenwell T, et al. European Association of Urology Guidelines on Urethral Stricture Disease (Part 1): Management of Male Urethral Stricture Disease. European Urology 2021. In press.

[2] Goulao B, Carnell S, Shen J, et al. Surgical Treatment for Recurrent Bulbar Urethral Stricture: A Randomised Open-label Superiority Trial of Open Urethroplasty Versus Endoscopic Urethrotomy (the OPEN Trial). European Urology 2020;78:572-580.

[3] Virasoro R, Delong J, Estrella R, et al. The optilume drug coated balloon for recurrent anterior urethral strictures: 3-year results for the ROBUST I study. European Urology 2021;79:S555.

[4] Virasoro R, Delong J, Coutinho K, Robertson K, D'Anna R, Elliott SP. ROBUST III: Interim results of a randomized trial of the optilume drug coated balloon for anterior urethral strictures. European Urology 2021;79:S554.

Wortprotokoll

Gemeinsamer Bundesausschuss

einer Anhörung zum Beschlussentwurf des Gemeinsamen Bundesausschusses über eine Erprobungs-RL: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen (BVh-20-002)

Vom 23. September 2021

Vorsitzende:	Frau Dr. Lelgemann
Beginn:	11:00 Uhr
Ende:	11:30 Uhr
Ort:	Videokonferenz des Gemeinsamen Bundesausschusses Gutenbergstraße 13, 10587 Berlin

Teilnehmer der Anhörung

Kalms Consulting GmbH (vertritt Urotronic):
Frau Dr. Schröder
Frau Dr. Knorr

Deutsche Gesellschaft für Urologie e. V.(DGU):
Herr Dr. Philip Marks

Beginn der Anhörung: 11:00 Uhr

(Die angemeldeten Teilnehmer sind der Videokonferenz beigetreten.)

Vorsitzende Frau Dr. Lelgemann: Meine Damen und Herren, ich darf Sie alle ganz herzlich – und natürlich vor allen Dingen unsere Gäste – im Namen des Unterausschusses Methodenbewertung zum Unterausschuss Methodenbewertung begrüßen.

Ich darf Sie ganz herzlich begrüßen zu unserer Anhörung zur Richtlinie zur Erprobung gemäß § 137e Abs. 1 SGB V, und zwar: Medikamentenbeschichteter Ballondilatationskatheter zur transurethralen Behandlung von Harnröhrenstrikturen.

Einige kurze Vorbemerkungen zu dieser Anhörung. Ich gehe davon aus, dass Sie damit einverstanden sind, dass wir von dieser Anhörung ein Wortprotokoll erzeugen und deswegen diese Anhörung aufzeichnen. Falls nicht, haben Sie jetzt die Möglichkeit zu wiedersprechen – was ich nicht hoffe.

Zweitens bitte ich Sie, die üblichen technischen Regularien zu beachten. Wer gerade nicht spricht, schaltet bitte sein Mikrofon aus. Melden können Sie sich jederzeit über den Chat.

Ansonsten der Hinweis, dass wir uns für Ihre Stellungnahmen bedanken, die wir gelesen, durchdacht und verarbeitet haben. Von daher ist es also nicht erforderlich, dass Sie Ihre Stellungnahme hier noch einmal wiedergeben, sondern vielleicht auf ganz besondere Punkte abheben und wir dann die Möglichkeit haben, so Fragen sind, noch Fragen an Sie zu richten. Das wäre der Ablauf dieser Anhörung. – Vielen Dank.

Ich würde beginnen mit der Deutschen Gesellschaft für Urologie. Herr Dr. Marks, Sie haben das Wort.

Herr Dr. Marks (DGU): Schönen guten Morgen! Ich weiß nicht, inwiefern unsere Stellungnahme allen zugänglich war.

Vorsitzende Frau Dr. Lelgemann: Ich kann Ihnen versichern: Alle haben alle Stellungnahmen.

Herr Dr. Marks (DGU): Das ist perfekt, aber ich fasse ganz kurz zusammen, was uns in der Stellungnahme oder in der Forderung des G-BAs aufgefallen war.

