JCAMD001 Core Submission Dossier

Optilume® Urethral Drug Coated Balloon for the treatment of anterior urethral stricture

Submitted by: Laborie Medical Technologies Corp.,

Pease International Tradeport,

180 International Drive,

Portsmouth, NH, 03801,

USA

Contact details for administrative purposes

Name of contact person: James Wright

Contact details: jwright@laborie.com

For agency completion

Date of receipt: June 9, 2023
Version: 1.0
Identifier: JCAMD001

DOCUMENT HISTORY

Version	Date	Description
V0.1	09/01/2023	Initial Core Submission Dossier
V0.2	16/03/2023	Updated Core Submission Dossier based on Missing Items following from completeness check by JCAMD001 authoring team
V1.0	09/06/2023	Publication of final version (editorial changes only)

Submission Dossier for JCAMD001 under EUnetHTA 21

Title	Optilume® Urethral Drug Coated Balloon for the treatment of anterior urethral stricture
HTD Name	Laborie Medical Technologies
HTD Corporate Address	Laborie Medical Technologies Corp., Pease International Tradeport, 180 International Drive, Portsmouth, NH, 03801, USA
Brand Name	Optilume® Urethral Drug Coated Balloon Catheter
Approved Name	Optilume®
Intended Use	The Optilume Urethral Drug Coated Balloon (DCB) Catheter is intended for the treatment of strictures in the anterior urethra in adult males
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.
Contraindications	The Optilume Urethral DCB Dilation Catheter is contraindicated for use in: Patients with known hypersensitivity to paclitaxel or structurally related compounds, and patients with lesions that cannot be crossed with a 0.038" guidewire
CE Mark, Notified Body, Applicable Directive, Certificate Number(s), Classification, Date of Authorisation, Date of expiry, Declaration of Conformity	CE 1434 Polskie Centrum Badad I Certyfikacji S.A. (PCBC) MDD 93/42/EEC 1434-MDD-033/2021 and 1434-MDD-034/2021 Class III (Rule 13) Date of authorisation: 14/01/2021 Date of expiry: 27/05/2024 Annex II of Directive MDD 93/42/EEC
Manufacturer	Urotronic Inc.
Manufacturer Address	2495 Xenium Lane North Plymouth, MN, 55441 USA
HTD Submission Date – original submission	9th January 2023
Supporting Documentation	**List of supporting documentation**: 1) Optilume NICE Recommendations MTG73, 2) Optilume Product Specifications, 3)

	Optilume Product Brochure, 4) Optilume Patient Brochure, 5) Optilume Step-By-Step Procedure Guide, 6) Paclitaxel Information Brochure, 7) Optilume Post- Procedure Patient Care Instructions, 8) Optilume EMEA Instructions For Use, 9) ROBUST I Three Year Publication, 10) ROBUST II One Year Publication, 11) ROBUST III RCT One Year Publication
EMDN/GMDN	U0399 – 'Devices for Urinary Tract Dilation – Other'
Basic UDI-DI	08530950081110L6
Executive Summary	Urethral stricture is a relatively common medical condition in men. The consequences of this obstruction can enormously impair a patient's quality of life, notwithstanding costs associated with the treatment of primary and recurrent disease. The rationale for preventing urethral stricture is to avoid morbidity to the individual, avoid additional pressures to the healthcare system, and costs to the health economy. Treatment care pathway of urethral stricture depends on stricture aetiology, localisation (anterior or posterior), the length of stricture, the degree of spongiofibrosis, the previous history of treatment, and the patient's age. Urethral strictures are typically diagnosed with a flow test and a retrograde urethrogram. European guidelines for the management of urethral stricture outline a specific pathway of diagnosis and treatment for patients diagnosed with urethral stricture. First line treatment for anterior urethral stricture is typically endoscopic management. A prospective randomized study showed no better results between the two forms of endoscopic management, dilation and internal urethrotomy (DVIU). A further randomized study identified that endoscopic treatments of the same stricture are proven to lead to progressively worse outcomes. After a third endoscopic treatment, the success rate is as low as 25% by 6 months and 0% by two-years post-treatment. Subsequent recurrences can lead to a chronic stricture state requiring self-catheterisation and/or repeat treatments. Urethroplasty is recommended when first-line treatment fails if stricture length exceeds 1.5cm. Men undergoing urethroplasty in the UK have had a median of three and five previous endoscopic urethral stricture treatments, thus resource utilisation and costs associated with carrying out multiple endoscopic procedures prior to urethroplasty are a prolonged and significant issue to healthcare providers and patients. Urethroplasty is a specialist procedure, only offered in healthcare facilities that have healthcare professionals with specialist training in this procedure. The first randomized trial comparing urethrotomy and urethroplasty, performed in the UK, found that both treatments can improve voiding symptoms. However, reintervention is lower after urethroplasty but with this comes a greater risk of morbidity to the patient. The Optilume Urethral Drug Coated Balloon (DCB) is an innovative technology intended for the treatment of anterior urethral stricture in

	adult males. It is used to treat men ≥18 years of age with bothersome urinary symptoms associated with recurrent anterior urethral stricture. Optilume Urethral DCB is novel compared to existing endoscopic standard of care as the technology incorporates urethral balloon dilation to dilate the urethral stricture, with an anti-proliferative drug (Paclitaxel) that is pre-coated onto the balloon, which is delivered to the inner urethral wall during the procedure to prevent the fibrotic tissue response associated with urethral stricture recurrence. Post-operative side effects are no different to endoscopic standard of care with the exception that the risk of urethral stricture recurrence is reduced by using Optilume Urethral DCB as published, peer-reviewed clinical evidence has shown the treatment to reduce the need for further reintervention. Pooled data analysis of all three (3) ROBUST studies estimates approximately 85% of subjects being free from reintervention at 1-years. IPSS improved from a mean of 21.8 at baseline to 6.5 at 1-year. QoL, Qmax, and PVR volume improved significantly from baseline. The ROBUST series of clinical trials will continue to follow up patients to 5 years and publish these findings. In November 2022, the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) published medical technologies guidance recommendations (MTG73) for the use of Optilume Urethral DCB in the National Health Service (NHS). As part of an alternative pathway including the technology, it is proposed to treat patients presenting with anterior urethral strictures <3cm with the Optilume Urethral DCB as a standalone treatment or as an adjunctive therapy to existing endoscopic management of urethral stricture. There is an urgent need to reduce the requirement for repeated reintervention of urethral stricture, often seen in this patient cohort, that is associated with existing endoscopic standards of care which is a burden to patients, healthcare providers and health economies long-term. Through adoption of Optilume Urethral DCB, as part of a standard care pathway for the management of anterior urethral stricture disease, there is the potential to address the clinical need while meeting the requirements of the patient population and providing valuable cost and resource savings to healthcare providers and health economies throughout Europe.

Contents

1 PICO Scope

The PICO scope in Table 1 was consolidated by EUnetHTA21 on 23rd November 2023.

Table 1: PICO Scope

	PICO 1	PICO 2	PICO 3
Population	According to intended use: Men 18 years of age and over with bothersome urinary symptoms associated with recurrent anterior urethral strictures equal to or less than 3 cm in length	The same as for PICO 1	The same as for PICO 1
Intervention	According to intended use: Optilume Urethral Drug Coated Balloon Catheter is intended to be used as a dilation balloon for a single, tandem, or diffuse anterior urethral stricture equal to or less than 3 cm in length or used as an adjunctive therapy with other dilation devices and/or procedures*.	The same as for PICO 1	The same as for PICO 1
Comparator(s)	Urethrotomy	Dilation	Urethroplasty
Outcomes	- All cause mortality - Urinary function (lower urinary tract symptoms related to stricture) measured by: International Prostatic Symptom Score (IPSS), Post-Void Residual urine volume (PVR), peak flow rate (Qmax) - Erectile function measured by: International Index of Erectile Function (IIEF) - Pain - Treatment success preferably measured by stricture-free rate, recurrence rate, reintervention, or time to treatment failure (preferably at a minimum of 6 months, 1 year, 2 years and in the long term) - Anatomical success preferably measured by stricture tightness - Health-Related Quality of Life (generic and disease- or population specific measure), any other patient-centred outcome and health status measured by PROMs - Safety, including a description of each adverse event included in the following categories:		

	Any adverse events and device-related adverse events including but not limited to peri-and post-operative complications, urinary tract infection (UTI), urinary retention, incontinence, erectile dysfunction • Drug-related adverse events • Serious adverse events
Subgroups to be considered	None identified
Special considerations, including issues related to equality	Optilume Urethral Drug Coated Balloon is intended for men with recurrent bulbar urethral strictures. These can be caused by injury to the penis, surgery, or infection. Some people may not identify as men but have a penis. Urethral strictures become more common in people over 55. Sex, gender reassignment and age are protected characteristics under the Equality Act (2010).
*The other dilation devices and/or procedures used with Optilume Urethral DCB are specified in the description of the procedure used in the clinical studies in the Section 7.	

2 Urethral stricture characteristics

A urethral stricture is a narrowing of the urethra caused by scarring, which functionally has the effect of obstructing the lower urinary tract (LUT). The consequences of this obstruction can enormously impair a patient's quality of life (QoL) by causing micturition disturbances; they can also damage the entire urinary tract, resulting in loss of renal function. It is therefore essential that urethral strictures, which can occur at any age and in either men or women (though they are much rarer in women), are recognized early and appropriately treated[1].

ICD-10 code N35.9 for Urethral stricture, unspecified is a medical classification as listed by the World Health Organization (WHO) under the range - Diseases of the genitourinary system. N35.91 Urethral stricture, unspecified, male and N35.92 Unspecified urethral stricture, female.

Urethral stricture is a relatively common medical condition in men, with an associated prevalence of 229-627 per 100,000 males, or 0.6% of the at-risk population[2]. In the United Kingdom (UK), 16,000 men require admission to hospital each year following diagnosis of urethral stricture, with 12,000 needing an operation at an annual cost of £10 million[2]. The estimated prevalence in the UK is 10/100 000 men in their youth, rising to about 20/100 000 by the age of 55 years, then to 40/100 000 by the age of 65 years and to over 100/100 000 thereafter[2]. Still, higher rates have been reported from the USA[3]. Patients with urethral stricture are typically considered a vulnerable population as they experience high rates of Urinary Tract Infections (UTI) (41%) and incontinence (11%) as sequelae of the disease[4].

In 2021, 13,388 patients were treated in Germany with the main diagnosis code for urethral stricture (N35.1, N35.2, N35.8, N35.9 and N99.1). Source; www.gbe-bund.de (January 2023).

Urethral stricture	ICD 10-GM	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Post-traumatic urethral stricture	N35.0	933	921	836	815	711	781	708	633	643	482	441
Postinfective urethral stricture, not elsewhere classified	N35.1	778	588	555	548	415	371	339	335	287	238	213
Other urethral stricture	N35.8	6.917	7.326	7.315	7.799	7.543	7.496	7.135	7.126	6.976	6.374	6.261
Urethral stricture, unspecified	N35.9	5.037	5.051	5.014	4.768	4.620	4.729	4.704	4.806	4.593	3.458	3.332
Postprocedural urethral stricture, Post catheterization urethral stricture	N99.1	6.182	5.887	5.286	4.757	4.490	4.293	3.980	3.529	3.551	3.245	3.141
		19.847	19.773	19.006	18.687	17.779	17.670	16.866	16.429	16.050	13.797	13.388

In 2021, 23,115 urethrotomies were performed in Germany via OPS Code 5-585.0, 5-585.1, 5-585.2 and 5-585.x. Source; Destatis (January 2023). Again, in 2021, 3,276 procedures were performed in Germany associated with urethral reconstruction.

OPS-Code	Description	2014	2015	2016	2017	2018	2019	2020	2021
5-585.0	Urethrotomia interna, w/o vision	12.875	12.065	11.639	11.001	10.368	9.845	8.480	7.723
5-585.1	Urethrotomia interna, under vision	20.557	19.171	18.831	17.938	17.362	17.396	15.404	14.996
5-585.2	Urethrotomia interna, with Laser	700	648	670	555	480	422	335	362
5-585.x	Other	157	117	68	61	36	46	38	32
		34.289	**32.001**	**31.208**	**29.555**	**28.246**	**27.709**	**24.257**	**23.113**

In 2022, OPS 8-139.11 and 5-585 plus 8-139.1 was implemented for the use of Optilume in German hospitals “Ballondilation der urethra – Mit Medikamentenbeschichtung des ballonkatheters”. Source; InEK Datenbrowser – OPS-catalogue BfArm (January 2023).

5-584 Rekonstruktion der Urethra

Exkl.: Verschluss einer urethrovaginalen Fistel (5-706.5 ff.)
Plastik bei männlicher Epispadie (5-644 ff.)
Plastik bei männlicher Hypospadie (5-645 ff.)
Plastik bei Urethrozystozele der Frau (5-704.0 ff.)

5-584.0 Rekonstruktion der Pars prostatica oder der Pars membranacea (nach Verletzung)
5-584.1 Rekonstruktion des distalen Teils (nach Verletzung)
5-584.2 Verschluss einer Urethrostomie
Inkl.: Zweite Sitzung einer zweizeitigen Urethroplastik
5-584.3 Verschluss einer urethrokutanen Fistel
5-584.4 Verschluss einer urethrorektalen Fistel
5-584.5 (Re-)Anastomose nach Verletzung
5-584.6 (Re-)Anastomose mit Strikturresektion
5-584.7 Plastische Rekonstruktion, einzeitig
.70 Mit Präputialhaut
.71 Mit Penishaut
.72 Transplantation von Mundschleimhaut
Exkl.: Transplantation von in vitro hergestelltem Gewebe aus autogener Mundschleimhaut (5-584.74)
.73 Transplantation von Harnblasenschleimhaut
.74 Transplantation von in vitro hergestelltem Gewebe aus autogener Mundschleimhaut
.7x Sonstige
5-584.8 Plastische Rekonstruktion, zweizeitig, erste Sitzung
.80 Mit Präputialhaut
.81 Mit Penishaut
.82 Transplantation von Mundschleimhaut
Exkl.: Transplantation von in vitro hergestelltem Gewebe aus autogener Mundschleimhaut (5-584.84)
.83 Transplantation von Harnblasenschleimhaut
.84 Transplantation von in vitro hergestelltem Gewebe aus autogener Mundschleimhaut
.8x Sonstige
5-584.9 Plastische (Re-)Konstruktion bei weiblicher Epispadie
5-584.a Plastische (Re-)Konstruktion bei weiblicher Hypospadie
5-584.x Sonstige
5-584.y N.n.bez.

OPS-Code	2014	2015	2016	2017	2018	2019	2020	2021
5-584.0	75	102	67	70	87	83	96	55
5-584.1	121	114	133	115	137	137	104	98
5-584.2	125	186	271	332	328	321	297	320
5-584.5	84	89	95	97	76	124	84	97
5-584.6	315	289	307	325	302	296	303	330
5-584.70	229	275	305	256	298	284	314	382
5-584.71	159	160	183	163	169	177	129	133
5-584.72	**1.164**	**1.143**	**1.143**	**1.160**	**1.133**	**1.173**	**1.040**	**1.054**
5-584.73	7	7	10	11	7	8	7	1
5-584.74	16	13	25	35	54	11	6	2
5-584.7x	**307**	**304**	**406**	**424**	**398**	**444**	**416**	**477**
5-584.80	24	30	22	23	34	43	29	27
5-584.81	24	27	27	23	34	25	29	31
5-584.82	59	79	75	77	81	93	79	72
5-584.83	1	3	1	0	1	1	2	0
5-584.84	0	0	1	2	0	1	0	0
5-584.8x	101	138	134	147	168	185	188	197
	2.811	**2.959**	**3.205**	**3.260**	**3.307**	**3.406**	**3.123**	**3.276**

In France, in 2021, a total of 13,786 urethrotomy procedures were performed for urethral stricture CCAM codes.

Code CCAM	Number of urethrotomy procedures per year in France						
	2015	2016	2017	2018	2019	2020	2021
JEPD001	1233	1245	1358	1223	1246	1007	1110
JEPE002	12518	12708	13149	13011	12674	11046	11957
JEPA006	286	317	238	243	276	268	297
JEFE004	430	415	491	382	429	405	422
TOTAL	**14 467**	**14 685**	**15 236**	**14 859**	**14 625**	**12 726**	**13 786**

A further total of 609 urethroplasty procedures were performed in France in 2021.

Code CCAM	Number of uretroplasty procedures per year in France						
	2015	2016	2017	2018	2019	2020	2021
JEMA010	85	94	127	181	200	235	291
JEMA007	216	166	154	185	156	114	156
JEMA015	67	81	77	78	87	75	85
JEFA008	19	10	16	13	14	11	15
JEFA011	43	49	62	68	66	49	62
TOTAL	**430**	**400**	**436**	**525**	**523**	**484**	**609**

Stricture aetiology differs significantly throughout different regions in the world, due to differences in healthcare quality and environmental and practice patterns[5]. Almost all strictures for which a cause can be identified are acquired[6,7]. The largest group (45%) are iatrogenic and result from urethral manipulations (traumatic indwelling catheter, transurethral interventions, correction of hypospadias, prostatectomy, brachytherapy)[6,7]. Thus, for example, the incidence of urethral stricture after transurethral prostate resection (the most common prostate intervention) is 3% to 5%[8,9]. Another cause of urethral stricture is traumatic urethral rupture associated with pelvic fracture. Bacterial urethritis can also lead to stricture (around 20% of cases); classically, these are cases of untreated gonorrhoea[1].

