

1 **Title**

2 Surgical treatment for recurrent bulbar urethral stricture: A randomised open label superiority trial
3 of open urethroplasty versus endoscopic urethrotomy (The OPEN Trial).

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27

1 *Abstract*

2 *Background*

3 Urethral stricture affects 0.9% of men. Initial treatment is urethrotomy. Approximately, half of the
4 strictures recur within four years. Options for further treatment are repeat urethrotomy or open
5 urethroplasty.

6 *Objectives*

7 To compare the effectiveness and cost-effectiveness of urethrotomy with open urethroplasty in
8 adult men with recurrent bulbar urethral stricture.

9 *Design, Setting and Participants*

10 Open label, two-arm, patient randomised controlled trial. UK NHS hospitals were recruited and
11 randomised 222 men to urethroplasty or urethrotomy.

12 *Interventions*

13 Urethrotomy is a minimally invasive technique whereby the narrowed area is progressively widened
14 by cutting the scar tissue with a steel blade mounted on a urethroscope. Urethroplasty is a more
15 invasive surgery to reconstruct the narrowed area.

16 *Main outcome measures*

17 The primary outcome was the profile over 24 months of a patient-reported outcome measure, the
18 ICIQ voiding symptom score. The main clinical outcome was time until re-intervention.

19 *Results*

20 The primary analysis included 69 (63%) and 90 (81%) of those allocated to urethroplasty and
21 urethrotomy respectively. The mean difference between urethroplasty and urethrotomy group was -
22 0.36 (95% confidence interval - CI (-1.74 to 1.02)). Fifteen men allocated to urethroplasty needed a
23 re-intervention compared to 29 allocated to urethrotomy, hazard ratio (95% CI) 0.52 (0.31 to 0.89).

24 *Conclusion*

25 In men with recurrent bulbar urethral stricture both urethroplasty and urethrotomy improved
26 voiding symptoms. The benefit lasted longer for urethroplasty.

27 *Patient summary*

28 There was uncertainty about the best treatment for men with recurrent bulbar urethral stricture.
29 We randomised men to receive one of two treatment options: urethrotomy or urethroplasty. At the
30 end of the study, both treatments resulted in similar and better symptom scores. However, the
31 urethroplasty group had fewer re-interventions.

32

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2

1 **Main Report**

2 **Introduction**

3 Registry studies from the United States estimate the prevalence of urethral stricture to be up to
4 0.9% of adult men (1). The annular urethral scar, which commonly occurs in the bulbar segment of
5 the urethra, results in difficulty voiding, threatening urinary retention (2). The first occurrence of
6 urethral stricture is usually treated by a minimally invasive technique whereby the narrowed area is
7 progressively widened by either cutting the scar tissue with a steel blade mounted on a
8 urethroscope, so-called endoscopic urethrotomy, or by the use of graduated urethral dilators. An
9 estimated half of men will suffer a recurrence within 4 years needing further intervention (3). This
10 can be by an endoscopic technique or by more invasive surgery to reconstruct the narrowed area:
11 open urethroplasty (4). Hospital activity data suggest that repeated endoscopic urethrotomy is the
12 most frequently used alternative (5) to treat bulbar stricture recurrence but specialist clinical
13 guidelines, based on cohort studies identified by systematic review, recommend that open
14 urethroplasty should be performed (4,6). In this randomised trial, we aimed to clarify which
15 procedure was best, primarily in providing symptom control but also considering duration of benefit
16 prior to disease recurrence.

17

18 **Methods**

19 **Study design**

20 This was an open-label patient-randomised parallel group superiority trial recruiting across 53
21 National Health Service (NHS) secondary care providers in the United Kingdom (38 recruited at least
22 one participant). The trial protocol was published and it contains details about the methods (7).

23

24 **Participants**

25 Adult men presenting with bulbar urethral stricture disease having previously undergone at least
26 one surgical intervention for this condition were identified. Exclusion criteria were current perineal
27 sepsis and/or urethra-cutaneous fistula. Patients were approached and introduced to the study by
28 clinical staff at site. Those deciding to participate completed written consent forms for the 24-month
29 trial period.

30

31 **Randomisation and masking**

32 Randomisation was performed using a centralised, automated application hosted by the Centre for
33 Healthcare and Randomised Trials, University of Aberdeen, UK and accessed by telephone or
34 through the internet. Participants were allocated to urethroplasty or urethrotomy in a 1:1 ratio with

1 recruitment site and time since last procedure (< 12 months or ≥ 12 months) as minimisation
2 covariates. Clinical trial unit staff were masked to allocation, but participants and surgeons could not
3 be blinded.

4

5 **Procedures**

6 Participants were sent the trial questionnaire — which included the patient reported outcome
7 measure (PROM) — at baseline, pre-intervention, 3, 6, 9, 12 and 24 months post-intervention, at 18
8 and 24-months post-randomisation and before and after a re-intervention. At the end of the study
9 (December 2016) we sent the questionnaire to every participant in the trial. At 3, 12 and 24-month
10 post-intervention research staff at site contacted participants to complete case report forms (CRF)
11 face-to-face or by telephone, with supplementation by health care record review. Clinical outcomes,
12 including adverse events, were collected in the CRF. Uroflowmetry was obtained at baseline, 3 and
13 between 12 and 24 months after surgery.