Zu zwei Punkten haben wir Stellung genommen, zum einen aus unserer Expertise hinsichtlich dessen, wie lange so eine Rekrutierungszeit für die geforderte Studie mit 400 Patienten dauert. Da hatten wir gesagt, dass wir es mitunter sogar als unrealistisch betrachten würden, das so zu machen. Ich kann gleich ein paar Beispiele nennen, was solche Studien bisher rekrutiert haben oder über welche Zeiträume wir sprechen, so viel Patienten zu gewinnen, um sie zu analysieren.

Das andere war die für uns noch nicht so dargestellte Betrachtung einer bereits durchgeführten multiinstitutionalen Beobachtung, der ROBUST-III-Studie, wo der Optilume-Katheter schon zur Anwendung kam in einer sehr nah an dem geforderten Design vollführten Studie mit Randomisierung und – ich glaube – insgesamt 127 Patienten.

Von daher denken wir, dass die Betrachtungen und das, was noch vom G-BA gefordert werden kann, doch noch einmal neu evaluiert werden sollte.

Vorsitzende Frau Dr. Lelgemann: Vielen Dank erst einmal für diese kurze Stellungnahme. – Ich gebe jetzt erst einmal den weiteren Gästen Gelegenheit und eröffne dann die Fragerunde.

Frau Dr. Schröder oder Frau Dr. Knorr, wer von Ihnen möchte beginnen?

Frau Dr. Schröder (Kalms Consulting GmbH, vertritt Urotronic): Sehr geehrte Frau Dr. Lelgemann! Sehr geehrte Damen und Herren! Ich werde im Namen von Kalms Consulting bzw. von Urotronic hier Stellung nehmen. Ich beginne zunächst mit den Neuigkeiten im Vergleich zu unserer schriftlichen Stellungnahme:

Das eine ist: Urotronic wird in Kürze ein Manuskript der Resultate der ROBUST-III-Studie nach einem Jahr Nachbeobachtungszeit einreichen. Das habe ich jetzt ganz frisch bekommen. Ich denke, in zwei Wochen in etwa wird es eingereicht werden. Und wie Herr Dr. Marks schon ausführte: Es ist eine randomisierte Studie, in der die Behandlung von Harnröhrenstrikturen mittels medikamentenbeschichteter Ballonkatheter mit dem Standardvorgehen zur Behandlung von Harnröhrenstrikturen verglichen wird. Ich komme darauf gleich zu sprechen.

Zunächst die zweite Neuigkeit: Sie besteht darin, dass das NIHR in Großbritannien aufgrund der Pandemiesituation jetzt doch die Finanzierung von Studien, die nicht direkt im Kontext mit der Pandemie stehen, abgelehnt hat. Das heißt, die ReBUS-Studie – die Finanzierung – ist zunächst abgelehnt. Der Studienleiter plant im nächsten Jahr eine erneute Einreichung, aber das hat für die jetzt anstehende Entscheidung natürlich keine Relevanz mehr.

Umso wichtiger ist die ROBUST-III-Studie, und jetzt komme ich wieder auf jenes Manuskript zurück: Auf der Basis dieses Manuskripts sehen wir nun – und das ist neu im Vergleich mit dem, was der G-BA ja schon in Abstracts bzw. auch im Studienbericht erhalten hat: die Endpunkte oder einen vollständigeren Datensatz für den Endpunkt Freiheit von Reinterventionen nach einem Jahr. Und das Resultat der Kaplan-Meier-Schätzer lag in der Interventionsgruppe bei gut 83 Prozent der Patienten, die keine Reintervention benötigten, im Vergleich zur Kontrollgruppe, wo es knapp 22 Prozent waren. Der Unterschied ist hochsignifikant, und wir werden das Manuskript dem G-BA dann direkt nach der Anhörung übermitteln.

An dieser Stelle möchte ich einen Kernaspekt unserer Stellungnahme kurz herausstellen. Der G-BA möchte mit der Erprobungsstudie ja eine Erkenntnislücke schließen, und Urotronic ist der Auffassung, dass mit der ROBUST-III-Studie auch aufgrund ihres Studiendesigns bereits eine Studie nicht nur durchgeführt wird, sondern sogar bereits deren Resultate vorliegen, um diese Erkenntnislücke zu schließen.