Around 30% of urethral strictures are idiopathic[6]. In these cases, the most likely trigger is some forgotten minor trauma that occurred a long time in the past (e.g., perineal injury while riding a bicycle)[10].

The urethra is divided into different segments that are involved in stricture with varying frequency. The segments passing through the prostate (prostatic urethra) and pelvic floor musculature (membranous urethra) are referred to collectively as the posterior urethra, while the anterior urethra is made up of the segment fixed to the pelvic floor (bulbar urethra) and the segment passing through the pendulous portion and glans penis (penile and glandular urethra). Bulbar strictures are most common (around 50%), followed by penile strictures (around 30%) and strictures of the navicular fossa (around 20%)[7,11]

Regardless of geography, urethral stricture adversely impacts physical health and quality of life (QoL)[12,13], notwithstanding costs associated with the treatment of primary and recurrent disease[14,3]. The rationale for preventing urethral stricture is to avoid morbidity to the individual and the healthcare system, and costs to the health economy.

The main symptoms of urethral stricture are those of obstructed and irritated micturition, with increased urination time and a feeling of incomplete bladder emptying, combined with increased micturition frequency and urgency[7]. Particularly in patients who have previously undergone transurethral interventions or had a long-term indwelling catheter during treatment for another disease, these symptoms should suggest the possibility of stricture[7].

In addition to the typical history, urethral strictures are typically diagnosed with a flow test and a retrograde urethrogram[1]. Urethroscopy can show where the stricture is located, but if the stricture cannot be passed by the cystoscope, no information can be obtained about the length of the lesion or about any additional, more proximal strictures that may be present. For this reason, urethroscopy does not have a major role in the diagnostic work-up of urethral stricture[15]. Other primary diagnostic procedures required are ultrasonography to determine any urinary retention and ultrasound examination of the upper urinary tract to rule out hydronephrosis. Urine sediment is examined to rule out acute infection[1].

Treatment care pathway of urethral stricture depends on stricture aetiology, localisation (anterior or posterior), the length of stricture, the degree of spongiofibrosis, the previous history of treatment, and the patient's age[16] (
Figure 1).

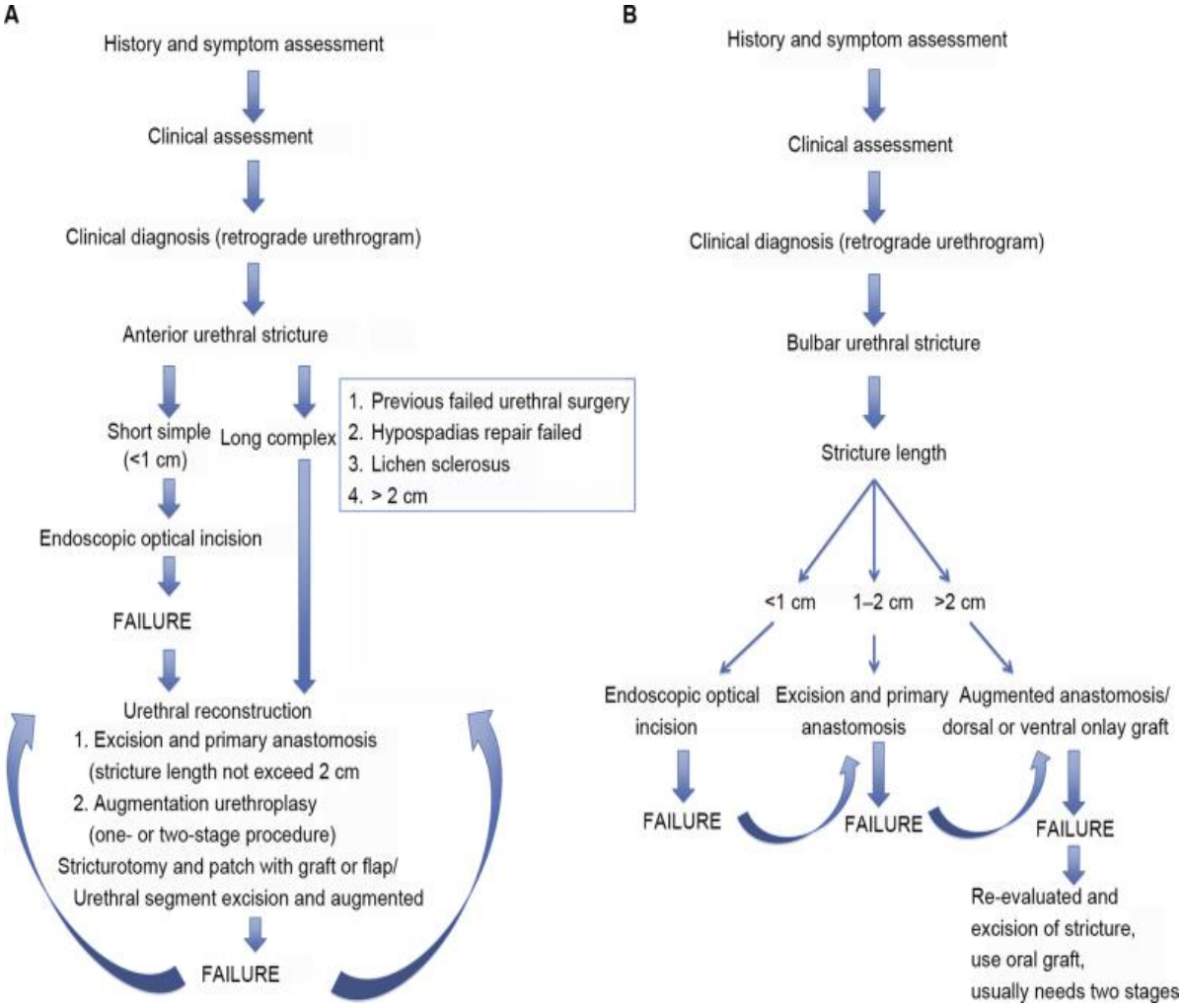


Figure 1: Algorithm of anterior urethral stricture treatment (A) and bulbar urethral stricture treatment (B)

This typical treatment care pathway is further defined in published European Guidelines for the management of urethral stricture[18] (

Figure 2).

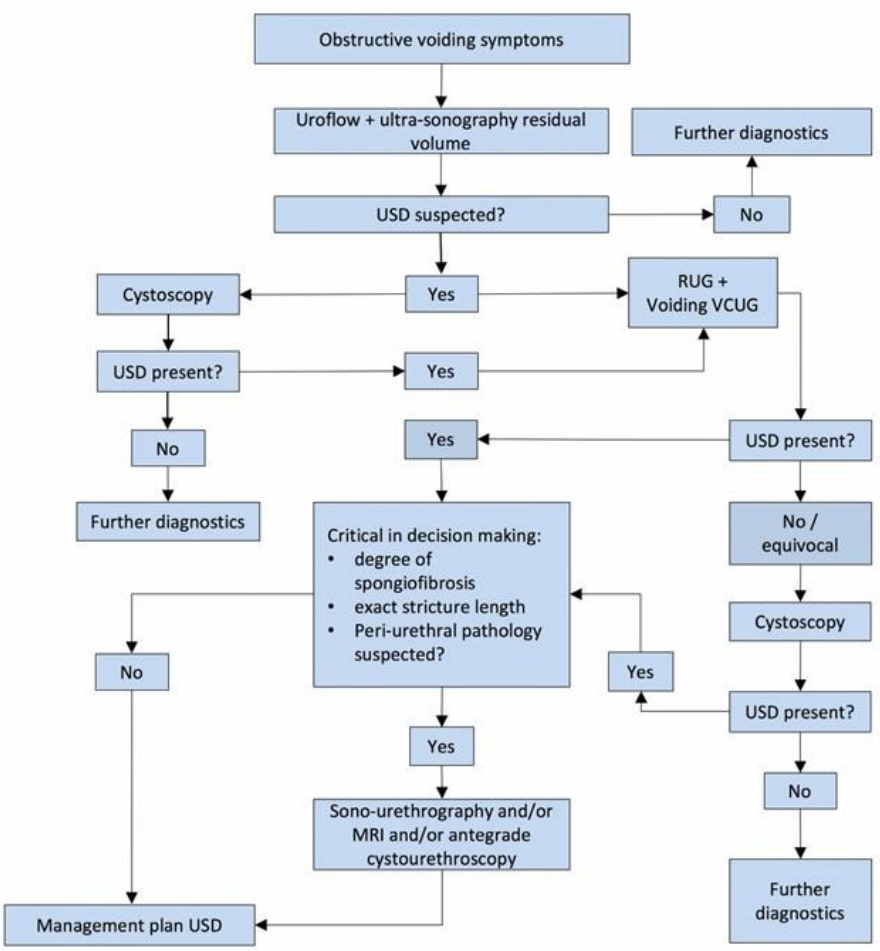


Figure 2: Diagnostic flowchart of patients with suspected urethral stricture disease[1]

MRI = Magnetic resonance imaging; RUG = retrograde urethrography, USD = urethral stricture disease; VCUG = voiding cysto-urethrogram

First line treatment for anterior urethral stricture, following appropriate clinical assessment and diagnostics, is typically endoscopic management via urethral dilation or, more commonly, direct vision internal urethrotomy (DVIU)[17]. Endoscopic procedures are typically considered for a urethral stricture shorter than 1.5cm[18].

Urethral dilation is performed typically under general anaesthesia or light sedation. It involves the use of rigid rods/bougienage or uncoated balloon dilators to dilate (widen) the urethral lumen at the stricture site stretching the spongiofibrosis, thus producing innumerable microlesions in the scar tissue, leading to further scarring. For this reason, bougienage can only ever have a temporary effect on the obstruction, and as a rule the stricture may be expected to recur after 4 to 6 weeks[19].

Direct Visual Internal Urethrotomy (DVIU), or 'Optical Urethrotomy', is performed under general anaesthesia and involves making an incision in the urethra to widen the urethral lumen. Since the resulting wound margins expand, healing is by secondary intention. This in turn leads to scar formation, explaining the high recurrence rate. Recurrence must be expected in at least 50% to 60% of cases[20,21], some authors report long-term success rates of only 20%[19]. The recurrence rate depends on the length of the stricture; better results may be expected only for short (<1.5 cm), first-time strictures of the bulbar urethra (up to 75% success[20]).

A prospective randomized study showed that internal urethrotomy produces no better results than bougienage[19]. Multiple endoscopic treatments of the same stricture are proven to lead to progressively worse outcomes. After a third endoscopic treatment, the success rate is as low as 25% by 6 months and 0% by two-years post-treatment[22]. Patients may be catheterized for several days following either procedure. Subsequent recurrences can lead to a chronic stricture state requiring self-catheterisation and/or repeat treatments.

Urethroplasty is recommended when first-line treatment fails if stricture length exceeds 1.5cm[18], if the stricture is a result of trauma, and, in patients presenting with lichen sclerosis. Patients presenting with penile strictures which are unlikely to respond to DVIU and are also candidates for primary urethroplasty.

Urethroplasty is an open surgical procedure performed under general anaesthesia taking an average of two to three hours operative time[2] and an associated length of stay of two days on average[2]. The scar tissue is cut away and the urethra is re-joined, or a tissue graft (from cheek lining) is used to widen the scarred urethra. Patients remain in hospital for recovery and are catheterized for several weeks after their surgery. Treatment success after urethroplasty in correctly selected patients according to publication, achieves success rates of around 90%[23,24].

Men undergoing urethroplasty in the UK have had a median of three and five previous endoscopic urethral stricture treatments[2], thus resource utilisation and costs associated with carrying out multiple endoscopic procedures prior to urethroplasty are a prolonged and significant issue to healthcare providers and patients. Patients are required to be catheterised for two to three weeks post-surgery[2]. Urethroplasty is a specialist procedure, only offered in healthcare facilities that have healthcare professionals with specialist training in this procedure.

The first randomized trial comparing urethrotomy and urethroplasty, performed in the UK, found that both treatments can improve voiding symptoms[25]. However, reintervention is lower after urethroplasty but with this comes a greater risk of morbidity to the patient[24].

Patients who wish to avoid the morbidity associated with urethroplasty may opt to perform long term Intermittent Self-Catheter (ISC) or Intermittent Self-Dilation (ISD). This involves insertion of a dilatation catheter or foley catheter into the urethra 1 or more per week. The reason for performing ISC or ISD is due to stricture recurrence requiring repeated endoscopic reintervention or urethroplasty.

3 The Technology

The Optilume Urethral Drug Coated Balloon (DCB) is an innovative technology intended for the treatment of anterior urethral stricture in adult males. It 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[26].

The Optilume Urethral DCB is a coaxial catheter, compatible with a 0.038-inch (0.97 mm) guide and a flexible cystoscope, with two lumens and an atraumatic beveled tip. The distal end of the catheter is equipped with a semi-compliant inflatable balloon that is coated with paclitaxel and excipients. The device has two radiopaque marks that indicate the useful length of the balloon (Figure 3).

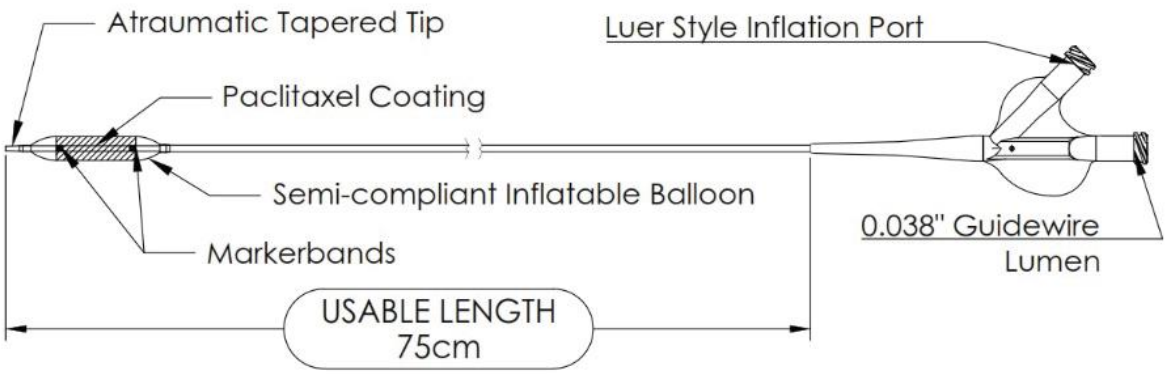


Figure 3: Technical diagram of Optilume Urethral DCB[26]

Optilume Urethral DCB is novel compared to existing endoscopic standard of care as the technology incorporates urethral balloon dilation to dilate the urethral stricture, with an anti-proliferative drug (Paclitaxel) that is pre-coated onto the balloon, which is delivered to the inner urethral wall during the procedure to prevent the fibrotic tissue response associated with urethral stricture recurrence. Paclitaxel is circumferentially delivered along the length of the urethral stricture to inhibit new scar tissue growth that is commonly associated with urethral stricture recurrence.

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. The Urethral DCB should be stored at room temperature in a dry location in its original packaging[26].

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 3.5µg/mm.[26] The key functional characteristic of the drug coating is to allow for release of the paclitaxel, an anti-mitotic pharmaceutical agent that specifically binds to and stabilizes microtubules, to the urothelium during balloon inflation. 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[26].

The procedure itself follows the established urological practice for urethral dilation, with the ability to be performed under direct visualization, compatible with existing hospital resources, and can be performed in an outpatient setting under local anaesthesia or conscious sedation removing the requirement for inpatient stay, general anaesthesia, and extensive theatre time.

The Optilume Urethral DCB procedure can be performed with rigid cystoscopy or with flexible cystoscopy in a clinic setting or an operating room. Fluoroscopy is not a must at the time of the procedure so long as the stricture length and location has been adequately assessed and confirmed preoperatively through appropriate diagnostic investigation. The Optilume Urethral DCB is passed over a guidewire under direct vision, placed in position along the length of the US, inflated using normal saline/sterile water with a pressure inflation device (provided with the Optilume Urethral DCB) leaving the Optilume Urethral DCB in-situ across the urethral stricture for minimum 5 minutes to facilitate drug uptake to the target tissue. Once drug delivery has been facilitated, the Optilume Urethral DCB is then deflated using the inflation device, removed, and disposed of via local biohazard disposal standard

protocols. A catheter may be placed at the discretion of the clinician and can be administered post-operatively as is seen in existing standard of care treatments.

Post-operative side effects are no different to endoscopic standard of care[19] with the exception that the risk of urethral stricture recurrence is reduced by using Optilume Urethral DCB as published, peer-reviewed clinical evidence has shown the treatment to reduce the need for further reintervention[27,28,29].

The Optilume Urethral DCB is approved in multiple geographies globally with US FDA, CE, Australian TGA and Health Canada approvals to note. The device is approved in Europe (CE1434) in 3 different diameters and 2 different lengths (Table 2). To date, including clinical study participants, over 3500 procedures have been performed globally.

Table 2: Optilume Products

Product Number	Description	Diameter	Length	Rated Burst Pressure	Paclitaxel Dose
OPTBDL7000C	Optilume Drug Coated Balloon & Inflation Device	18Fr	3cm	12atm	1,979µg
OPTBDL7001C		18Fr	5cm	12atm	3,299µg
OPTBDL7002C		24Fr	3cm	12atm	2,639µg
OPTBDL7003C		24Fr	5cm	12atm	4,398µg
OPTBDL7004C		30Fr	3cm	10atm	3,299µg
OPTBDL7005C		30Fr	5cm	10atm	5,498µg

A series of clinical trials (ROBUST I, II & III) was conducted to assess the safety and efficacy of the Optilume Urethral DCB (Table 3).