Wir sehen es so, dass diese Studie die überwiegende Mehrzahl der Qualitätskriterien bezüglich der Ergebnissicherheit auf Studien- und Endpunktebene erfüllt. Das haben wir ja auch schon schriftlich ausgeführt und gehen deshalb an dieser Stelle nicht weiter darauf ein.

Ich möchte an dieser Stelle einfach auch noch einmal die Situation von Patienten mit einer Harnröhrenstriktur in den Vordergrund stellen, vor allen Dingen mit einer Rezidivharnröhrenstriktur. Die haben jetzt die Wahl zwischen einem minimalinvasiven Verfahren, wo die Rezidivrate je nach Anzahl der vorhergehenden Behandlungen bei 70 Prozent oder höher liegt, oder eben einem rekonstruktiven Verfahren, dessen Erfolgsrate bei 80 bis 95 Prozent liegt.

Die Patienten präferieren vermutlich trotz höherer Erfolgsraten bei rekonstruktiven Verfahren jedoch eher minimalinvasive Verfahren. Diese Vermutung hat der G-BA ja auch in den Tragenden Gründen für den Beschlussentwurf ausgeführt. Diesen Patienten kann jetzt also erstmals gemäß den Resultaten der ROBUST-III-Studie wirklich ein minimalinvasives Verfahren mit einer deutlich niedrigeren Rezidivrate angeboten werden. Vor dem Hintergrund sehen wir es einfach als erstrebenswert an, dass den Patienten auch in der Regelversorgung diese Option angeboten werden kann und nicht noch vier bis fünf Jahre für eine Erprobungsstudie ins Land gehen.

Dann noch Anmerkungen für den Fall, dass der G-BA dennoch zu der Schlussfolgerung kommt, dass eine Erprobungsstudie unverzichtbar ist. Da haben wir einige Anmerkungen in der Stellungnahme, aber auf die gehe ich jetzt nicht weiter ein; das kann man gegebenenfalls in Fragen adressieren. Ich möchte abschließend aber auch noch einmal darauf hinweisen, dass natürlich der aktuell bestehe NUB-Status 2 einer erfolgreichen Rekrutierung in einer Erprobungsstudie im Weg steht. Wir hatten – wie die DGU, wie ich gerade vernommen habe – da ohnehin schon Bedenken geäußert, und das wird dadurch verschärft.

Vorsitzende Frau Dr. Lelgemann: Vielen Dank, Frau Dr. Schröder für die Beantwortung unserer antizipierten Fragen und die entsprechenden Darlegungen. – Frau Dr. Knorr, möchten Sie ergänzen?

Frau Dr. Knorr (Kalms Consulting GmbH, vertritt Urotronic): Nein, ich habe dem erst einmal nichts hinzuzufügen.

Vorsitzende Frau Dr. Lelgemann: Okay. Vielen Dank. – Dann würde ich die Fragerunde für die Mitglieder des Unterausschusses eröffnen. Wie gesagt, einige Fragen sind durch Ihre Darstellung im Prinzip schon beantwortet. – DKG. Bitte, Herr Brenske.

DKG: Uns würde noch interessieren, Sie haben jetzt ja von diesem Manuskript gesprochen, wann denn mit der Publikation dieser Daten zu rechnen ist, denn es sind ja möglicherweise da Aspekte enthalten, die unsere Entscheidung beeinflussen könnten, wie wir mit dem Erprobungsverfahren hier fortfahren oder eben auch nicht.

Frau Dr. Schröder (Kalms Consulting GmbH, vertritt Urotronic): Wann die Publikation genau erfolgen wird, kann ich Ihnen nicht sagen. Die Einreichung steht recht unmittelbar bevor. Mein Kenntnisstand ist: Es ist eine ziemlich finale Version. Alle Autoren müssen noch einmal draufschauen, und dann soll es eingereicht werden. Aber in der jetzigen Version würde ich es Ihnen einfach nach der Sitzung zukommen lassen.

Das Unternehmen sagt mir, es rechnet nicht mehr mit nennenswerten Änderungen. Den Studienbericht haben Sie ja ohnehin. Er steht ja seit April so, wie er ist. Und soweit es noch einmal eine kleine Aktualisierung am Manuskript gibt, was aber schätzungsweise nichts Großes sein wird, wird das dann auch folgen. Beantwortet das die Frage?

Vorsitzende Frau Dr. Lelgemann: Vielen Dank, Frau Schröder. – Dann übergebe ich an den GKV-SV. Frau Kuhnt.

GKV-SV: Ich habe noch zwei Fragen an Herrn Marks für den Fall, dass wir tatsächlich unsere Erprobungsstudie dann doch ins Leben rufen müssen.

Sie hatten als DGU ja gesagt, die Strikturlänge, die wir betrachten sollen, sollte maximal zwei Zentimeter betragen. Wir überlegen, auch noch Strikturlängen zwischen zwei bis drei Zentimetern mit zu betrachten. Wie sehen Sie das aus fachlicher Sicht? In diesem Zusammenhang würden wir dann mit der Urethrotomia interna, die wir ja hier als Vergleichsintervention gewählt haben, in Probleme kommen. Müsste man dann doch shiften zu einem rekonstruktiven Verfahren?

An der Stelle gleich meine zweite Frage: Die DGU hatte sich ja auch geäußert, sie würde raten, dass wir das Prädilatationsverfahren konkretisieren, ganz klar sagen: Es sollte eine Urethrotomia interna gemacht werden. – Mich würde interessieren, was denn aus Ihrer Sicht dagegen spräche, dass wir das der UWI freistellen?

Vorsitzende Frau Dr. Lelgemann: Vielen Dank, Frau Kuhnt. Kleiner Hinweis für nachher: Sie sind sehr, sehr leise. Man kann Sie kaum verstehen. – Herr Marks, Sie haben das Wort.

Herr Dr. Marks (DGU): Die Fragen passen gut zusammen, vielen Dank. Das ist nämlich ein Punkt. Wenn wir über eine randomisierte multizentrische Studie sprechen, dann müssen wir uns ja ein bisschen auf das beziehen, was wir bisher wissen. Zum einen glauben wir, dass das Verfahren des Optilume-Katheters wenn, dann verglichen werden sollte mit dem Standardverfahren der DVIU, also der Sichturethrotomie, wir glauben nicht, dass ein Dilatationsverfahren (einbezogen werden sollte), weil die bis heute ja auch kaum in Studien suffizient verglichen worden ist mit dem DVIU, also mit der Sichturethrotomie an sich. Das heißt, da machen wir ein Feld auf, was wir relativ schwer mit dem wissenschaftlichen (akustisch unverständlich) vergleichen können.

Was Ihre Frage zur Strikturlänge angeht, so konnte sich in vielerlei Studien zeigen lassen, dass die Strikturlänge auch im Bereich von einem Zentimeter deutlich auf das langfristige

postoperative Ergebnis Einfluss nimmt. Bei ein bis zwei Zentimetern sind wir bei den angesprochenen ungefähr 70 Prozent in der Erstbehandlungssituation auch für die Sichturethrotomie, bei zwei bis drei Zentimetern bei knapp 50 Prozent, zumindest in der Studie von Barbagli et al.

Ähnliches gilt dann auch für das, was wir als Zweites gesagt haben: ob wir das Prädilatationsverfahren dem Operateur freistellen.

Wir hatten gesehen, dass in der ersten Idee knapp 400 Patienten randomisiert werden sollten. Wenn wir die Gruppen immer breiter machen, müssen wir ja für jedes Verfahren selbst das gleiche angewendete Prädilatationsverfahren in die Auswertung hineinnehmen, um dann viele Subgruppenanalysen zu machen.