Table 3: Summary of ROBUST Clinical Studies

	ROBUST I	ROBUST II	ROBUST III RCT
Trial Design	Single arm, prospective, multicenter	Single arm, prospective multicenter	Randomized (2:1), prospective, single blind, multicenter
Geography	Latin America	United States	United States & Canada
# Of Sites	4	5	22
Total Enrollments	53	16	127 (79 Optilume; 48 Standard of Care)

ROBUST I

Fifty-three (53) adult men with recurrent bulbar urethral strictures ≤2 cm in length and 1–4 prior endoscopic interventions were treated with the Optilume Urethral DCB in the ROBUST I clinical study. Functional success was defined as ≥50% reduction in International Prostate Symptom Score (IPSS) without need for retreatment. Other outcomes included quality of life (QoL), peak flow rate (Qmax), post-void residual urine volume (PVR), erectile function (IIEF), and freedom from repeat intervention (FFRI). Functional success was achieved in 67% (29/43) and freedom from retreatment in 77% (33/43). Average IPSS improved from 25.2 at baseline to 5.5 at 3 years ($p<0.0001$). Significant improvements were observed in quality of life, flow rate and post-void residual urine volume[27].

ROBUST II

Sixteen (16) adult men with an average of 4.1 prior dilations were treated with the Optilume Urethral DCB. Anatomic success was achieved at 6 months in 73%. Average IPSS improved from 18.4 to 6.0 at 1 year ($P < 0.001$). Qmax improved from 6.9 mL/sec to 20.8 mL/sec ($P <$

0.001). There was no change in IIEF. Four subjects received additional treatment within 1 year. There were no treatment-related serious complications[28].

ROBUST III Randomized Control Trial (RCT)

Seventy-nine adult men (79) with anterior strictures ≤12Fr in diameter and ≤3 cm in length, at least 2 prior endoscopic treatments, IPSS ≥11 and Qmax <15 mL/sec, were randomized and treated with Optilume Urethral DCB versus a control group (standard of care). Freedom from repeat intervention was significantly higher in the Optilume DCB arm at 1 year (83.2% vs. 21.7% control). Immediate IPSS and Qmax improvement was significant in both groups, with the benefit being more durable in the Optilume Urethral DCB group. The most frequent adverse events included urinary tract infection (UTI), post-procedural haematuria and dysuria. Quality of Life (QoL), Qmax, and PVR volume improved significantly from baseline[29].

Summary of ROBUST I, II, & III

Pooled data analysis of all three (3) ROBUST studies estimates approximately 85% of subjects being free from reintervention at 1 year. IPSS improved from a mean of 21.8 at baseline to 6.5 at 1 year. QoL, Qmax, and PVR volume improved significantly from baseline The ROBUST series of clinical trials[27,28,29]will continue to follow up patients to 5 years and publish these findings.

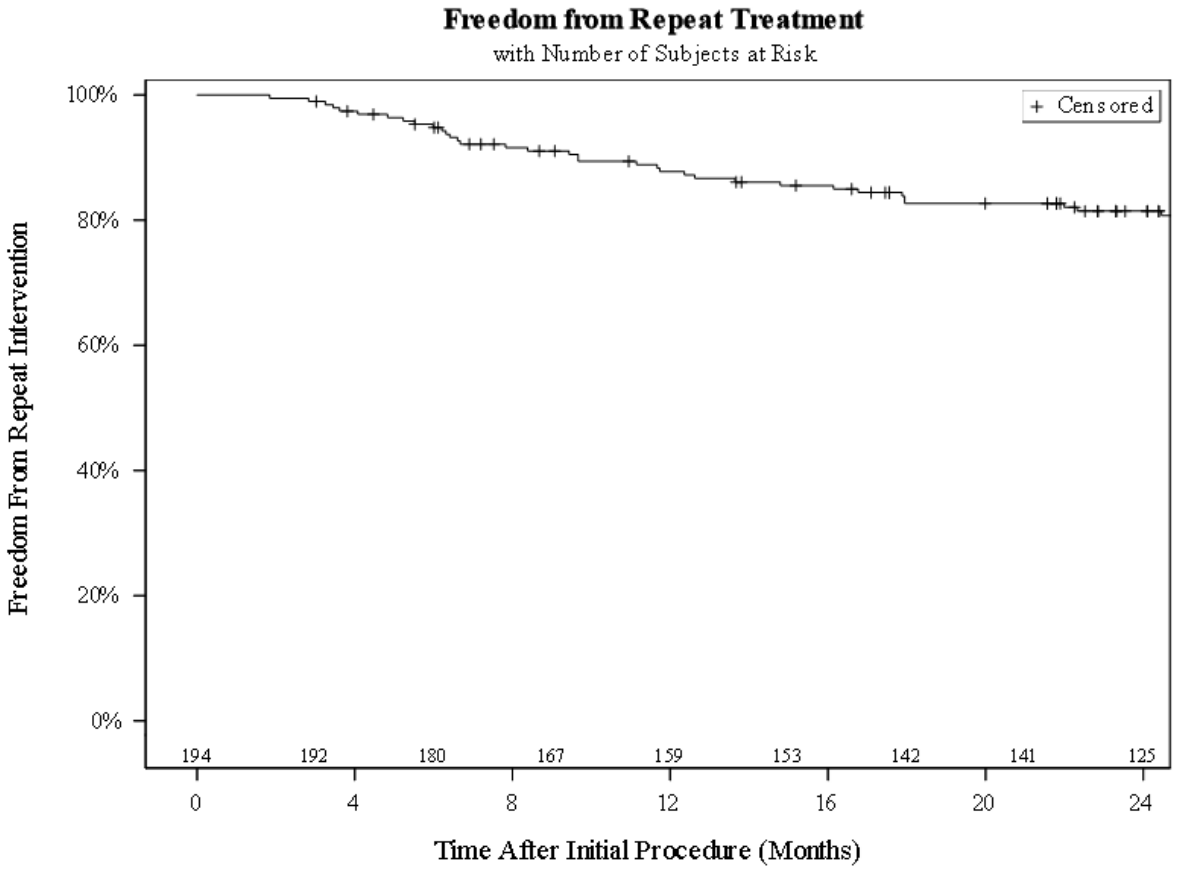


Figure 4: Freedom from reintervention Kaplan Meier Curve

Other Post-Market Studies in Europe

Furthermore, there is a current European Association of Urology (EAU) Research Foundation (RF) real-world registry currently enrolling patients from across the EU. This real-world registry will follow patients to 5 years.

In the UK on November 29th, 2022, the National Institute for Health and Care Excellence (NICE) published medical technologies guidance recommendations (MTG73) for the use of Optilume Urethral DCB in the National Health Service (NHS)[30]. NICE assessed both the clinical and economic benefits of the technology versus existing standard of care, highlighting benefits to patients and the healthcare economy in the UK National Health NHS. NICE's Medical Technologies Evaluation Program (MTEP) committee commented in its report, "Optilume done in an outpatient setting could reduce waiting times for the treatment of recurrent bulbar urethral strictures. The comparative clinical evidence shows that Optilume is effective in the short term (up to 2 years). The cost analysis shows that Optilume is cost saving at 5 years as compared with standard care (urethral dilatation, urethrotomy and urethroplasty)". Compared to standard endoscopic treatment over a 5-year time horizon cost savings due to adoption of Optilume Urethral DCB was £2,510 per patient[30]. Modelling suggests the introduction of Optilume Urethral DCB would provide a cost-saving alternative to further standard endoscopic procedures in men with recurrent bulbar urethral stricture who have previously undergone a failed endoscopic procedure[30].

Highlighted below in Table 4 are the claimed benefits from the HTD of the Optilume Urethral DCB for patients and Healthcare providers.

Table 4: Claimed benefits of using the technology for patients and Healthcare providers

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Rapid and sustained improvement in symptoms and urinary flow	ROBUST I[27] ROBUST II[28] ROBUST III[29]	Published outcomes show immediate and sustained improvement in IPSS, USS-PROM, and Qmax
Effective minimally invasive treatment	ROBUST III[29]	Optilume DCB showed superiority to standard of care endoscopic management
Reduces the need for retreatments or invasive surgical procedures	ROBUST III[29]	Optilume DCB had significantly lower rate of retreatment
Reduces the need for self-catheterisation management	ROBUST III[29]	Optilume DCB had significantly lower rate of retreatment
Reduced side effects and post-operative complications (e.g., UTI) compared with urethroplasty	ROBUST I[27] ROBUST II[28] ROBUST III[29]	Less invasive endoscopic treatment vs open surgical procedure
Rapid return to normal daily living and improved quality of life	ROBUST III[29]	ROBUST I, ROBUTS II, and ROBUST III studies

Claimed benefit	Supporting evidence	Rationale
Preservation of sexual function	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	No treatment related sexual function AEs, no change in function per IIEF questionnaire
Low risk of hospital acquired infection	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	Wound infection rates in urethroplasty ~4%, no wound created for endoscopic treatment
Potential for reduced waiting times	National Institute for Health and Care Excellence, Medical Technologies Guidance MTG73[30]	Limited surgeons trained in urethroplasty, while general urologist can perform Optilume procedure
Healthcare provider benefits		
Reduced burden of repeat procedures	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	ROBUST III lower repeat treatment
Reduced re-admission rates (elective or non-elective)	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	ROBUST III lower repeat treatment
Less risk of hospital acquired infection	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	Wound infection rates in urethroplasty ~4%, no wound created for endoscopic treatment
Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	Less repeat interventions
Reduced number of post-discharge follow up visits, providing physician resource saving	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	Less repeat interventions
Low rate of post-operative complications	ROBUST I[27] ROBUTS II[28] ROBUST III[29]	Less invasive endoscopic treatment vs open surgical procedure
Reduction in waiting list by offering a minimally invasive alternative to patients who have suffered recurrence awaiting open surgical consultation	National Institute for Health and Care Excellence, Medical Technologies Guidance MTG73[30]	Limited surgeons trained in urethroplasty, while general urologist can perform Optilume procedure

As part of an alternative pathway including the technology, it is proposed to treat patients presenting with anterior urethral strictures <3cm with the Optilume Urethral DCB as a standalone treatment or as an adjunctive therapy to existing endoscopic management of urethral stricture (Figure 5).

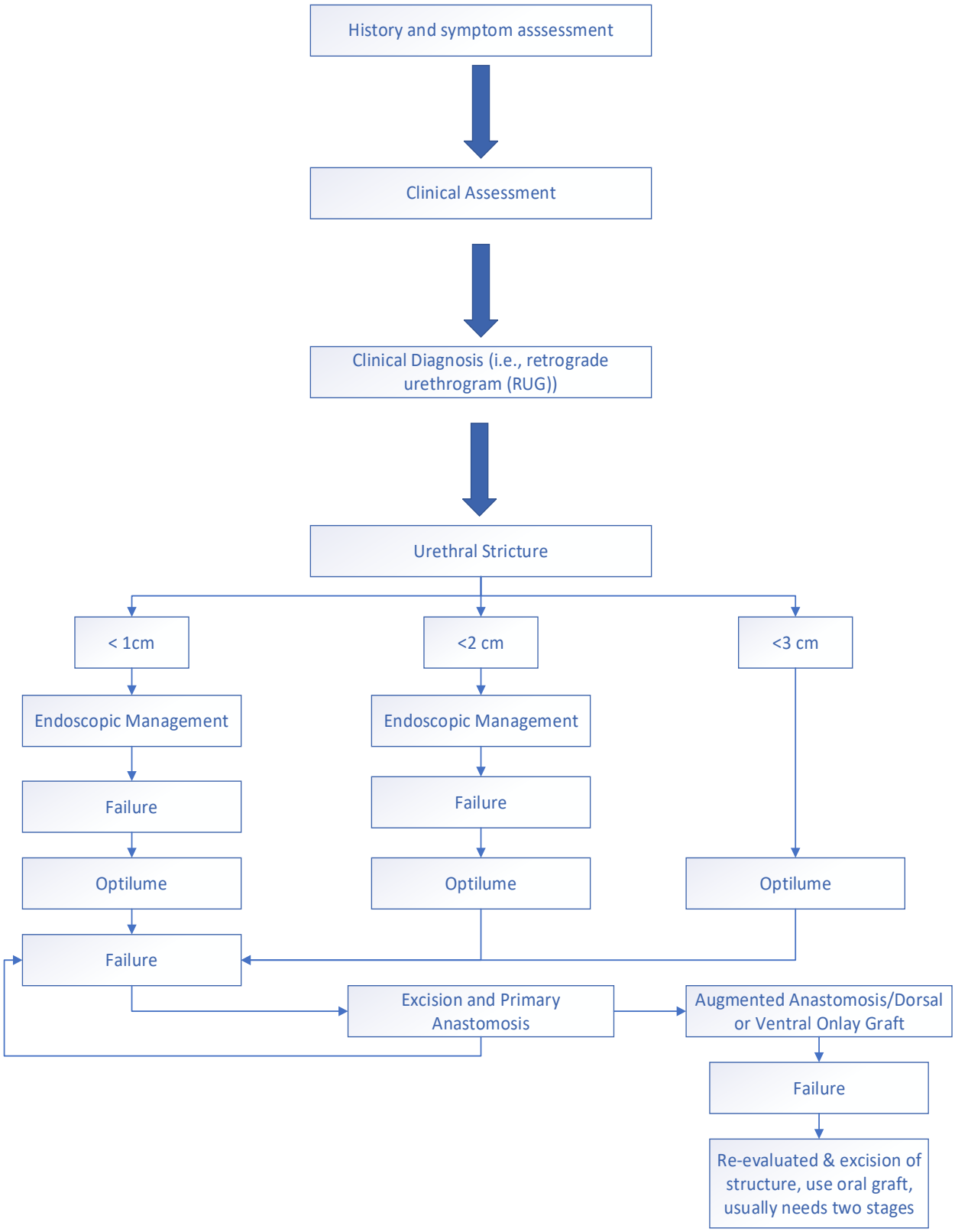


Figure 5: Proposed algorithm of urethral stricture treatment with Optilume Urethral DCB consideration

4 Published and unpublished clinical evidence

4.1 Identification and selection of studies

Table 5: Summary of Identified and Selected Studies

Number of studies identified in a systematic search. Date range: 1982- January 12, 2023		2,990
Number of studies identified as being relevant to the decision problem.		17
Of the relevant studies identified:	Number of published studies (included in Table 6).	17
	Number of abstracts (included in Table 7).	4
	Number of ongoing studies (included in Table 8).	5

4.2 List of relevant studies

Table 6: Summary of all relevant published studies

Data source	Author, year, and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Optilume Urethral DCB						
Journal Article	Elliott SP, 2022, J Urology[29]	Prospective, randomized, multi-center	Recurrent anterior urethral stricture, average ~1.6cm in length, 3.2 prior dilations	Optilume DCB	Dilation/DVIU	Recurrence Retreatment Symptom scores Peak flow rate
Journal Article	Virasoro R, 2022, Research and Reports in Urology27	Prospective, single arm, multi-center	Recurrent anterior urethral stricture, average 0.9cm	Optilume DCB	N/A	Recurrence Retreatment Symptom scores

			length, 1.7 prior dilations			Peak flow rate
Journal Article	DeLong J, SIU Journal, 202228[28]	Prospective, single arm, multi-center	Recurrent anterior urethral strictures, average 2.1cm length, 4.1 prior dilations	Optilume DCB	N/A	Recurrence Repeat Intervention Symptom scores Peak flow rate
Endoscopic Management						
NIHR HTA	Pickard R, 2020, Health Technology Assessment[25]	Prospective, randomized, multi-center	Recurrent anterior urethral stricture, average ~2cm in length, 1.8 prior dilations	Urethroplasty (n=109 randomized, n=69 treated)	DVIU (n=112 randomized, n=90 treated)	Symptom Scores Peak flow rate Recurrence Retreatment
Journal Article	Steenkamp JW, J Urol, 1997[19]	Prospective, randomized, single center	Mixed recurrent and primary (30% recurrent), 2.3cm stricture length	DVIU (n=104)	Dilation (n=106)	Recurrence
Journal Article	Heyns CF, J Urol, 1998[22]	Prospective, randomized, single center	Recurrent anterior urethral strictures, 2.3cm stricture length	DVIU (n=104)	Dilation (n=106)	Recurrence
Journal Article	Azab SS, Scand J Urol, 2020[31]	Prospective, randomized, single center	Primary anterior urethral strictures, average 1cm length	Amplatz renal dilator (n=44)	DVIU (n=44)	Symptom scores Peak flow rate Recurrence
Journal Article	Cecen K, Urol Int, 2014[32]	Prospective, randomized, single center	Primary anterior urethral strictures, average 1.3cm length	Laser urethrotomy (n=70)	DVIU (n=66)	Recurrence Peak Flow Rate
Journal Article	Guo FF, World J Urol[33]	Prospective, single arm, single center	Primary anterior urethral strictures, 2.6cm length	Laser urethrotomy (n=238)	N/A	Recurrence Symptom scores Peak flow rate
Journal article	Jordan GH, J Urol, 2013[34]	Prospective, randomized, multi-center	Recurrent anterior urethral strictures, 2.7cm length, average 2 prior dilations	MemokathTW44 (n=63)	DVIU (n=29)	Recurrence Symptom scores Peak flow rate