Da wir glauben, dass die Standardtherapie die Sichturethrotomie ist, wenn wir über endoskopische Strikturtherapeutika sprechen, in den Bereichen, wo auch der Optilume-Katheter angewendet werden kann – Dilatation von anderen Strikturen jetzt einmal außen vor gelassen –, dann glaube ich, dass wir besser fahren, wenn wir den Standard gegen den Standard plus des Optilume-Katheterverfahrens nutzen und nicht Dinge ausprobieren oder mit in diese Subgruppen einführen, die gar nicht unbedingt dem wissenschaftlichen Standard entsprächen. Das ist der Grund, warum wir da zurückhaltend sind und nicht sagen: Wir können alle Strikturen bis drei Zentimeter dann einbeziehen. – Denn dann müssten wir nachher, so, wie sich das bisher in den Daten liest – da gab es sogar schon multivariate Analysen und Reviews, wo man gesehen hat, dass wirklich für jeden Zentimeter bestimmte hazard ratios errechnet werden konnten –,dann auch in Zentimeterschritten die Subgruppen bilden. Und da die Sichturethrotomie bis zu zwei Zentimetern empfohlen wird, ist das für uns eine Strikturlänge, die wir da als gegeben für die Optilume-Katheterisierung betrachten.

Vorsitzende Frau Dr. Lelgemann: Vielen Dank, Herr Dr. Marks. Frage, glaube ich, ausreichend beantwortet, Frau Kuhnt, ohne Ihnen vorgreifen zu wollen. – Gut.

Gibt es Ergänzungen seitens Frau Dr. Schröder oder Frau Dr. Knorr zu diesem Thema? – Wenn das nicht der Fall ist, würde ich an den nächsten Fragenden weitergeben. Aber selbstverständlich könnten Sie auch noch ergänzen. Oder wir lassen erst einmal weitere Fragen zu und sammeln am Ende noch einmal. – KBV, Herr Adam bitte.

KBV: Vielen Dank für die Ausführungen bislang. Wir hätten noch eine Frage an Herrn Marks, insbesondere auch noch einmal mit Blick auf die ROBUST-III-Studie und die Übertragbarkeit dieser Daten auf den deutschen Versorgungskontext, denn ich habe da auch gerade vielleicht einen kleinen Widerspruch herausgehört.

Wir fragen uns, ob die ROBUST-III-Studie geeignet ist für die Bewertung des deutschen Versorgungskontextes, weil hier ja vorne nicht die Urethrotomia interna durchgeführt wird und dort im Vergleichsinterventionsarm ja drei Interventionen möglich sind, eben auch die Aufbougierung oder ein Ballonkatheter ohne Beschichtung, und wir insofern bislang noch schwer beurteilen können, inwiefern diese Daten dann auf Deutschland, wo eben vornehmlich die Urethrotomia interna durchgeführt wird, übertragbar sind. Wie vergleichbar sind diese unterschiedlichen Aufdehnungsverfahren untereinander?

Vorsitzende Frau Dr. Lelgemann: Das ist natürlich **die** Frage, insbesondere vor dem Hintergrund, dass die andere Studie jetzt erst einmal nicht laufen wird.

Herr Dr. Marks (DGU): Darauf gehe ich gern ein. Im internationalen Kontext gab es europäische Guidelines für die Harnröhrenstrikturbehandlung jetzt erstmalig in den letzten zwei Jahren. Das heißt, dieser wissenschaftliche Kontext in der Behandlung von Strikturen und die Standardisierung sind nicht ganz einfach.

Die Ballondilatation mit normalen Ballons – nicht beschichtet – ist ein Verfahren, was nirgendwo verboten ist und wo auch niemand sagt: Das kann man nicht tun. – Das ist ein

normales Aufdilatationsverfahren. Aber wir wollen ja zeigen, dass etwas besser ist, und wir glauben einfach, dass es dann wichtig ist, sich die richtigen Subgruppen da herauszulesen.

Was die Gesamtergebnisse angeht: Da die meisten Studien die Ergebnisse von Sichturethrotomien berichten, alles keine randomisierten Vergleichsstudien sind, sondern entweder retrospektiv, zum Teil auch prospektiv erhobene Datensätze sind, die ausgewertet werden, sich aber auch in den systematischen Reviews decken von ihren Erfolgsaussichten – mitunter sind da große Diskrepanzen zu sehen, aber gerade was die Behandlung im ersten und im Rezidivsetting angeht – wir reden ja hier vom Rezidivsetting –, wissen wir, dass die normale Erfolgsraten weit unter 50 Prozent liegen im Rezidivsetting.

In den ROBUST-Studien haben wir mitunter mehr als zwei oder drei Vorbehandlungen, wo es Studien gibt, die sagen, dass da eine Sichturethrotomie – und ich sage mal, das ist das invasivste Verfahren von Ballondilatation und normaler Dilatation – keine langfristigen Erfolge abbildet.

Was die Datenbetrachtung angeht, ist die Erfolgsrate nach sechs Monaten von den 76 Prozent aus der ROBUST-III-Studie vielversprechend, insbesondere wenn man – ich habe die Abstracts auf den Kongressen gesehen, da ist ja auf jeden Fall auch eine signifikante Reinterventionsnotwendigkeit herabgesetzt in dem Arm der Optilume-Katheter selbst – sieht, dass die Rezidive gerade in der Rezidivsituation in dem größten Teil im ersten Jahr zu finden sind. Also zumindest sind das die berichteten Daten: Zwischen 50 und 60 Prozent, manche sagen, sogar noch mehr Rezivivstrikturen finden wir nach den ersten 12 Monaten, sodass man zumindest aus den Gesamtergebnissen aus der Studie schon etwas lesen kann.

Die Behandlung selbst: Da muss man natürlich auch immer sagen, bei welcher Striktur, in welcher Lage welches Verfahren wo angewendet wird, das ist auch aus den Studien natürlich schwer zu sagen; da müsste sich jeder einzelne Operateur äußern, in welcher Situation er was macht. Das würde ja aber tatsächlich auch in der geforderten Erprobungsstudie schwierig, desto mehr Arme man dafür nimmt.

Vorsitzende Frau Dr. Lelgemann: Ist die Frage ausreichend beantwortet, Herr Adam? – Okay.

Herr Hofmann, KBV.

KBV: Nein, ist sie nicht. Es bleibt da immer noch was offen, Herr Marks, da Sie ja für die Erprobungsstudie ebenso vehement für diese Urethrotomia interna als Vergleichsintervention und ausschließlich eintreten, aber jetzt dann doch auf der anderen Seite reklamieren die Ergebnisse der ROBUST-III-Studie, wo diese Vergleichssituation ja offensichtlich nur an einer Minderheit angewendet worden ist, dann doch zu übernehmen. Da bleibt bei uns jetzt noch ein Fragezeichen.

Ich würde aber gern noch auf einen anderen Punkt zu sprechen kommen, den Sie einleitend so – –

Vorsitzende Frau Dr. Lelgemann: Herr Hofmann, wollen wir nicht erst einmal bei dem Fragezeichen bleiben, wenn ich Sie unterbrechen darf?

KBV: Ja, ich weiß nicht. Wenn Herr Marks dazu noch etwas beitragen kann, sehr gerne. Dann stelle ich das andere zurück.

Herr Dr. Marks (DGU): Da würde ich ganz gern etwas anfügen. Ich versuche ja nur, ein bisschen darzustellen – auch vor dem wissenschaftlichen Hintergrund –, wie schwierig die Datenerhebung und -interpretation betreffend Harnröhrenchirurgie und Harnröhrenrekonstruktion ist.

Ich bin nicht dafür da, zu erklären, dass eine Studie alles macht, was Sie gefordert haben. Das wollte ich nur noch einmal klarstellen.

Ich wollte nur erörtern, warum ich welche Daten wie sehe. Und wie gesagt, man müsste sich ja dann jede Striktur einzeln angucken. Es müsste ja ein zentrales Review geben, wenn wir

ganz exakt darüber sprechen wollen, dass eine Person beurteilen kann, ob alles genau miteinander vergleichbar ist, und das haben wir ja bei allen randomisierten Studien, unabhängig von der Harnröhrenchirurgie. – Das nur einmal ganz kurz – war mir wichtig.

Vorsitzende Frau Dr. Lelgemann: Okay. Vielen Dank. – Herr Hofmann.

KBV: Sie haben einleitend in einem Nebensatz – und das kommt ja auch schon aus der Stellungnahme heraus von den, um es mal vorsichtig auszudrücken, Problemen, die Sie mit der Fallzahl haben und den zu erwartenden Rekrutierungsschwierigkeiten – angekündigt, dass Sie das gern noch vertiefen können. Das würde mich mal interessieren, wie Sie das gemeint haben und was Sie dazu sagen können.