Journal Article	Isen K, Int Urol Nephrol, 2015[35]	Prospective, single arm, single center	Primary urethral strictures, average 0.7cm length	DVIU (n=21)	N/A	Peak flow rate Retreatment
Journal Article	Pansadoro V, J Urol, 1996[36]	Retrospective, single arm, single center	Primary anterior urethral stricture, average length 1.6cm	DVIU (n=224)	N/A	Recurrence
Journal Article	Santucci R, J Urol, 2010[37]	Retrospective, single arm, single center	Recurrent anterior urethral stricture, average length of 1.5cm	DVIU (n=76)	N/A	Recurrence
Urethroplasty						
Journal Article	Hoy NY, Urology, 2013[38]	Prospective, single arm, single center	Recurrent anterior urethral stricture, average length 4.9cm	Dorsal onlay buccal mucosal graft urethroplasty (n=163)	N/A	Recurrence
Journal Article	Aldaqadossi H, Int J Urol, 2014[39]	Prospective, randomized, single center	Mostly recurrent anterior stricture, average ~4.5cm length, average 1.7 prior dilations	Dorsal onlay buccal mucosal graft urethroplasty (n=25)	Dorsal inlay buccal mucosal graft urethroplasty (n=22)	Recurrence
Journal Article	Elkady E, Urology, 2019[40]	Prospective, randomized, single center	Recurrent anterior urethral strictures, average length 3.2cm	Standard urethroplasty (n=25)	Muscle/nerve sparing urethroplasty (n=25)	Recurrence
Journal Article	Erickson, BA, Urology, 2014[41]	Prospective, single-arm, multi-center	Anterior urethral strictures	Urethroplasty	N/A	Recurrence

Table 7: Summary of Relevant Abstracts

Data source	Author, year, and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Published Abstract	Elliott SP, 2022, AUA, New Orleans USA[42]	Prospective, single arm, multi-center	Recurrent anterior urethral stricture	Optilume DCB	N/A	Recurrence Retreatment Symptom scores Peak flow rate
Published Abstract	Lau G, 2022, ICS, Vienna, Austria[43]	Prospective, single arm, single center	Recurrent anterior urethral stricture	Optilume DCB	N/A	Patient experience receiving treatment in outpatient setting versus day surgery Tolerability of procedure under local anaesthetic only and post-procedure pain Recovery Comparison to conventional treatments for urethral stricture
Published Abstract	Zhong W, 2022, USANZ, Gold Coast, Australia[44]	Prospective, single arm, single center	Recurrent and challenging anterior urethral strictures	Optilume DCB	N/A	Safety Average flow rate Peak flow rate Symptom scores
Published Abstract	Aube-Peterkin M, 2022, CUA, Charlottetown, Canada[45]	Prospective, randomized, multi-center	Recurrent anterior urethral stricture	Optilume DCB	Dilation/DVIU	Recurrence Retreatment Symptom scores Peak flow rate Safety

Table 8: Summary of all ongoing/unpublished studies

Study reference/ID	Study type	Study population	Study arms (No. of randomized/included patients)	Study duration, data cut off(s) and locations	Study endpoints
ROBUST I (NCT03014726)	Interventional, prospective, open label, single arm, multi-center	Male subjects ≥18 years old, Visual confirmation of stricture via cystoscopy or urethrogram, Single lesion anterior urethral stricture or bladder neck contracture ≤2cm, ≥1≤4 prior diagnosis and treatment of the same urethral stricture (inc. self-catheterization, dilation and/or DVIU but no prior urethroplasty), significant LUTs symptoms, IPSS ≥13, urethral lumen diameter <12Fr by urethrogram, able to complete validated questionnaire independently, Qmax <10ml/s	Optilume Urethral DCB; N = 53	Study Duration: 5 years Start date: November 2016 Primary Completion Date: October 2018 Est. Study Completion Date: April 2023 Location (No. of Sites): Latin America (4)	Primary: Rate of treatment related serious complication [timeframe: 90 days post-procedure], Device related formation of fistula; device related de novo severe urinary retention Secondary: Stricture recurrence rate ([timeframe: 90 days post-procedure, Improvement in IPSS (International Prostate Symptom Score)
ROBUST II (NCT03270384)	Interventional, prospective, open label, single arm, multi-center	Male subjects ≥18 years old, Visual confirmation of stricture via cystoscopy or urethrogram, Single lesion anterior urethral stricture ≤3cm, ≥2 prior diagnosis and treatment of urethral stricture (inc. self-catheterization, dilation and/or DVIU but no prior urethroplasty), significant LUTs symptoms, IPSS ≥13, urethral lumen diameter <12Fr by urethrogram, able to complete validated questionnaire independently, Qmax <15ml/s, guidewire must be able to cross the lesion	Optilume Urethral DCB; N = 16	Study Duration: 5 years Start date: October 25, 2017 Primary Completion Date: November 1, 2019 Est. Study Completion Date: June 2024 Location (No. of Sites): United States (5)	Primary: Safety – Rate of Device Related Serious Complications [timeframe: 90 days] Secondary: Safety – Change in IIEF (International Index of Erectile Function) [timeframe: 90 days], Efficacy – Stricture Recurrence [timeframe: 6 months]
ROBUST III (NCT03499964)	Interventional, prospective,	Male subjects ≥18 years old, Visual confirmation of stricture via cystoscopy	Intervention group: Optilume	Study Duration: 5 years Start date: June 22, 2018	Primary: Safety – Rate of Device Related Serious

	randomized (2:1), single blinded, multi-center	or urethrogram, Single tandem or diffuse lesion anterior urethral stricture(s) ≤3cm, ≥2 prior treatments of the same urethral stricture (including DVIU and/or dilation, but no prior urethroplasty), significant LUTs symptoms, IPSS ≥11 (assumed to be "35" if suprapubic catheter is present), urethral lumen diameter <12Fr by urethrogram, able to complete validated questionnaire independently, Qmax <15ml/s (assumed to be "0" if suprapubic catheter is present), guidewire must be able to cross the lesion	Urethral DCB; N = 79 Control Group(s): DVIU; N = 12 Dilation; N = 36	Primary Completion Date: December 10, 2020 Est. Study Completion Date: December 2025 Location (No. of Sites): United States (21), Canada (1)	Complications [timeframe: 90 days] Secondary: Safety – Change in IIEF (International Index of Erectile Function) [timeframe: 90 days], Efficacy – Stricture Recurrence [timeframe: 6 months]
Optilume Registry for the treatment anterior urethral stricture (NCT05479422)	Observational, prospective, Open label, single arm, multi-centre	Male subjects ≥18 years old, subjects diagnosed with recurrent urethral stricture ≤3cm in the anterior urethra to be treated with Optilume Urethral DCB in accordance with approved instructions for use, subjects provide written informed consent using approved consent forms and willing to comply to standard follow-up assessments	Optilume Urethral DCB; N = 150	Study Duration: 5 years Start date: June 22, 2018 Primary Completion Date: August 15, 2029 Est. Study Completion Date: August 15, 2029 Location (No. of Sites): Pan-European (15)	Primary: Responder rate defined as proportion of subjects experiencing <30% improvement in IPSS without repeat intervention [timeframe: 12 months], Rate of treatment related serious adverse events [timeframe; 3 months]
STREAM (NCT05383274)	Interventional, Prospective, single arm, multi-center	Male subjects ≥22≤55 years old, subjects diagnosed with a stricture in the anterior urethra to be treated with Optilume Urethral DCB in accordance with approved instructions for use, subjects provide written informed consent and willing to comply to standard follow-up assessments, subjects able to provide viable semen samples and baseline semen quality characteristics are above reference values based on WHO criteria (average 2 samples); ejaculate volume	Optilume Urethral DCB; N = 34	Study Duration: 2 years Start date: February 14, 2022 Primary Completion Date: November 30, 2023 Est. Study Completion Date: August 30, 2024 Location (No. of Sites): United States (5)	Primary: Safety [timeframe: 3 months] (average change in sperm concentration from baseline) Secondary: Safety [timeframe: 6 months] (proportion of subjects experiencing ≥50% decrease in sperm concentration from baseline at 3 and 6 months)

		≥1.5mL, total sperm ≥39 million, sperm concentration ≥15 million/mL, total motility ≥40%, progressive motility ≥32%, morphology ≥4%			

Table 9: Results of relevant studies (from tables 1, 2 and 3)

Study	Results
ROBUST I[27]	Study Population A total of 53 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture length was 0.9cm, while average number of prior dilations was 1.7. The first 25 subjects were treated with a 24F drug coated balloon, and the last 28 subjects were treated with a 30F drug coated balloon. Efficacy Outcomes Subjects were assessed for anatomic success at 6 months and 12 months via the ability to pass a 16F flexible cystoscope. Success was achieved in 75% (36/48) of subjects at 6 months and 77% (36/47) at 12 months. Symptom scores (IPSS, USS-PROM) showed immediate improvement that was sustained through 4-year follow-up. A total of 71% of subjects exhibited functional success at 4 years, defined as at least a 50% improvement from baseline in IPSS score without repeat intervention. Freedom from repeat intervention was 83% at 1 year, 81% at 2 years, 77% at 3 years, and 73% at 4 years. Only 2 of 24 (8.3%) subjects treated with a 30F DCB received repeat treatment at 2 years. Safety Outcomes Device-related adverse events were mild or moderate in nature and resolved quickly after onset. The most common adverse event was urinary tract infection (20.8%), followed by dysuria, fever, acute urinary retention, and urethral stricture (9.4% for each event). There were no serious treatment-related adverse events.
ROBUST II[28]	Study Population A total of 16 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture length was 2.1cm and the average number of prior dilations was 4.1. Subjects were treated with a mix of 30F and 24F balloons based on urethrogram measurements, with the majority (88%) utilizing 30F. Efficacy Outcomes Anatomic success was measured at 6 months post-procedure, with 11 of 15 subjects (73%) exhibiting success. Symptom scores (IPSS and USS-PROM) showed immediate improvement from baseline that was sustained through 1 year. Qmax also showed immediate improvement sustained through 1 year. Safety Outcomes There were no treatment related serious complications. There were 4 device-related events: 2 mild events of haematuria, 1 case of mild bladder spasms, and 1 case of acute urinary retention within 24 hours of Foley catheter removal. All 4 events resolved without sequelae within a month of onset.

Study	Results
ROBUST III[29]	Study Population A total of 127 subjects with recurrent anterior urethral strictures were randomized 2:1 to receive the Optilume DCB (n=79) or dilation/DVIU (n=48). Average stricture length was 1.7cm, and subjects had an average of 3.6 prior dilations. Most subjects (~90%) received treatment with a 30F DCB. Control group strictures were treated with standard dilation (~75%) or DVIU (~25%). Efficacy Outcomes Ancillary endpoints evaluating clinical and symptomatic improvement showed immediate improvement post-procedure that was sustained through the 1-year follow up for the Optilume arm, consistent with 1 year published results from ROBUST I and II. Anatomical success for Optilume Urethral DCB was significantly higher than control at 6 months (75% vs 27%, p<0.001). Subjects improved from an average IPSS of 22.0 at baseline to 9.0 at 1-year follow up. Qmax improved from an average of 7.6 mL/sec at baseline to 15.5 mL/sec at 1 years for the Optilume arm. Outcomes were consistent among subgroups with ≥5 vs <5 dilations and for lengths <2cm vs ≥2cm. The Control group showed an immediate functional and symptomatic improvement, but this improvement was not sustained through the 1 year follow up. Control subjects had an average IPSS of 22.9 at baseline that improved to 9.5 at 30 days but returned to near baseline levels (19.8) at 1-year. Similarly, Qmax improved from an average of 7.4 mL/sec at baseline to 15.8 at 30 days but returned to 8.0 mL/sec at the 1-year timepoint. Freedom from repeat intervention was significantly higher in the Optilume Urethral DCB arm with 83.2% of subjects remaining free from repeat intervention of their stricture at 1-year follow up. Freedom from repeat intervention was only 21.7% at 1-year post-procedure for the Control group. Observed results for the rate of stricture recurrence in the Control arm were consistent with those reported in literature for patients undergoing repeat dilation[22]. Immediate symptom and urinary flow rate improvement was significant in both groups, with the benefit being more durable in the Optilume Urethral DCB group. Safety Outcomes No subjects experienced a primary safety endpoint event in either arm, while the rate of acute urinary retention through 6 months was numerically lower in the Optilume DCB arm (1.3% vs 6.3%). AE types and rates were well matched between groups, except that the DCB group had higher rates of post-procedure haematuria and dysuria compared to controls (11.4% vs 2.1% for both event types). These events were judged as mild in nature and resolved within 30 days in 10 of 11 men.
Pickard R, The OPEN RCT Health Technology Assessment, 2020[25]	Study Population The OPEN RCT enrolled subjects with recurrent bulbar urethral strictures. Subjects were randomized to receive urethroplasty or urethrotomy. Baseline characteristics included an average stricture length of 2.0cm in the urethroplasty group and 1.7cm in the urethrotomy group. Patients had undergone an average of 1.9 or 1.8 prior urethrotomies at the time of the index procedure for urethroplasty and urethrotomy groups, respectively. A total of 71 of 108 (66%) of subjects randomized to urethroplasty underwent the surgery, while 90 of 112 (83%) of those

Study	Results
	randomized to urethrotomy underwent the procedure. Only 47.2% of subjects randomized to urethroplasty completed 24-month questionnaires, while 50.9% randomized to urethrotomy completed 24-month questionnaires. Efficacy Endpoint: The primary efficacy endpoint was the Area Under the Curve (AUC) over 24 months for symptom scores according to the USS-PROM questionnaire (0 to 24, higher being more symptomatic). The AUC for urethroplasty was 7.4 ± 3.8 at 24 months, while the AUC for urethrotomy was 7.8 ± 4.2. The outcome was not significantly different between arms. Freedom from repeat intervention was seen in 78 of 93 (84%) men in the urethroplasty arm and 75 of 104 (72%) in the urethrotomy arm. Initiation of intermittent self-dilation was not considered a repeat intervention. Recurrence, identified as repeat intervention or significant evidence of stricture recurrence (symptoms or flow), occurred in 19 of 93 urethroplasty patients (20.4%) and 39 of 104 (37.5%) in the urethrotomy arm. Freedom from recurrence was therefore 79.6% and 62.5% respectively. Safety Endpoints Reported complications over the course of the study are summarized by adding those reported in the perioperative period to those during follow-up. Complications included mouth pain (13.9%), urinary tract infection (8.0%), erectile dysfunction (5.0%), wound pain (5.0%), wound infection (4.0%), bladder spasm (2.0%), and urethrocutaneous fistula (1.0%) in the urethroplasty arm. Urethrotomy complications included urinary tract infection (5.8%), mouth pain (5.7%), erectile dysfunction (1.9%), and wound infection (1.9%).
Steenkamp, J Urol, 1997[19]	Study Population Subjects presenting with anterior urethral strictures were randomized to receive dilation with bougies/sounds (n=106) or DVIU (n=104). Approximately 30% of subjects in each arm had received a prior dilation of the study stricture. Average stricture length was 2.4cm in the dilation arm and 2.2cm in the urethrotomy arm. Strictures were in the bulbar urethra in 53% of dilation subjects and 67% of urethrotomy subjects. Subjects were followed every 3 months for one year, and annually thereafter. Assessments for stricture recurrence included urethrogram and/or passage of a 16F catheter. Efficacy outcomes Freedom from stricture recurrence was noted in approximately 50% of subjects at 12 months and was maintained above 40% through 4 years. Rate of recurrence was maximal at 6 months post-treatment and was not different between arms. Strictures >4cm in length had the worst outcomes. Safety Outcomes Adverse events were not reported
Heyns, J Urol, 1998[22]	Study Population

Study	Results
	Population is the same as reported by Steenkamp (J Urol, 1997). Further analysis was conducted evaluating performance after repeat dilation/urethrotomy. Follow-up included on 163 of original 210 subjects. Efficacy Outcomes Freedom from stricture recurrence was evaluated through 48 months follow-up and was not different between dilation and urethrotomy. Repeat urethrotomy/dilation performed progressively worse, with higher recurrence rates and faster time to recurrence for each subsequent endoscopic treatment. Subjects undergoing a third dilation/urethrotomy for recurrent stricture had a 20% success rate at both 6 and 12 months, compared to an approximately 55% success rate for a second dilation/urethrotomy, and approximately 70% for a single dilation/urethrotomy at 12 months. Long-term success for 2 or 3 dilations was 0%. Safety Outcomes Adverse events were not reported
Jordan, J Urol, 2013[34]	Study Population The study evaluated the Memokath 044TW urethral stent against standard of care endoscopic dilation/urethrotomy in the treatment of recurrent bulbar strictures, randomized in a 2:1 fashion. A total of 63 subjects were randomized to receive Memokath, 29 randomized to Control. Average stricture length was 2.7cm for Memokath and 2.7cm for Control. Subjects in both arms had an average of 2 prior interventions for the study stricture. Efficacy Outcomes Stricture recurrence was measured by the ability to pass a calibrated 16F cystoscope through the treated area during follow up. Freedom from recurrence was noted in approximately 80% of subjects in the Memokath arm and 40% of subjects in the Control arm at 6 months. This figure decreased to 45% and 20% in Memokath and Control, respectively, at 12 months. In the entire study period (15 months), 3 of 27 (11.1%) of subjects were free from recurrence in the Control arm. IPSS and Qmax showed immediate improvement in both arms post procedure. Safety Outcomes Bacteriuria/UTI was noted in 49% of subjects in the Memokath group and 7% in the Control group. The Memokath group also experienced high rates of incontinence (19%) and hematuria (16%).
Hoy NY, Urology, 2013[38]	Study Population A total of 163 underwent open reconstruction of bulbar urethral strictures utilizing a buccal mucosal graft in a dorsal onlay fashion. Follow-up data was collected prospectively at 3 weeks (Foley removal), 6 months (cystoscopy), and 12 months if findings of concern at 6 months. Mean stricture length was 4.9cm and 93% had at least one prior dilation. Efficacy Outcomes Freedom from stricture recurrence was identified in 157 of 163 patients (97%) at 6 months. Safety Outcomes