Herr Dr. Marks (DGU): Wir haben zwei Dinge dazu. Das eine ist das, was wir bisher so an Daten haben. Ich habe ja noch einmal alle in die Guideline *[EAU Guidelines (European Association of Urology; Guidelines on Urethral Strictures)]* eingeflossenen Studien angeschaut, wie viele Zahlen das so waren, und ich kann darüber berichten, dass Pansadoro et al. einer der wenigen war, die eine Veröffentlichung gemacht hatten, also alles, was jetzt in hochrangigen Journals publiziert wurde. Der hat es geschafft: 200 - 220 Patienten nachzubetrachten für die Auswertung von 220 Patienten, die eine Urethrotomia interna gehabt haben, und davon die entsprechenden Datensätze und Long-term follow up, über 15 Jahre rekrutiert als ein Zentrum. Und die internationalen Studien oder auch die aus unserem Haus besagen: Wir haben eine Fallzahl von knapp 120 Patienten zwischen 2009 und 2016 gehabt, die man dann auch wirklich nachverfolgen kann.

Das sind so die Zahlen, die uns ein bisschen sagen lassen würden, dass wir es als sehr, sehr schwierig ansehen würden, diese Patienten in einem randomisierten Setting zu finden.

Ich habe eben schon gesagt, dass die Harnröhrenchirurgie ein relativ spezielles Fach ist. Viele Patienten kommen mit einer sehr konkreten Vorstellung dessen, was sie haben wollen. Und nach wie vor ist in der Randomisierung ja zu sagen, in dem Rezidivsetting: Das Therapieverfahren mit den besten validierten Ergebnissen bleibt ja zunächst die offene Urethroplastik, gerade wenn wir über mehr als zwei Voreingriffe sprechen. Das heißt, die Patientenklientel für den Optilume-Katheter reduziert sich daraus schon ein bisschen, und den Patienten, denen man dann anbieten würde, an einer Studie teilzunehmen, ist auch aus eigener Erfahrungen nicht immer unbedingt – ist ja auch nicht unser Wunsch – eine bestimmte Therapie auszureden, hin zu einer Studie, wo wir keine sicheren Verweise auf die langfristigen Erfolge machen können. Daraus resultiert ein bisschen unsere Einschätzung, dass diese Studie – das wäre wahrscheinlich eine großartige, die könnten wir höchstrangig publizieren, wenn da irgendwer dran teilnimmt – nicht in einem adäquaten Zeitraum abbildbar wäre, selbst wenn man es multiinstitutionell machte.

KBV: Danke.

Vorsitzende Frau Dr. Lelgemann: Vielen Dank, Herr Dr. Marks. Ich denke, die Frage ist ausreichend beantwortet, Herr Dr. Hofmann. – Gibt es Ergänzungen zu den Ausführungen? Ich habe Ihnen ja eben ein bisschen das Wort abgeschnitten, Frau Dr. Schröder.

Frau Dr. Schröder (Kalms Consulting GmbH, vertritt Urotronic): Ja. Dann kommen wir natürlich auf einige Punkte zurück, die wir auch in unserer Stellungnahme ausgeführt hatten, zum Beispiel die Frage, ob zwei oder drei Zentimeter.

Ich denke, die DVIU Vergleichsgruppe ist absolut unstrittig. Ich kann auch unter wissenschaftlichem Aspekt nachvollziehen, dass man sagt, das wäre natürlich viel schöner, wissenschaftlich sauberer sozusagen, wenn man dann auch für die Prädilatation bei den Patienten, bei denen es notwendig ist – aber es ist ja nicht bei allen Patienten notwendig, sondern auch da sind ja klare Kriterien auch formuliert –, die gleiche Technik nehmen würde. Aber damit hätten wir dann in jedem Fall auch zwei Subgruppen, nämlich die Patienten, die keine Prädilatation vor Anwendung des Optilume benötigen und auf der anderen Seite die, die eben eine benötigen.

Auf der anderen Seite denke ich: Was die Resultate angeht, die bislang bezüglich Prädilatationsverfahren aus Studien vorliegen, hat man eben einfach eine Mischung. Also, wenn man sagt, wir wollen Optilume so machen, wie es bisher in Studien untersucht ist, dann kann man es auch tatsächlich gemäß dem Vorschlag der KBV und der Patientenvertretung dem überlassen – diese Wahl. Jetzt habe ich es ein bisschen gemischt.

Was zwei Zentimeter angeht: Wir wissen, der Zulassungsstatus von Optilume hat sich gegenüber der ersten Einreichung im Oktober letzten Jahres geändert. Da war es auf zwei Zentimeter beschränkt auf Basis der Resultate der ROBUST-I-Studie, mittlerweile ist es ausgedehnt auf drei Zentimeter, weil jetzt eben Resultate der ROBUST-II-Studie und vor allen Dingen auch der ROBUST-III-Studie vorliegen.

Daher ist die Frage, wenn es zu einer Erprobungsstudie käme mit einer klaren Beschränkung auf zwei Zentimeter bereits durch die Erprobungsrichtlinie – ich meine, möglicherweise käme ja auch die in der Variante der KBV – die unabhängige wissenschaftliche Institution – zu der gleichen Schlussfolgerung –: Würde das von vornherein den Patienten, die eine Rezidivstriktur von drei Zentimetern Länge haben, diese Therapieoption komplett versperren, obwohl es, wie wir in der ROBUST-III-Studie sehen, zumindest sehr gute Hinweise, wenn nicht einen Beleg gibt, dass es auch für diese Patienten einen Vorteil bietet?

Vorsitzende Frau Dr. Lelgemann: Vielen Dank. – Gibt es weitere Fragen? – Herr Hecken würde sagen: Da stehen wir jetzt im kurzen Hemdchen! – Gibt es noch Fragen bzw. Antworten, die unser Hemd verlängern können? – Wenn das nicht der Fall ist, dann möchte ich mich bei Ihnen sehr herzlich bedanken. Unser Dilemma habe ich schon dargestellt. Wir müssen da jetzt also eine kluge Entscheidung treffen. Vielen Dank für Ihre Ausführungen. – Herr Dr. Marks?

Herr Dr. Marks (DGU): Eine Sache, wenn das von Interesse ist: Wir haben uns – auch in unserer rekonstruktiven Arbeitsgruppe – über den Katheter an sich Gedanken gemacht. Die Schwierigkeit, das Ganze in einen wissenschaftlichen Hintergrund zu verpacken, haben wir gerade erläutert. Aber wenn es von Interesse ist, würde ich ganz gern noch kurz etwas dazu sagen, warum wir auch als DGU und als rekonstruktive Urologen doch gespannt darauf wären, wie sich so ein Katheter schlägt – auch in der Anwendung.

Wir haben ja mitunter gerade vor dem Hintergrund der demographischen Entwicklung und der Zunahme von chirurgischen Eingriffen auch im Harntrakt durchaus ein Patientenklientel, die wir einer offenen Operation ungern unterziehen aufgrund von Vorerkrankungen, von Vorbestrahlungen, aufgrund von Nebenmedikation und eben auch aufgrund der Einschränkung, was diese Zentimeter angeht, was die Urethrotomia interna angeht.

Ich kann mir durchaus vorstellen, dass gerade diese Idee der proliferativen Beschichtung und der Dilatation, ohne dass man das macht wie bisherige Versuche mit zum Beispiel Mitomycin mit Injektionen in multipel eingeschnittene Harnröhren, durchaus ein Kollektiv an Patienten erwarten würde. Und deswegen sind wir auf Ihre Einschätzung sehr gespannt und stehen für Rückfragen weiterhin zur Verfügung.

Vorsitzende Frau Dr. Lelgemann: Ganz herzlichen Dank, Herr Dr. Marks. Ganz herzlichen Dank an Sie, Frau Dr. Schröder und Frau Dr. Knorr. – Wenn Fragen bestehen, melden wir uns.

Das Manuskript erhalten wir, und wir versuchen, kluge Entscheidungen zu treffen.

Vielen Dank.

Schluss der Anhörung: 11:30 Uhr