Study	Results
	Post-void dribbling was noted in 68 of 163 subjects (41.7%), UTI noted in 6 (3.7%), ED in 5 (3.1%), and testicular pain in 17 (10.4%).
Cecen K, Urol Int, 2014[32]	Study Population A total of 136 male patients with urethral stricture were randomized between PlasmaKinetic urethrotomy (n=70) vs cold knife urethrotomy (DVIU, n=66). Most strictures (57%) were in the bulbar urethra, and none had received prior dilations/urethrotomy. Average stricture length was 1.3cm. Follow up was conducted at 3 months, 9 months, and 18 months. Efficacy Outcomes Stricture recurrence was monitored by uroflowmetry, with subjects exhibiting Qmax <12mL/sec having urethrogram/cystoscopy to verify stricture recurrence. In the PlasmaKinetic group, 14% of subjects exhibited a recurrence at 9 months while 37% had recurrence at 18 months. The DVIU group had 30% and 33% recurrence rates at 9 and 18 months, respectively. Measured Qmax at 3 months was 16.1 mL/sec in PlasmaKinetic group vs 15.2 mL/sec in the DVIU group. Safety Outcomes Adverse events were not reported.
Azab SS, Scan J Urol, 2020[31]	Study Population A total of 88 subjects with verified strictures were randomized to Amplatz dilators (n=44) or DVIU (n=44). Strictures were primarily located in the bulbar urethra (45% and 41% for Amplatz and DVIU. Average stricture length in each group was 1cm, and all were primary (i.e. no prior interventions). Follow-up continued through 12 months. Efficacy Outcomes Symptom scores measured via IPSS improved from 21 at baseline to 16 and 18 at 12 months for Amplatz and DVIU, respectively. Qmax improved from 8mL/sec at baseline to 18 and 22 mL/sec for Amplatz and DVIU, respectively, at 12 months. No recurrence was noted in either arm through 12 months, however this was not clearly defined. Safety Outcomes The Amplatz group showed a 16% rate of mild hematuria, while the DVIU group had 11% of patients develop intra-operative bleeding and 7% showing urethral extravasation.
Elkady E, J Urol, 2018[40]	Study Population A total of 60 patients were randomized to standard urethroplasty (n=30) or muscle/nerve sparing technique urethroplasty (n=30). Mean stricture length was 3.3cm and 3.5cm for these groups, respectively. Efficacy Outcomes Success reported as freedom from repeat intervention, which was achieved in 88% of the standard urethroplasty group and 92% of the muscle-sparing group.

Study	Results
	Safety Outcomes Subjects in the standard urethroplasty group experienced complications including ejaculatory dysfunction (40%), post-void dribbling (36%), wound infection (4%), and urethral extravasation (4%). Subjects in the muscle sparing group experienced ejaculatory dysfunction (8%), post-void dribbling (4%), and wound infection (4%).
Isen K, Int Urol Nephrol, 2015[35]	Study Population A total of 21 subjects with short (<1cm) primary urethral strictures were treated with DVIU utilizing endoscopic scissors. Mean stricture length was 0.7cm, with no prior dilations. Efficacy Outcomes Stricture recurrence as measured by urethrogram was 0% at 3 months. Mean follow-up was 8 months, with 3 of 21 (14%) requiring repeat DVIU in that time period. Qmax increased from 8mL/sec at baseline to 19.4mL/sec at 3 months. Safety Outcomes Urinary tract infection was reported in 2 of 21 subjects (9.5%).
Guo FF, World J Urol, 2010[33]	Study Population A total of 238 subjects were treated with thulium laser urethrotomy. Stricture length was 2.6cm on average, with no detail given on prior interventions. Efficacy Outcomes Stricture recurrence occurred in 43 of 238 subjects (18%) through 6-month follow-up. IPSS improved from 28 to 5.3 at 6 months, while Qmax improved from 3.2mL/sec to 19.2mL/sec. Safety Outcomes Seven patients (3%) experienced incontinence (type not specified).
Aldaqadossi H, Int J Urol, 2014[39]	Study Population Subjects were prospectively randomized to receive dorsal onlay buccal graft urethroplasty (n=25) vs dorsal inlay (n=22). Mean stricture length was 4.9cm for the onlay group and 4.4cm for the inlay group. Strictures were primarily penile (56% onlay, 55% inlay). Strictures were recurrent in 34 of 47 (72%), with an average of 1.7 prior interventions per patient/ Efficacy Outcomes Freedom from stricture recurrence was experienced in 88% in the dorsal onlay group vs 86.4% in the dorsal inlay group through 12 months. IPSS and Qmax improved postoperatively, with no timeframe given for measurements. Safety Outcomes

Study	Results
	One patient in the dorsal onlay group (4%) required blood transfusion during the surgery. Wound infections were noted in 12% and 13.6% of patients in the onlay and inlay group, respectively. Other complications included chordee (8%), extravasation (4%), and post-void dribble (16%).
Pansadoro V, J Urol, 1996[20]	Study Population A total of 450 subjects with anterior urethral stricture were evaluated, with 224 subjects treated with DVIU included in this series. Subjects were excluded if they had less than 5 years of follow-up. Mean stricture length was 1.6cm, with only 12% being recurrent. Efficacy Outcomes Overall success was achieved in 62% at 1 year, 46% at 2 years. Urethrotomy failed in all subjects with recurrent strictures. Stricture length >1cm was a significant predictor for recurrence, with only 18% of subjects with a bulbar stricture >1cm in length having a successful outcome. Safety Outcomes Urethral bleeding occurred in 24 of 224 (10.7%), extravasation in 6 (2.7%), and chordee in 2 (0.9%).
Erickson BA, Urology, 2014[41]	Study Population Subjects were prospectively enrolled in a multi-institutional study with defined cystoscopic follow-up at 3 months and 12 months. No information was given on stricture characteristics, but the techniques used were excision and primary anastomosis (63.8%) and substitution (36.2%). The majority of urethroplasties being EPA indicate the stricture length was relatively short. Compliance with follow-up cystoscopy was 79.8% at 3 months and 54.4% at 12 months, indicating poor follow-up compliance. Efficacy Outcomes Stricture anatomic success was defined as the ability to pass a 16F flexible cystoscope. Success was 97.2% for EPA and 85.5% for substitution urethroplasty at 3 months. Those outcomes at 12 months were 85.5% and 77.5%, respectively. Safety Outcomes No safety outcomes were reported here.
Santucci R, J Urol, 2010[37]	Patient Population A retrospective chart review was conducted to review outcomes after multiple repeat DVIU procedures in non-complex anterior strictures. Average stricture length was 1.5cm in the 50 subjects in whom this data was available. Efficacy Outcomes Freedom from stricture recurrence (repeat intervention) was approximately 35% at 1 year and 30% at 2 years for those receiving only 1 DVIU. Freedom from recurrence after the third DVIU was approximately 20% at 1 year and 0% at 2 years.

Study	Results
	Safety Outcomes None listed

5 Details of relevant published studies

ROBUST I[27]	
How are the findings relevant to the decision problem?	A total of 53 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB. Average stricture length was 0.9cm, while average number of prior dilations was 1.7. Subjects were assessed for anatomic success at 6 months and 12 months via the ability to pass a 16F flexible cystoscope. Success was achieved in 75% (36/48) of subjects at 6 months and 77% (36/47) at 12 months. Symptom scores (IPSS, USS-PROM) showed immediate improvement that was sustained through 3-year follow-up. A total of 67% of subjects exhibited functional success at 3 years, defined as at least a 50% improvement from baseline in IPSS score without repeat intervention. Freedom from repeat intervention was 83% at 1 year, 81% at 2 years, and 77% through 3 years. Only 2 of 24 (8.3%) subjects treated with a 30F DCB received repeat treatment at 2 years. In comparison, multiple endoscopic treatments of the same stricture are proven to lead to progressively worse outcomes. After a third endoscopic treatment, the failure rate is as high as 75% by 6 months and 100% by two-years post-treatment[22].
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	The study is small in terms of patient numbers and was done in the Dominican Republic and Panama. Pre-dilation was a requirement as part of the design protocol in the study. Non-comparative study.
How was the study funded?	Urotronic, Inc. (the Manufacturer)
ROBUST II[28]	
How are the findings relevant to the decision problem?	A total of 16 subjects with recurrent bulbar urethral strictures were enrolled and treated with the Optilume DCB without prior pre-dilation in 56% of the study population (N=9/16). Average stricture length was 2.1cm and the average number of prior dilations was 4.1. Anatomic success was measured

	at 6 months post-procedure, with 11 of 15 subjects (73%) exhibiting success. Symptom scores (IPSS and USS-PROM) showed immediate improvement from baseline that was sustained through 1 year. Qmax also showed immediate improvement sustained through 1 year.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	The study is small in terms of patient numbers in a limited number of US centres. Non-comparative study and lacked a control arm.
How was the study funded?	Urotronic, Inc. (the Manufacturer)
ROBUST III[29]	
How are the findings relevant to the decision problem?	A total of 127 subjects with recurrent anterior urethral strictures were randomized 2:1 to receive the Optilume DCB (n=79) or dilation/DVIU (n=48). Average stricture length was 1.7cm, and subjects had an average of 3.6 prior dilations. Most subjects (~90%) received a 30F DCB. Control group strictures were treated with standard dilation (~75%) or DVIU (~25%). Anatomic success was measured at 6 months post-procedure, with 75% of DCB subjects exhibiting success compared to 27% in the Control arm. This treatment effect was consistent among subgroups, including stricture length (≥2cm vs <2cm) and prior dilations. Outcomes were not statistically different between dilation and DVIU in the Control group, with DVIU having an anatomic success rate of 17%). IPSS and Qmax improved in both arms immediately post-procedure. These improvements were sustained through 1 year in the Optilume DCB group, while they returned to approximately baseline levels in the Control group by 1 year. Kaplan Meier estimates of freedom from repeat intervention at one year (395 days) were 83.2% in the Optilume arm and 21.7% in the Control arm.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population Effective minimally invasive treatment

What are the limitations of this evidence?	Pre-dilation was a requirement as part of the design protocol in the study.
How was the study funded?	Urotronic, Inc. (the Manufacturer)
The OPEN RCT[25]	
How are the findings relevant to the decision problem?	The OPEN RCT represents a large-scale, multi-centre randomized trial comparing endoscopic management with urethroplasty for recurrent bulbar strictures. The study encountered numerous issues during execution of the study, including slow enrolment leading to early termination/sample size adjustment. Randomization was completed well before treatment (approximately 3 months on average), leading to a large proportion of subjects opting to not receive their randomized therapy. Only 67% of subjects randomized to receive urethroplasty received the treatment. The authors attempt to account for this issue by only reporting results for those that received each therapy (As-Treated), however the large degree to which this population differs from the Intent-to-Treat (ITT) analysis set largely negates the benefit of randomization and introduces a high degree of bias. Lastly, follow-up was conducted remotely via mailing of questionnaires to the subjects. Subject response to questionnaires was below 50% at the 2-year timepoint. Despite the challenges identified with study design and execution, the data offer one of the only multi-institution comparative analyses of endoscopic and surgical management of urethral strictures. It appears as though symptom improvement was similar between the two therapies throughout the 24-month follow-up, with both showing immediate improvement that was generally sustained through 24 months. The low rate of questionnaire response may introduce bias, although the direction of bias is unclear (i.e., no response because feeling good or no response because unhappy with outcomes and sought treatment elsewhere). Freedom from repeat intervention was assessed via patient response to a questionnaire, so the low rate of response leads to uncertainty in the outcome. However, freedom from repeat intervention rates in the urethroplasty group were comparable to those reported in the ROBUST I trial at 2 years in a similar patient population.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Could include only 159/220 (72%) participants in the primary analysis: 69 (63%) allocated to urethroplasty and 90 (81%) to urethrotomy. The study timeframe ceases at 24-months whereas previous published data indicate further subject deterioration out to 48-months in the group of patients

	receiving endoscopic treatment, suggesting longer term evidence would be more applicable to determine true freedom from recurrence and reintervention. Whilst the study is a comparative study, the study sites included are all reconstructive urology sites with experienced urethral reconstructive experts familiar in treating urethral stricture disease thus, findings likely represent a better than real world experience outside of the reconstructive urology field
How was the study funded?	National Institute of Health Research (NIHR)
Steenkamp, J Urol, 1997[19]	
How are the findings relevant to the decision problem?	This study represents one of the largest randomized comparisons between different endoscopic therapies, i.e., dilation with sounds/bougies or direct vision internal urethrotomy. The follow-up protocol was also one of the most extensive reported, with urethral calibration (i.e., determination of urethra diameter) conducted at each visit to screen for recurrence. Key findings from this study that have been confirmed in subsequent analyses include the fact that recurrence outcomes after dilation and DVIU are statistically similar. Additionally, long-term outcomes after dilation/DVIU are sub-optimal, with success below 50% at 4 years. Other key learnings include a hazard analysis for recurrence, which shows the highest risk for recurrence is centred around 6 months post-procedure.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Dated, single centre study
How was the study funded?	Unknown
Heyns, J Urol, 1998[22]	
How are the findings relevant to the decision problem?	This publication is a follow-on to the Steenkamp publication listed above. Subjects in the initial cohort that had recurrence and required subsequent repeat dilation were continued to be followed. Key learnings from this publication are the fact that subsequent dilation or internal urethrotomies lead to increasingly poor outcomes, with repeat dilation/DVIU exhibiting recurrence 100% of the time by 2 years.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective)

	Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Dated, Single centre study
How was the study funded?	Unknown
Jordan, J Urol, 2013[34]	
How are the findings relevant to the decision problem?	The Memokath 044TW is a self-expanding urethral stent intended to be placed in the intermediate term (e.g., <12m) and eventually removed. This study was well designed and executed, with follow-up including both anatomic assessments and symptom/flow rate assessments. A 6-month endpoint for recurrence, assessed by passage of a 16Fr flexible scope, was chosen largely on the outcomes reported by Steenkamp indicating stricture recurrence was likely to occur by 6-9 months. Anatomic success and repeat intervention outcomes for the Control arm in this study were generally similar to those reported in ROBUST III and the Heyns publication for repeat dilation. This study confirms that repeat DVIU has low long-term success, with only 11% of subjects in the Control arm being free from recurrence at 15 months.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Relatively short follow-up duration, small population,
How was the study funded?	Unknown
Hoy NY, Urology, 2013[38]	
How are the findings relevant to the decision problem?	This is one of the largest cohort studies published utilizing currently accepted urethroplasty techniques for dorsal onlay buccal mucosal graft. Pre-specified follow-up was well documented, and compliance was high. Success rates at 6 months were very high, potentially owing to the high-volume nature of the center leading to significant experience and skill for the single surgeon performing the surgeries. Hospital stay (48hrs) and catheter dwell time (3 weeks) for urethroplasty are much longer than for endoscopic procedures, it is uncertain the degree to which mild adverse events were documented through the full follow-up period
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Rapid return to normal daily living and improved quality of life Reduces the need for retreatments or invasive surgical procedures Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources

What are the limitations of this evidence?	Lack of surgeon heterogeneity, a reliance on the patients to report obstructive symptoms after the second follow-up period at 12 months after surgery, which might have led to an underestimation of stricture recurrence, and the smaller number of patients with long-term follow-up data. Dependence on both subjective reporting of symptoms and a normal cystoscopic appearance at 6 months to determine the need for 12-month cystoscopy might have led to an underestimation of cystoscopic recurrence but not symptomatic recurrence. Single arm, Single centre
How was the study funded?	Unknown
Cecen K, Urol Int, 2014[32]	
How are the findings relevant to the decision problem?	This large, randomized study evaluated a 'hot knife' or laser urethrotomy device against the standard 'cold knife' urethrotome for DVIU. The strictures under study were primary, meaning they had not received prior treatment. Both arms showed freedom from recurrence around 65% at 18 months even for treatment-naïve strictures, which is a much easier population than those enrolled in the ROBUST series.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Single centre
How was the study funded?	Unknown
Azab SS, Scan J Urol, 2020[31]	
How are the findings relevant to the decision problem?	This moderately sized randomized study compared dilation with DVIU and showed only modest improvement in symptom scores (IPSS) with more apparent improvement in peak flow rate. These short, treatment naïve strictures did not recur over the course of follow-up, however it is not clear how diligent the follow-up program and compliance were. Of note, this study was one of the only to report peri-procedural adverse events, noting mild hematuria in up to 16% of subjects and a relatively high rate of extravasation after DVIU which required extended Foley catheter time.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population

What are the limitations of this evidence?	Single centre, all primary treatments of small stricture length >3cm
How was the study funded?	Unknown
Elkady E, J Urol, 2018[40]	
How are the findings relevant to the decision problem?	This small, randomized study evaluated a new technique to attempt to reduce the rate of post-void dribbling and ejaculatory dysfunction. Follow-up was short (1 year) and success was approximately 90%, with minimal surveillance criteria for recurrence.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Single centre, long average stricture length
How was the study funded?	Unknown
Isen K, Int Urol Nephrol, 2015[35]	
How are the findings relevant to the decision problem?	This small case series on DVIU utilizing endoscopic scissors on short, treatment naïve strictures. Follow-up was short (mean 8 months), however freedom from recurrence was 86%. The rate of UTI noted in this study after DVIU was comparable to ROBUST III.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Single centre, single arm, small study of short stricture length, all primary stricture treatments
How was the study funded?	Unknown
Guo FF, World J Urol, 2010[33]	
How are the findings relevant to the decision problem?	This large cohort study from China reported the use of a 'hot knife' urethrotomy device in treatment naïve strictures. Follow-up was generally short, with 82% free from recurrence at 6 months.

Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Single centre, single arm, small study, all primary stricture treatments
How was the study funded?	Unknown
Aldaqadossi H, Int J Urol, 2014[39]	
How are the findings relevant to the decision problem?	Freedom from stricture recurrence was experienced in 88% in the dorsal onlay group vs 86.4% in the dorsal inlay group through 12 months. IPSS and Qmax improved postoperatively, with no timeframe given for measurements.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	No timeframe given for IPSS and Qmax measurements, single centre
How was the study funded?	Unknown
Pansadoro V, J Urol, 1996[20]	
How are the findings relevant to the decision problem?	This is one of the earliest large reports of DVIU outcomes with long-term follow-up. Most strictures were treatment naïve, with freedom from recurrence only 62% at 1 year. Recurrent strictures had a 0% success rate. Complications reported included urethral bleeding/hematuria at a similar rate to that reported for Optilume in ROBUST III
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Dated, Single centre, single arm

How was the study funded?	Unknown
Erickson BA, Urology, 2014[41]	
How are the findings relevant to the decision problem?	This multi-institutional report on anatomic outcomes after urethroplasty offers one of the only multi-institution reports of urethroplasty outcomes. Success at 1 year ranged from 77.5% to 85.5% depending on surgery type. These lower rates of success than those reported previously may indicate that outcomes may vary by surgeon and by experience/skill level.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	Study design was meant only to analyze the utility of the short-term cystoscopic protocol, compliance rates for follow-up were poor, perhaps biasing our anatomic success rates. Dated, Single centre study
How was the study funded?	Unknown
Santucci R, J Urol, 2010[37]	
How are the findings relevant to the decision problem?	This article reinforces the idea that repeat treatments, including repeat DVIU, lead to progressively worse outcomes. After the second treatment, subsequent treatments would be expected to fail 100% of the time.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Rapid and sustained improvement in symptoms and urinary flow Reduces the need for self-catheterisation management Rapid return to normal daily living and improved quality of life Preservation of sexual function Reduced burden of repeat procedures Reduced re-admission rates (elective or non-elective) Reduction in hospital resource use, such as theatre operating time, associated staffing costs and in-patient resources Stricture characteristics represent a difficult patient population
What are the limitations of this evidence?	It was a retrospective review and there was no standard objective measure for recurrence. Not all urethrotomies were performed by the same surgeon. Single arm, single center study
How was the study funded?	Unknown

6 Adverse events

No adverse events/incidents have been reported in any regulatory database. Event rates and types for the Optilume Urethral DCB are generally similar to other endoscopic therapies. There was a trend toward higher rates of mild haematuria (blood in urine) and dysuria (pain/discomfort during urinary) in the immediate post-operative setting, however the differences did not reach statistical significance and these events did not require any treatment.

7 Characteristics of the interventions in the included studies

Table 10: Interventions and comparators for all relevant included studies

Study reference/ID	Study Intervention	Study comparator
ROBUST I (NCT03014726)	Optilume Urethral DCB + pre-dilation using uncoated balloon (31/53 subjects), DVIU (8/53) & Balloon + DVIU (14/53)	None
ROBUST II (NCT03270384)	Optilume Urethral DCB + pre-dilation using uncoated balloon (3/16 subjects), DVIU (2/16), Balloon + DVIU (1/16) and NONE (10/16)	None
ROBUST III (NCT03499964)	Optilume Urethral DCB pre-dilation using uncoated balloon (73/79 subjects), DVIU (4/79) & Balloon + DVIU (2/79).	Standard of care: Urethral sounds (8/48 subjects), uncoated balloon (28/48) & DVIU (12/48)

Table 11: Information on the course for all relevant included studies

Study reference/ID	Study Intervention (Optilume Urethral DCB)	Relevant Comparator (standard of care; urethral sounds, uncoated balloon and/or DVIU)
ROBUST I (NCT03014726)	N = 53	N/A
Treatment duration [mins] Median [Min; Max] Mean (SD)	Intraoperative	N/A
Observation period [months] IPSS, QOL, Qmax (mL/Sec), PVR (mL), USS PROM, IIEF-OS, IIEF-EF, Freedom From Repeat Intervention Median [Min; Max] Mean (SD) Functional (Anatomic) Success Rate %, Median [Min; Max] Mean (SD)	Baseline, 3 months, 6 months, and annually through to 5 years Baseline, 6 months	N/A
ROBUST II (NCT03270384)	N = 16	N/A
Treatment duration [<month/weeks>] Median [Min; Max] Mean (SD)	Intraoperative	N/A

Observation period [months] IPSS, QOL, Qmax (mL/Sec), PVR (mL), USS PROM, IIEF, Freedom From Repeat Intervention, IPSS Responder Rate Median [Min; Max] Mean (SD) Functional (Anatomic) Success Rate %, Median [Min; Max] Mean (SD)	Baseline, 3 months, 6 months, and annually through to 5 years Baseline, 6 months	N/A
ROBUST III (NCT03499964)	N = 79	N = 48
Treatment duration [mins] Median [Min; Max] Mean (SD)	Intraoperative	Intraoperative
Observation period [months] IPSS, QOL, Qmax (mL/Sec), PVR (mL), USS PROM, IIEF, Freedom from Repeat Intervention, IPSS Responder Rate Median [Min; Max] Mean (SD) Functional (Anatomic) Success Rate %, Median [Min; Max] Mean (SD)	Baseline, 3 months, 6 months, and annually through to 5 years Baseline, 6 months	Baseline, 3 months, 6 months, and annually through to 5 years Baseline, 6 months

Table 12: Comparative studies included in the assessment by patient population for Optilume Urethral DCB by PICO

PICO 1 – Optilume Urethral DCB vs Urethrotomy	
Study Reference/ID	**Analysed Population**
ROBUST III https://clinicaltrials.gov/ct2/show/NCT03499964 Optilume Urethral DCB – N = 79 Urethrotomy – N = 12	Male subjects ≥18 years old, Visual confirmation of stricture via cystoscopy or urethrogram, Single tandem or diffuse lesion anterior urethral stricture(s) ≤3cm, ≥2 prior treatments of the same urethral stricture (including DVIU and/or dilation, but no prior urethroplasty), significant LUTs symptoms, IPSS ≥11 (assumed to be "35" if suprapubic catheter is present), urethral lumen diameter <12Fr by urethrogram, able to complete validated questionnaire independently, Qmax <15ml/s (assumed to be "0" if suprapubic catheter is present), guidewire must be able to cross the lesion
PICO 2 – Optilume Urethral DCB vs Dilation	
ROBUST III https://clinicaltrials.gov/ct2/show/NCT03499964	Male subjects ≥18 years old, Visual confirmation of stricture via cystoscopy or urethrogram, Single tandem or diffuse lesion anterior urethral stricture(s) ≤3cm, ≥2 prior treatments of the same

Optilume Urethral DCB – N = 79 Uncoated balloon – N = 28 Urethral sounds – N = 8	urethral stricture (including DVIU and/or dilation, but no prior urethroplasty), significant LUTs symptoms, IPSS ≥11 (assumed to be "35" if suprapubic catheter is present), urethral lumen diameter <12Fr by urethrogram, able to complete validated questionnaire independently, Qmax <15ml/s (assumed to be "0" if suprapubic catheter is present), guidewire must be able to cross the lesion
PICO 3 – Optilume vs Urethroplasty	
N/A - no studies have been conducted that compare Optilume to Urethroplasty.	N/A - no direct comparator exists. Endoscopic vs. Surgical management was evaluated in the OPEN trial[25]. The patient population in the OPEN trial closely matches that studied in ROBUST I[27]evaluating Optilume DCB.

Table 13: Patient baseline characteristics of the patients in the studies included in the assessment of Optilume Urethral DCB

Study Reference/ID	**Study Intervention**	**Relevant Comparator**	**Relevant Statistics**
ROBUST I https://clinicaltrials.gov/ct2/show/NCT03014726	Optilume Urethral DCB	N/A	N/A
Age [years], Mean (SD), Range, Median Sex [f/m], N (%) Race of subjects [Black or African, Hispanic or Latino, Other], N% Suprapubic Catheter at Baseline Stricture Etiology, N (%) [iatrogenic, idiopathic, traumatic] Stricture measurements, mean ± SD [stricture length (mm), urethral diameter at stricture (mm), urethral diameter at area of healthy tissue (mm) Pretreatment, N% [uncoated balloon, DVIU, uncoated balloon + DVIU] Number of previous endoscopic treatments, N% [1, 2, 3, 4]	50.7±15.47, 22.0-81.0, 50 M, 53, 100% (15.1%), 44 (83.0%), 1 (1.9%) 7 (13.2%) 24 (45.3%), 2 (3.8%), 27 (50.9%) 9.00±5.20, 2.47±1.97, 10.2±3.62 31 (59%), 8 (15%), 14 (26%)	N/A	N/A

	30 (57%), 13 (25%), 8 (15%), 2 (4%)		
ROBUST II https://www.clinicaltrials.gov/ct2/show/NCT03270384	Optilume Urethral DCB	N/A	N/A
Age [years], Mean (SD) Sex [f/m], N (%) Stricture Etiology, N (%) [iatrogenic, idiopathic, traumatic] Stricture measurements, mean ± SD [stricture length (mm), urethral diameter at stricture (mm), urethral diameter distal to stricture (mm) Procedure Type, N % [direct Optilume Urethral DCB dliation, Optilume Urehtral DCB with pre-dilation using uncoated balloon or DVIU, direct Optilume Urethral DCB dilation with post-dilation] Number of prior dilations, Mean (SD)	63.8±15.7 M, 16 (100%) 2 (12.5%), 11 (68.8%), 3 (18.8%) 2.1±0.7, 2.3±0.9, 10.5±5.2 (62.5%), 6 (37.5%), 0 (0%) 4.1±4.9	N/A	N/A
ROBUST III https://clinicaltrials.gov/ct2/show/NCT03499964	Optilume Urethral DCB	Standard of Care	P Value
Age [years], Mean (SD) Sex [f/m], N (%) Race of subjects [Black or African, White, Other], N % No. ethnicity (%) [Hispanic or latino, not hispanic or latino] Mean±SD BMI (No. patients) Stricture Etiology, N (%) [iatrogenic, idiopathic, inflammatory, traumatic, prior radiation] Anatomic location, N (%) [Bulbar, Penile] Stricture measurements, mean ± SD [stricture length (cm), stricture diameter (mm) Number of prior dilations, Mean (SD), Median, No. ≥5 overall (%)	58.7±15.5 M, 79 (100%) 9 (11.5%), 65 (83.3%), 4 (5.1%) 3 (3.8%), 75 (96.2%) 30.5±6.7 (77) 21 (26.9%), 42 (53.8%), 1 (1.3%), 14 (17.9%), 9 (11.4%) 71 (89.9%), 8 (10.1%)	60.6±16.0 M, 48 (100%) 6 (12.5%), 39 (81.3%), 3 (6.3%) 3 (6.3%), 45 (93.8%) 28.9±6.9 (48) 21 (26.9%), 42 (53.8%), 1 (1.3%), 14 (17.9%), 9 (11.4%) 45 (95.7%), 2 (4.3%)	0.500 0.838 0.673 0.206 0.566 (>0.999 Prior Radiation) 0.319 0.528, 0.470

	1.63±0.76, 2.46±0.96 3.2±1.73, 3.0, 13 (16.5%)	1.72±0.73, 2.33±0.88 4,.3±7.5, 3.0, 10 (20.8%)	0.321 (Mean SD), 0.636 (No. ≥5 overall)

Table 14: Safety outcome results – Direct Comparison: Optilume Urethral DCB vs Standard of Care (PICO 1 & 2)

Study Reference/ID	**Optilume Urethral DCB**	**Standard of Care**
ROBUST III (NCT03499964)	**Patients with event, N (%)**	**Patients with event, N (%)**
Any adverse event	58 (73.4%)	39 (81.3%)
Serious Adverse Event	11 (13.9%)	8 (16.7%)
Non-Serious Adverse Event	58 (73.4%)	38 (79.2%)
Treatment related Adverse Event	31 (39.2%)	10 (20.8%)
Device related	28 (35.4%)	4 (8.3%)
Procedure related	10 (12.7%)	6 (12.5%)
Treatment related SAE	2 (2.5%)	2 (4.2%)
Device related	1 (1.3%)	0 (0.0%)
Procedure related	1 (1.3%)	2 (4.2%)

Table 15: Health outcome results – Direct Comparison: Optilume Urethral DCB vs Standard of Care (PICO 1 & 2)

Outcome	**Study Arm**	**Baseline**	**30 Days**	**3months**	**6months**	**1year**
IPSS (N, Mean±SD, Median, Min;Max)	Control	47, 22.9 ± 6.87, 22.0, 12;35	47, 9.5 ± 7.40, 7.0, 1;35	45, 12.4 ± 9.17, 11.0, 0;35	43 15.4 ± 9.57 14.0 1, 35	43 19.8 ± 7.39 18.0 7, 35
	Optilume	79 22.0 ± 6.78 22.0 11, 35	78 7.6 ± 5.70 6.0 0, 26	75 7.4 ± 5.75 6.0 0, 24	71 8.3 ± 6.15 8.0 0, 26	67 9.0 ± 7.12 8.0 0, 26
QOL (N, Mean±SD, Median, Min;Max)	Control	47 4.7 ± 1.21 5.0 2, 6	47 2.0 ± 1.60 2.0 0, 5	45 2.7 ± 1.83 3.0 0, 6	43 3.4 ± 1.79 3.0 0, 6	43 4.0 ± 1.30 4.0 1, 6
	Optilume	79 4.5 ± 1.27 5.0 1, 6	78 1.7 ± 1.37 1.5 0, 5	75 1.5 ± 1.43 1.0 0, 5	71 1.7 ± 1.33 2.0 0, 5	67 1.9 ± 1.47 2.0 0, 5

Outcome	Study Arm	Baseline	30 Days	3months	6months	1year
Qmax (N, Mean±SD, Median, Min;Max)	Control	47 7.4 ± 3.5 7.9 0.0, 14.5	44 15.8 ± 8.5 14.8 1.3, 38.5	39 13.3 ± 9.3 11.4 0.0, 41.9	44 11.1 ± 7.6 9.8 0.0, 31.2	42 8.0 ± 4.6 7.6 0.0, 23.0
	Optilume	78 7.6 ± 3.4 7.2 0.0, 14.9	75 18.3 ± 9.1 17.4 1.6, 44.4	71 18.6 ± 10.9 15.1 1.6, 54.0	67 16.6 ± 8.9 15.0 1.6, 48.5	65 15.5 ± 9.0 13.5 1.6, 48.8
PVR (N, Mean±SD, Median, Min;Max)	Control	47 133.7 ± 153.8 80.0 0.0, 703.0	45 79.1 ± 87.3 43.0 0.0, 402.0	41 113.4 ± 124.2 59.0 0.0, 467.0	44 141.4 ± 194.1 90.5 0.0, 999.0	43 179.2 ± 199.9 118.0 0.0, 999.0
	Optilume	77 109.8 ± 116.9 60.0 0.0, 557.0	75 75.6 ± 86.1 39.0 0.0, 378.0	70 103.4 ± 134.4 54.0 0.0, 650.0	67 73.1 ± 117.7 30.0 0.0, 634.0	66 94.6 ± 121.8 50.5 0.0, 546.0
Functional Success	Control	N/A	N/A	11 (26.8%)	N/A	N/A
	Optilume	N/A	N/A	50 (74.6%)	N/A	N/A
IPSS Responder Rate, N %, 90% CI	Control	N/A	29/47 (61.7%) 48.7%, 73.6%	21/45 (46.7%) 33.8%, 59.9%	12/43 (27.9%) 17.0%, 41.3%	2/43 (4.7%) 0.8%, 13.9%
	Optilume	N/A	57/78 (73.1%) 63.6%, 81.2%	57/75 (76.0%) 66.5%, 83.9%	50/71 (70.4%) 60.3%, 79.2%	39/67 (58.2%) 47.4%, 68.4%
IIEF	Control	46 6.0 ± 3.2 6.0 2, 10	46 5.7 ± 3.0 6.0 2, 10	40 6.0 ± 3.0 6.0 2, 10	30 6.6 ± 3.2 7.5 2, 10	14 5.9 ± 2.6 6.0 2, 10
	Optilume	72 5.8 ± 2.9 6.0 2, 10	75 5.8 ± 2.8 6.0 2, 10	72 6.8 ± 2.7 7.0 2, 10	68 6.5 ± 2.8 6.5 2, 10	59 6.9 ± 3.1 8.0 2, 10
Freedom from repeat intervention	Control	N/A	N/A	N/A	N/A	21.7%
	Optilume	N/A	N/A	N/A	N/A	83.2%

Table 16: Health outcome results – Direct Comparison: Optilume Urethral DCB vs Standard of Care (PICO 1 & 2)

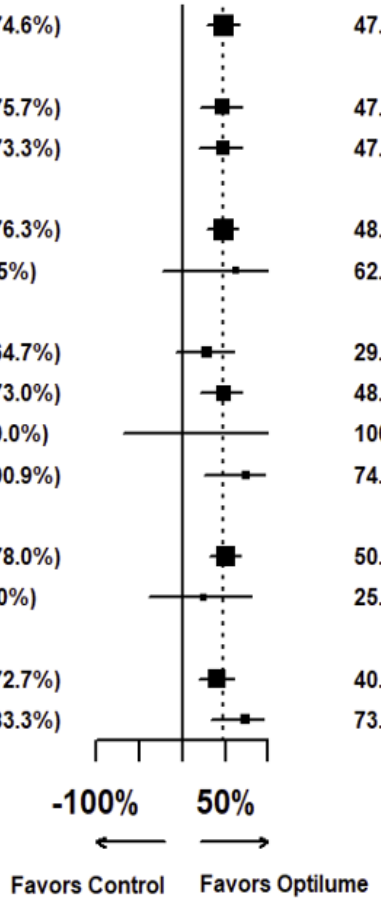
Table 9-15. Primary Efficacy Treatment Effect Among Clinical Sub-groups.

Subgroup	Control Arm (N=48)	Optilume Arm (N=79)	Difference (95% CI)
Baseline Stricture Length			
<median stricture length	4/10 (40.0%)	20/29 (69.0%)	29.0% (-7.2% , 60.2%)
≥median stricture length	7/30 (23.3%)	30/38 (78.9%)	55.6% (33.2% , 73.3%)
Baseline Stricture Length			
<2 cm	6/21 (28.6%)	28/37 (75.7%)	47.1% (20.8% , 68.8%)
≥2 cm	5/19 (26.3%)	22/30 (73.3%)	47.0% (18.6% , 69.7%)
Anatomic Location			
Bulbar	11/39 (28.2%)	45/59 (76.3%)	48.1% (28.7% , 64.7%)
Penile	0/2 (0.0%)	5/8 (62.5%)	62.5% (-24.1% , 98.7%)
Urethral Stricture Etiology			
Iatrogenic	5/14 (35.7%)	11/17 (64.7%)	29.0% (-7.5% , 60.2%)
Idiopathic	5/20 (25.0%)	27/37 (73.0%)	48.0% (21.1% , 69.6%)
Inflammatory	0/1 (0.0%)	1/1 (100.0%)	100.0% (-68.4% , 100.0%)
Traumatic	1/6 (16.7%)	10/11 (90.9%)	74.2% (24.7% , 96.3%)
Age			
<50 years	2/10 (20.0%)	13/19 (68.4%)	48.4% (8.9% , 75.8%)
≥50 years	9/31 (29.0%)	37/48 (77.1%)	48.1% (26.2% , 66.3%)
Race			
Non-White	3/9 (33.3%)	9/10 (90.0%)	56.7% (9.0% , 86.6%)
White	8/32 (25.0%)	41/57 (71.9%)	46.9% (26.0% , 65.3%)

Subgroup	Control Arm (N=48)	Optilume Arm (N=79)	Difference (95% CI)
Baseline IPSS Score			
<20	6/15 (40.0%)	19/24 (79.2%)	39.2% (6.7% , 66.1%)
≥20	5/26 (19.2%)	31/43 (72.1%)	52.9% (29.7% , 71.2%)
Presence of Supra-pubic Catheter at Baseline			
No	11/39 (28.2%)	48/65 (73.8%)	45.6% (26.5% , 62.3%)
Yes	0/2 (0.0%)	2/2 (100.0%)	100.0% (-20.5% , 100.0%)
Prior Radiation			
No	10/37 (27.0%)	46/59 (78.0%)	50.9% (31.5% , 67.2%)
Yes	1/4 (25.0%)	4/8 (50.0%)	25.0% (-39.5% , 80.6%)
Number of Prior Treatments			
<5 prior treatments	10/31 (32.3%)	40/55 (72.7%)	40.5% (18.8% , 59.3%)
≥5 prior treatments	1/10 (10.0%)	10/12 (83.3%)	73.3% (33.4% , 93.9%)
Confidence Intervals (CI) for the difference are estimated using the exact approach.			

Table 17: Health outcome results – Direct Comparison: Optilume Urethral DCB vs Standard of Care (PICO 1 & 2)

Subgroup	Control Arm	Optilume Arm	Difference (95% CI)
Overall	11/41 (26.8%)	50/67 (74.6%)	47.8% (28.7%, 66.9%)
Baseline Stricture Length			
<2 cm	6/21 (28.6%)	28/37 (75.7%)	47.1% (20.8% , 68.8%)
>=2 cm	5/19 (26.3%)	22/30 (73.3%)	47.0% (18.6% , 69.7%)
Anatomic Location			
Bulbar	11/39 (28.2%)	45/59 (76.3%)	48.1% (28.7% , 64.7%)
Penile	0/2 (0.0%)	5/8 (62.5%)	62.5% (-24.1% , 98.7%)
Urethral Stricture Etiology			
Iatrogenic	5/14 (35.7%)	11/17 (64.7%)	29.0% (-7.5% , 60.2%)
Idiopathic	5/20 (25.0%)	27/37 (73.0%)	48.0% (21.1% , 69.6%)
Inflammatory	0/1 (0.0%)	1/1 (100.0%)	100.0% (-68.4% , 100.0%)
Traumatic	1/6 (16.7%)	10/11 (90.9%)	74.2% (24.7% , 96.3%)
Prior Radiation			
No	10/37 (27.0%)	46/59 (78.0%)	50.9% (31.5% , 67.2%)
Yes	1/4 (25.0%)	4/8 (50.0%)	25.0% (-39.5% , 80.6%)
Number of Prior Treatments			
<5 prior treatments	10/31 (32.3%)	40/55 (72.7%)	40.5% (18.8% , 59.3%)
>=5 prior treatments	1/10 (10.0%)	10/12 (83.3%)	73.3% (33.4% , 93.9%)



8 Qualitative Review

A quantitative review is not appropriate for this literature summary, as the outcome measures reported and follow-up protocols for each of the referenced studies were very heterogeneous. This would lead to over-simplification of outcome definitions/measures and high uncertainty in outcome results for a quantitative assessment.

The clinical program sponsored by Urotronic Inc., the manufacturer of the Optilume Urethral DCB, includes three separate studies. ROBUST I was a first-in-man study conducted in Panama and the Dominican Republic that enrolled 53 subjects. Follow-up has been completed through 3 years and will continue through 5 years. ROBUST II is an early feasibility study conducted in the United States and enrolled 16 subjects. Follow-up is complete through 1 years, with published, peer-reviewed evidence to and is planned through 5 years. ROBUST III is a large, randomized study evaluating the Optilume Urethral DCB against standard-of-care endoscopic management, which included both dilation and DVIU. A total of 127 subjects were enrolled at 22 sites, with 79 randomized to receive the Optilume DCB and 48 randomized to receive Standard of Care (SOC). Follow-up is complete through 1 years with published, peer-reviewed evidence, and will continue through 5 years for those treated with the Optilume Urethral DCB. The sizing approach for the Optilume Urethral DCB was under investigation in ROBUST I, with approximately half the subjects treated with a 24F diameter DCB and half with a 30F DCB. Outcomes from ROBUST I lead to a recommendation of using the 30F balloon when the healthy urethra is >23F to

allow for adequate expansion of the urethra and more complete drug delivery in the ROBUST II and ROBUST III studies.

Reported literature for the Optilume Urethral DCB includes journal articles for 1-, 2- and 3-year results from the ROBUST I study, 1-year results for the ROBUST II study and 1-year results for the ROBUST III study.

The patient populations enrolled in the ROBUST studies are comprised of recurrent anterior urethral strictures, with ROBUST I enrolling a relatively less complex patient population (0.9cm length, 1.7 prior dilations) and ROBUST II and III enrolling a more difficult population (1.7-2.1cm length, ~3.5 average prior dilations, ROBUST III included ~10% penile strictures and ~10 with prior pelvic radiation). Anatomic outcomes at 6 months were similar across all three studies, with approximately 75% exhibiting freedom from recurrence as measured by the ability to pass a 16F cystoscope. ROBUST I additionally measured anatomic success at 1 year, again with approximately 75% experiencing freedom from recurrence. Anatomic success at 6 months in the Control arm of the ROBUST III study was 27%, representing a significantly lower success rate than the Optilume Urethral DCB. Freedom from repeat intervention was also similar between studies and ranged from 75-85% at one year, with ROBUST I reporting 81% and 77% freedom from repeat intervention at 2 and 3 years, respectively. Freedom from repeat intervention in ROBUST I was 91.7% in those subjects treated with a 30F DCB. Freedom from repeat intervention in the Control arm of ROBUST III was estimated at 21.7% at 12 months via Kaplan-Meier, representing a significantly lower success rate than Optilume Urethral DCB when compared via the log-rank test.

IPSS and Qmax were reported to improve significantly post-treatment with the Optilume Urethral DCB in all studies. Improvement in IPSS from 20-25 at baseline to 5-8 at follow-up was seen in each study, with IPSS remaining below 10 through 3 years in ROBUST I. Qmax improved from 5-8mL/sec at baseline to >15mL/sec at all follow-up timepoints in each study, including 15.5mL/sec at 3 years in the ROBUST I study. Pooled ROBUST series data determines consistent improvement in clinical and symptomatic endpoints showing immediate improvement post-procedure sustained through follow up. IPSS and Qmax initially improved in the Control arm of the ROBUST III study but returned to baseline levels by 1 year.

The reported evidence largely supports the ease and availability of endoscopic treatments for anterior urethral stricture, and the similarity in outcomes regardless of endoscopic method utilized (dilation vs DVIU). Long-term outcomes reflect poor durability even for those subjects with short, treatment naive strictures (Steenkamp 1997[19], Pansadoro 1996[20]), with 2–5-year success ranging from 40-60%. Multiple publications have identified that repeated dilation/DVIU of the same stricture will lead to progressively worsening outcomes, with higher rates and earlier recurrence with each additional procedure (Heyns 1998[22], Santucci 2010[40]). Reported rates of freedom from recurrence for the third dilation approached 20-30% at 6 months and 0% at 24 months.

Urethroplasty has been identified consistently as the ‘gold standard’ for anatomic resolution of anterior urethral stricture. Publications reviewed in this literature search were limited to those evaluating strictures of a similar complexity (i.e., <5cm, non-revision, no obliterative or hypospadias repair). Freedom from stricture recurrence was reported in 77-96% at varying follow-up timepoints, which is largely similar to a recently published systematic review (Lumen N, Eur Urol, 2021[18]) that summarized available literature and concluded one could generally expect freedom from recurrence >80% for urethroplasty over medium term follow-up (1-5 years). Complications were infrequently and inconsistently reported, with the most common being post-void dribbling (16-40%), ejaculatory dysfunction (highly varied), wound infection (4-15%), and UTI (~4%). Duration of hospitalization and Foley duration were infrequently reported but were typically 2-5 days for hospitalization and at least 3 weeks for Foley catheter placement. Most publications were from single, high-volume centres, with outcomes reported for the two multi-centre studies being less than those reported for single-centre series. This may point to outcomes being less consistent in more ‘community’ based practice, where they are not conducting such significant volumes of surgeries.

9 Summary and interpretation of clinical evidence

The primary clinical evidence for the Optilume Urethral DCB is the ROBUST III study, which is a large, multi-centre, randomized trial comparing the Optilume to standard-of-care endoscopic management. The Optilume Urethral DCB showed significant benefit over standard of care in anatomic success at 6 months (74.6% vs 26.8%, p<0.001), freedom from repeat intervention at 12 months (83.2% vs 21.7%, p<0.001), symptom scores (IPSS 9.0 vs 19.8) at 12 months, and Qmax (15.5 vs 8.0mL/sec) at 12 months. Adverse event rates were generally similar between arms, with a trend toward higher rates of mild haematuria and dysuria post procedure that resolved within 30 days without treatment.

Outcomes from ROBUST III were consistent with earlier studies such as ROBUST I and ROBUST II. ROBUST I has long-term published follow-up through 3 years, with freedom from repeat intervention maintained in 77% of subjects.

The study population evaluated in ROBUST III was more difficult than those reported elsewhere, with the eligibility criteria focusing on subjects with multiple recurrences that have historically not performed well with endoscopic management. Outcomes in the Control group of ROBUST III were similar to those reported by Heyns and Santucci for multiple prior dilations, with success approaching 20% at 1 year. Even in this difficult population, the Optilume DCB showed a success rate comparable to that of urethroplasty.

The patient population evaluated in ROBUST I was generally more like those reported by Pickard et al. in the OPEN trial. The rate of freedom from repeat intervention at 2 years for urethroplasty in the OPEN trial was 84%, which compares favourably with the 81% rate observed for the Optilume DCB at 2 years (87% for 30F DCB at 2 years), sustaining to 77% rate observed for the Optilume DCB at 3 years (83% for 30F DCB at 3 years).

Risks with the Optilume DCB are comparable with other endoscopic treatments for urethral stricture, while recovery, catheter dwell time, and complications are lower for these less invasive technologies when compared to open reconstruction via urethroplasty. Endoscopic treatment avoids potential complications such as wound infection, urethro-cutaneous fistula, and sexual dysfunction associated with urethroplasty. The rate of complications reported in the literature for urethroplasty is inconsistent and likely under-reported when compared to a large, actively managed clinical trial such as the ROBUST III study.

10 Relevance of the evidence base to the PICO scope

The published and unpublished evidence from the ROBUST clinical program support claimed benefits of lower rates of repeat stricture treatments (repeat dilation, urethroplasty, self-catheterization) for the Optilume Urethral DCB compared to standard endoscopic management (17% vs 78%). The ROBUST program also showed immediate and sustained improvement in IPSS, USS-PROM, and Qmax immediately after the procedure through to 3 years follow-up. Rapid return to daily living can be claimed based on comparison to urethroplasty, which requires extended hospital stay (>2d) and Foley catheter usage (~3 weeks). Reduced complication rates compared to urethroplasty are generally based on the Optilume DCB being a minimally invasive procedure, compared to the open surgical procedure of urethroplasty.

The poor performance of repeat urethrotomy and dilation has been published across many geographies, such as South Africa (Steenkamp), Italy (Pansadoro), the UK (Pickard), and the United States (ROBUST III). As discussed, the patients in the ROBUST III study likely represent a more difficult patient population than those receiving routine care for the treatment of anterior urethral stricture. The longer-term

outcomes of the ROBUST I study are likely most comparable with those reported in the OPEN RCT in the UK.

The evidence base for the Optilume Urethral DCB has been generated in patients with anterior urethral strictures <3cm in length. Patients with posterior strictures (e.g., membranous, bladder neck) have not been studied, although the treatment effect and benefits are not expected to be different from anterior strictures.

The ROBUST clinical program represents a large, multi-national series of studies that have shown a significant benefit over standard endoscopic management when patients are treated with the Optilume Urethral DCB. This benefit was shown directly in the ROBUST III randomized study, which also compares favourably to published literature for both endoscopic and surgical management. ROBUST III represents level 1 clinical evidence.

Limitations of the ROBUST clinical program include lack of EU population in the clinical studies, although the poor performance of repeat urethrotomy has been published internationally. The Control arm of the ROBUST III study included both urethrotomy and dilation at the physician's discretion. Urethrotomy is typically the standard of care for endoscopic treatment in the EU, however multiple studies (including ROBUST III) have shown comparable outcomes for subjects treated with dilation and urethrotomy.

11 Appendices

Appendix A: Search strategy for clinical evidence

Search terms were developed by concept utilizing the PICO approach (Population, Intervention, Comparator, Outcome). The population under study included male urethral stricture, the intervention of interest was drug coated balloons, the comparator of interest was standard of care endoscopic treatments or urethroplasty, and the outcomes of interest were stricture recurrence.

The search was conducted the MEDLINE library via PubMed utilizing the search terms and Boolean operators as listed in Table A-1. Search #31 and #33, returned large numbers of results and were further filtered for 'Clinical Trial' and 'Randomized Controlled Trial'.

Table A-1. MEDLINE Search terms and operators

Search	Search Terms	Search	Search Terms
1	Urethral Stricture [mh]	16	Urethral Dilation [tiab]
2	Urethral Stenosis [mh]	17	S-curve dilator [tiab]
3	Urethral Stricture [tiab]	18	s-curve dilator [tiab][all]
4	Urethral Stenosis [tiab]	19	Bougie Dilation [tiab]
5	#1 OR #2 OR #3 OR #4	20	Urethrotomy [tiab]
6	Drug Coated Balloon [tiab]	21	Optical Urethrotomy [tiab]
7	Drug Eluting Balloon [tiab]	22	DVIU [tiab]
8	Paclitaxel Coated Balloon [tiab]	23	Urethroplasty [tiab]
9	Optilume [tiab]	24	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
10	In.Pact Admiral [tiab]	25	Stricture Recurrence [tiab]
11	Lutonix [tiab]	26	Redilation [tiab]
12	Ranger Drug Coated Balloon [tiab]	27	Revision Urethroplasty [tiab]
13	Stellarex [tiab]	28	Repeat Urethrotomy [tiab]
14	Biolux [tiab]	29	#24 OR #25 OR #26 OR #27
15	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	30	#5 AND #15
		31	#5 AND #24
		32	#5 AND #15 AND #29
		33	#5 AND #24 AND #29
		34	#5 AND #15 AND #24 AND #29

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

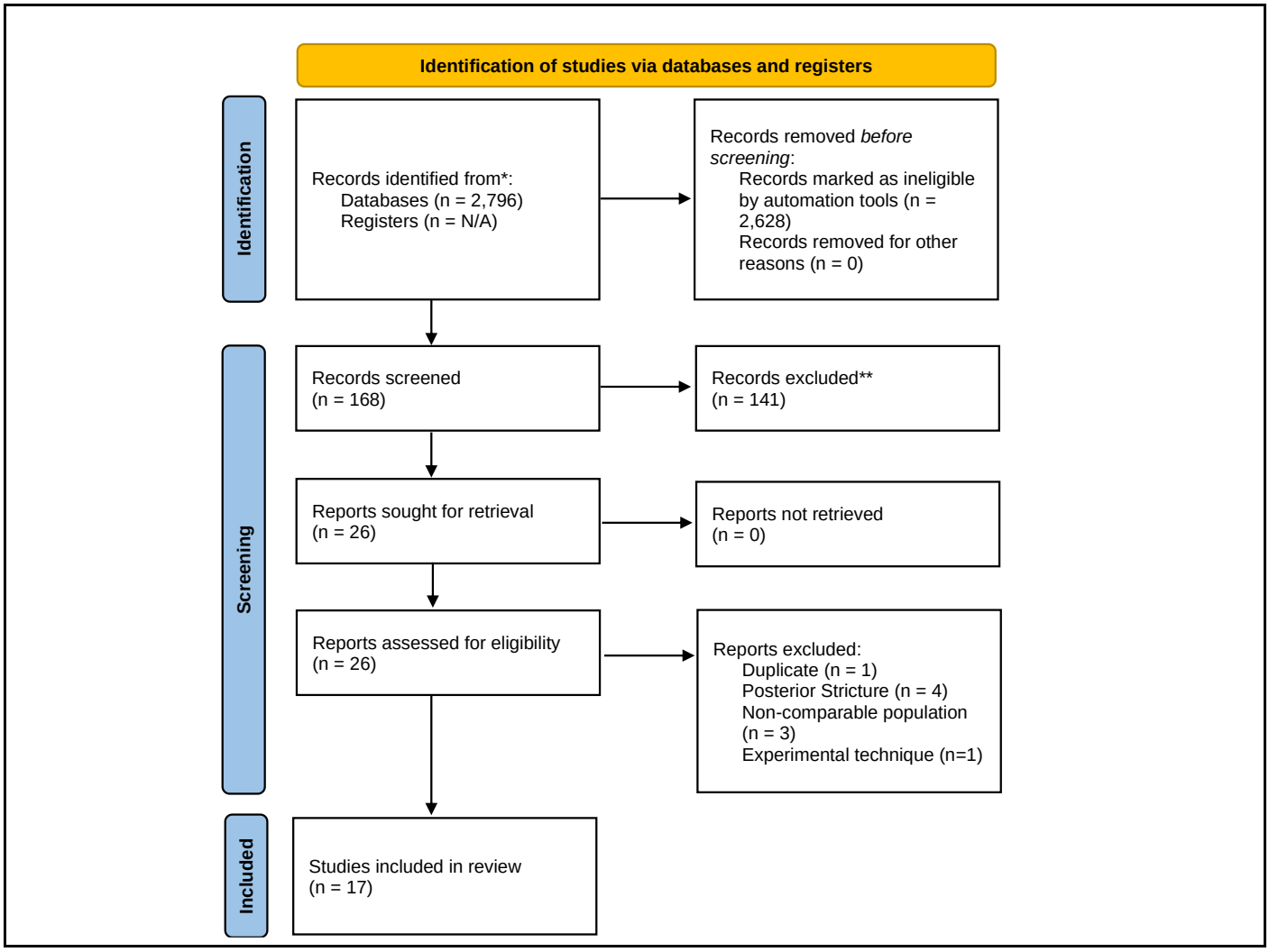
Additional searches were conducted to identify ongoing studies that may report results in the near future. Two clinical trial registration databases were searched (US National Library of Medicine registry [clinicaltrials.gov/ct2/home] and EU Clinical Trials Register [https://www.clinicaltrialsregister.eu/ctr-search/search]) using the keyword 'Urethral Stricture'.

Inclusion and exclusion criteria:
Inclusions: - Male urethral stricture - Outcomes after endoscopic treatment, single arm - Outcomes after open surgical treatment (urethroplasty), single arm - Randomized comparative studies Exclusions: - Preclinical/animal studies - In-vitro studies - Paediatric studies - Case reports or early experimental techniques - Editorials, commentary, technology assessments - Posterior or membranous strictures - Hypospadias repair, meatal/glans stricture repair - Studies of adjunct therapies (e.g., steroids, mitomycin C) - Diagnostic assessments - Female strictures - Cost effectiveness or other non-recurrence outcome measures - Clean intermittent catheterization or home dilation - Study protocol or design discussion - Non-comparable population (e.g., length >5cm, urethral dislocation)
Data abstraction strategy:
Summary search results (title, brief description) for Search 30-34 were reviewed for relevant articles (P&I, P&C, P&I&O, P&C&O, P&I&C&O). Articles possibly meeting inclusion were identified and abstracts were reviewed for exclusion criteria. Articles continuing to meet criteria after abstract review were given full text review and final determination for inclusion was made.

Table 18: Excluded Studies

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Guolao B, Eur Urol, 2020	OPEN randomized clinical trial	Duplicate	This was an abbreviated publication of results for the OPEN RCT. The Pickard reference included in the summary represented a more comprehensive reporting of study results.
Atak M, Kaohsiung Med, 2011	Randomized laser vs. cold-knife DVIU	Posterior urethral stricture	The Optilume DCB has not been evaluated in posterior strictures
Mehrsai A, Urology, 2007	Urethroplasty	Posterior urethral strictures	The Optilume DCB has not been evaluated in posterior strictures

Cai W, Clinics (Sao Paulo), 2016	Laser vs cold knife DVIU	Posterior urethral stricture	The Optilume DCB has not been evaluated in posterior strictures
Jablonowski Z, Photomed Laser Surg, 2010	Laser vs cold knife DVIU	Posterior urethral stricture	The Optilume DCB has not been evaluated in posterior strictures
Vasudeva P, Int J Urol, 2015	Dorsal vs ventral buccal graft urethroplasty	Non-comparable population (>5cm)	The Optilume DCB is limited to short urethral strictures that can be treated with a single DCB (<4cm max length)
Dubey D, J Urol, 2007	Dorsal vs penile skin graft urethroplasty	Non-comparable population (>5cm)	Non-comparable population (>5cm)
Soliman MG, Scand J Urol, 2014	Dorsal vs penile skin graft	Non-comparable population (>5cm)	Non-comparable population (>5cm)
Pansadoro V, J Urol, 1999	Buccal mucosal graft urethroplasty	Experimental technique	This was an initial reporting of outcomes from early experience with the buccal grafting technique.



Appendix B: Search strategy for adverse events

Date search conducted:	09Dec2021
Date span of search:	01/01/1900 to 09Dec2021
The MAUDE database and MHRA national database were searched with the word 'Optilume', no results were found	

Appendix C: Checklist of confidential information

Does your submission of evidence contain any confidential information? (Please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
	☐ Commercial in confidence ☐ Academic in confidence		
Details			
#	☐ Commercial in confidence ☐ Academic in confidence		
Details			

Confidential information declaration

I confirm that:

- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information.

Signed: 

Date: 9th January 2023

Print: James Wright

Role / organisation: Director, International Market Development – Laborie Medical Technologies

Contact email: jwright@laborie.com

12 References

[1] Tritschler S, Roosen A, Füllhase C, Stief CG, Rübben H. Urethral stricture: etiology, investigation and treatments. Dtsch Arztebl Int. 2013 Mar;110(13):220-6. doi: 10.3238/arztebl.2013.0220. Epub 2013 Mar 29. PMID: 23596502; PMCID: PMC3627163.
[2] 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.
[3] Santucci, R.A., et al. Male urethral stricture disease. J Urol, 2007. 177: 1667. https://pubmed.ncbi.nlm.nih.gov/17437780
[4] Alwaal A, Blaschko SD, McAninch JW, Breyer BN. Epidemiology of urethral strictures. Transl Androl Urol. 2014 Jun;3(2):209-13. doi: 10.3978/j.issn.2223-4683.2014.04.07. PMID: 26813256; PMCID: PMC4708169.
[5] Stein, D.M., et al. A geographic analysis of male urethral stricture aetiology and location. BJU Int, 2013. 112: 830.
[6] Lumen N, Hoebeke P, Willemsen P, De Troyer B, Pieters R, Oosterlinck W. Etiology of urethral stricture disease in the 21st century. J Urol. 2009;182:983–987.
[7] Fenton AS, Morey AF, Aviles R, Garcia CR. Anterior urethral strictures: etiology and characteristics. Urology. 2005;65:1055–1058.
[8] Santucci RA, McAninch JW. Urethral reconstruction of strictures resulting from treatment of benign prostatic hypertrophy and prostate cancer. Urol Clin North Am. 2002;29:417–427. viii.
[9] Tasci AI, Ilbey YO, Tugcu V, Cicekler O, Cevik C, Zoroglu F. Transurethral resection of the prostate with monopolar resectoscope: single-surgeon experience and long-term results of after 3589 procedures. Urology. 2011;78:1151–1155.
[10] Park S, McAninch JW. Straddle injuries to the bulbar urethra: management and outcomes in 78 patients. J Urol. 2004;171:722–725.
[11] Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA. 10th edition. Philadelphia: Elsevier; 2012. Campbell-Walsh Urology.
[12] Bertrand, L.A., et al. Lower urinary tract pain and anterior urethral stricture disease: prevalence and effects of urethral reconstruction. J Urol, 2015. 193: 184. https://pubmed.ncbi.nlm.nih.gov/25046621
[13] Lubahn, J.D., et al. Poor quality of life in patients with urethral stricture treated with intermittent self-dilation. J Urol, 2014. 191: 143.
[14] Greenwell, T.J., et al. Repeat urethrotomy and dilation for the treatment of urethral stricture are neither clinically effective nor cost-effective. J Urol, 2004. 172: 275. https://pubmed.ncbi.nlm.nih.gov/15201793
[15] Brandes SB. Totowa: Humana Press; 2008. Urethral Reconstructive Surgery.
[16] Simsek A, Aldamanhori R, Chapple CR, MacNeil S. Overcoming scarring in the urethra: Challenges for tissue engineering. Asian J Urol. 2018 Apr;5(2):69-77. doi: 10.1016/j.ajur.2018.02.002. Epub 2018 Feb 12. Erratum in: Asian J Urol. 2019 Apr;6(2):215. PMID: 29736368; PMCID: PMC5934514
[17] Wessells H., Angermeier K.W., Elliott S.P., Gonzalez C.M., Kodama R.T., Peterson A.C. 2016. Male urethral stricture: AUA guideline; pp. 1–32.
[18] Lumen N, Campos-Juanatey F, Greenwell T, Martins FE, Osman NI, Riechardt S, Waterloos M, Barratt R, Chan G, Esperto F, Ploumidis A, Verla W, Dimitropoulos K. European Association of Urology Guidelines on Urethral Stricture Disease (Part 1): Management of Male Urethral Stricture Disease. Eur Urol. 2021 Aug;80(2):190-200. doi: 10.1016/j.eururo.2021.05.022. Epub 2021 May 29. PMID: 34059397.
[19] Steenkamp JW, Heyns CF, de Kock ML. Internal urethrotomy versus dilation as treatment for male urethral strictures: a prospective, randomized comparison. J Urol. 1997 Jan;157(1):98-101. PMID: 8976225.
[20] Pansadoro V, Emiliozzi P. Internal urethrotomy in the management of anterior urethral strictures: long-term follow up. J Urol. 1996;156:73–75.
[21] Verges J, Desgrez JP, Claude JM, Cabane H. Internal urethrotomy. Resection of urethral stricture (over 5 years follow-up) Ann Urol. 1990;24:73–75.
[22] Heyns CF, Steenkamp JW, De Kock ML, Whitaker P. Treatment of male urethral strictures: is repeated dilation or internal urethrotomy useful? J Urol. 1998 Aug;160(2):356-8. doi: 10.1016/s0022-5347(01)62894-5. PMID: 9679876.
[23] Barbagli G, De Angelis M, Romano G, Lazzeri M. Long-term follow up of bulbar end-to-end anastomosis: a 18. retrospective analysis of 153 patients in a single center experience. J Urol. 2007;178:2470–2473.
[24] Barbagli G, Guazzoni G, Lazzeri M. One-stage bulbar urethroplasty: retrospective analysis of the results in 375 patients. Eur Urol. 2008;53:828–833.
[25] Pickard R, Goulao B, Carnell S, et al. (2020) Open urethroplasty versus endoscopic urethrotomy for recurrent urethral stricture in men: the OPEN RCT. Health Tech Assess. 24(61):
[26] Data on file – Optilume Urethral Drug Coated Balloon Instructions For Use 1111-002 Rev D
[27] Ramón Virasoro, Jessica M DeLong, Rafael E Estrella, Merycarla Pichardo, Ramón Rodriguez Lay, Gustavo Espino & Sean P Elliott (2022) A Drug-Coated Balloon Treatment for Urethral Stricture Disease: Three-Year Results from the ROBUST I Study, Research and Reports in Urology, 14:, 177-183, DOI: 10.2147/RRU.S359872
[28] DeLong, J. M., Ehlert, M. J., Erickson, B. A., Robertson, K. J., Virasoro, R., & Elliott, S. P. (2022). One-Year Outcomes of the ROBUST II Study Evaluating the Use of a Drug-Coated Balloon for Treatment of Urethral Stricture. Société Internationale d'Urologie Journal, 3(1), 21-27. https://doi.org/10.48083/MLXK5817
[29] Elliott SP, Coutinho K, Robertson KJ, D'Anna R, Chevli K, Carrier S, Aube-Peterkin M, Cantrill CH, Ehlert MJ, Te AE, Dann J, DeLong JM, Brandes SB, Hagedorn JC, Levin R, Schlaifer A, DeSouza E, DiMarco D, Erickson BA, Natale R, Husmann DA, Morey A, Olsson C, Virasoro R. One-Year Results for the ROBUST III Randomized Controlled Trial Evaluating the Optilume® Drug-Coated Balloon for Anterior Urethral Strictures. J Urol. 2022 Apr;207(4):866-875. doi: 10.1097/JU.0000000000002346. Epub 2021 Dec 2. PMID: 34854748.
[30] National Institute for Health and Care Excellence, Medical Technologies Guidance
[31] Azab SS. (2020) Comparative study between Amplatz renal dilator vs visual internal urethrotomy (cold knife) for the treatment of male urethral stricture. Can J Urol DOI: 10.1080/21681805.2020.1798504
[32] Cecen K, Karadag MA, Demir A, Kocaaslan R. (2014) PlasmaKinetic™ versus cold knife internal urethrotomy in terms of recurrence rates: a prospective randomized study. Urol Int 93:460-3.

[33] Guo FF, Lu H, Wang GJ, et al. (2010) Transurethral 2µm laser in the treatment of urethral stricture. World J Urol 28:173-5.
[34] Jordan GH, Wessells H, Secrest C, et al. (2013) Effect of a temporary thermo-expandable stent on urethral patency after dilation or internal urethrotomy for recurrent bulbar urethral stricture: Results from a 1-year randomized trial. J Urol 190:130-6
[35] Isen K, Nalcacioglu V. (2015) Direct vision internal urethrotomy by using endoscopic scissors. In Urol Nephrol DOI 10.1007/s11255-015-0960-x
[36] Pansadoro V, Emiliozzi P. (1996) Internal Urethrotomy in the Management of Anterior Urethral Strictures: Long-term Follow up. J Urol 156:73-5.
[37] Santucci R, Eisenberg L. (2010) Urethrotomy has a Much Lower Success Rate Than Previously Reported. J Urol 183:1859-62.
[38] Hoy NY, Kinnaird A, Rourke KF. (2013) Expanded use of dorsal onlay augmented anastomotic urethroplasty with buccal mucosa for long segment bulbar urethral strictures: Analysis of outcomes and complications. Urology 81:1357-61.
[39] Aldaqadossi H, Gamal SE, El-Nadey M, et al. (2014) Dosral onlay (Barbagli technique) versus dorsal inlay (Asopa technique) buccal mucosal graft urethroplasty for anerior urethral stricture: A prospective randomized study. Int J Urol 21:185-8.
[40] Elkady E, Dawod T. Teleb M, et al. (2018) Bulbospongiosus muscle sparing urethroplasty versus standard urethroplasty: A comparative study. Urology doi.org/10.1016/j.urology.2018.12.028
[41] Erickson BA, Elliott SP, Voelzke BB, et al. (2014) Multi-institutional 1-year bulbar urethroplasty outcomes using a standardized prospective cystoscopic follow-up protocol. Urology 84:213-7.
[42] Elliott SP et al, 2022, American Urology Association, Long-term outcomes of urethral stricture treatment with the Optilume paclitaxel-coated balloon: 4-year results from the ROBUST I study, PD31-08 https://www.auajournals.org/doi/pdf/10.1097/JU.0000000000002582.08
[43] Lau G et al, International Continence Society, Initial patient experiences of Optilume drug-coated balloon treatment for urethral stricture performed in Europe first outpatient setting, Abstract 567, https://www.ics.org/2022/abstract/567
[44] Zhong W et al, (2022), Concurrent Session Presentations. BJU Int, 129: 4-41. https://doi.org/10.1111/bju.15743
[45] Aube-Peterkin M et al, Can Urol Assoc J 2022;16(6Suppl1):S23-7. http://dx.doi.org/10.5489/cuaj.7923