14

15 **Outcomes**

16 The primary outcome was the profile of the urinary voiding symptom score component of the
17 surgery patient reported outcome measure (PROM) over 24 months following randomisation. The
18 questionnaire has been validated in this patient group (8). We used the area under the curve to
19 summarise each participants' profile. The PROM has six questions about: delay before starting to
20 urinate, poor strength of urinary stream, having to strain before urinating, intermittent urinary
21 stream, feeling of incomplete bladder emptying and post-micturition dribbling. Each item scored
22 from 0 (no symptoms) to 4 (symptoms all of the time) giving a total score of 0 to 24. The PROM was
23 chosen as OPEN's primary outcome to ensure a patient centred trial that can inform patient centred
24 healthcare delivery; symptoms are likely to be the central concern for patients with bulbar urethral
25 strictures and the reason why they look for treatment.

26

27 Patient-reported secondary outcomes were: a pictorial description of urine stream strength [from 1
28 (strong stream) to 4 (weak stream)], impact of urinary symptoms on daily activity [scored from 0
29 (not at all) to 3 (a lot)], overall satisfaction with sexual function [from 1 (very dissatisfied) to 5 (very
30 satisfied)], health-related quality of life using the EQ-5D-5L questionnaire reported elsewhere (9).

31

32 Secondary clinical outcomes included difference in re-intervention, rate of improvement of urinary
33 flow rate and any recurrence. We defined re-interventions for bulbar urethral stricture as any
34 intervention subsequent to the allocated trial procedure (excluding self-dilatation). Maximum

1 urinary flow rate (Q_{\max}) was measured by asking each participant to void at least 150 ml of urine into
2 a commercial, calibrated uroflowmeter available at their treating centre. An increase in $Q_{\max} \geq 10$
3 ml/s compared to baseline was considered as an improvement (10). Recurrence of bulbar stricture
4 occurred if at least one of the following conditions were met during the 24 months after
5 randomisation: a re-intervention had occurred or was scheduled; the maximum flow rate had
6 deteriorated to the pre-intervention value or the voiding score had deteriorated to baseline value.

7 8 **Sample size**

9 Sample size details were provided in the trial's published protocol (7). Three parameters informed a
10 revised sample size calculation (after poor recruitment was observed): the minimum clinically
11 important difference (MID) defined as a $> 10\%$ difference in effect estimate in the PROM profile;
12 power to detect any difference set at 90%; and the standard deviation (SD) of the primary outcome
13 measure. This was calculated from the 220 measurements of post-intervention PROM voiding score
14 submitted by the first 69 participants scaled from 0 to 1. The observed SD was 0.15 which was
15 increased to 0.21 to allow for subsequent changes over trial duration. This gave a revised sample size
16 of 170 men; we aimed to recruit 210 in total to allow for 19% attrition. The trial was also powered to
17 determine whether the use of urethroplasty would result in a 30% reduction in re-intervention at
18 24-months relative to urethrotomy. To detect this difference with 90% power 104 men were
19 required. Statistical significance was defined at the 2-sided 5% level with corresponding 95%
20 confidence intervals derived.

21

22 **Statistical analysis**

23 The statistical analysis plans are available from [https://www.abdn.ac.uk/hsru/what-we-do/trials-](https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/statistical-analysis-plans-611.php)
24 [unit/statistical-analysis-plans-611.php](https://www.abdn.ac.uk/hsru/what-we-do/trials-unit/statistical-analysis-plans-611.php). The PROM profile, calculated by summing its six questions
25 and using all available measurements (starting a baseline which was measured immediately prior to
26 randomisation) to then construct the area under the curve using the trapezoid rule, was analysed
27 using linear regression adjusted for minimisation covariates.

28 The primary analysis included all participants who had any surgery and completed at least three
29 voiding scores: one baseline measure, one early measure (up to 12 months after intervention), and
30 one later measure (18 or 24-months post-randomisation). We analysed as randomised, i.e.
31 participants were analysed according to their allocated group regardless of the intervention
32 received.

1 Given the pragmatic nature of the trial we planned sensitivity analysis to account for missing data
2 and non-compliance. We did a full intention-to-treat analysis using multiple imputation to include all
3 randomised participants in the model according to their allocated intervention. We did a modified
4 intention-to-treat analysis using multiple imputation to include only participants that had surgery in
5 the model. Both used the same imputation strategy. We explored differences between responders
6 and non-responders to inform our missing data model. The auxiliary variables included in the
7 multiple imputation model were either known predictors of the outcome (ie minimisation variables)
8 or predictors found by calculating their correlation with the outcome in the OPEN dataset (ie with a
9 correlation coefficient above 0.3). We calculated an area under the curve for each imputation and
10 combined these using Rubin's rules under a missing at random assumption (11,12). We also
11 explored, using pattern mixture models (11), imputation of a range of values estimated from
12 observed data using different missing not at random scenarios. For those scenarios we assumed
13 participants with missing data in the urethroplasty arm had a score from 0 to 10 units lower than the
14 observed values; we then tested the same for those in the urethrotomy arm. We used Stata's
15 command *rctmiss* to implement this. We did a per-protocol analysis including participants who got
16 the intervention they were allocated to (ie received the treatment as randomised).

17

18 Secondary outcomes were analysed using generalised linear models appropriate for the distribution
19 of the outcome with adjustment for minimisation and baseline variables as appropriate. We
20 analysed time to re-intervention using Cox regression (adjusting for minimisation variables and
21 centre). For this outcome we used the complete observation time available until database closure
22 (at least 24 months and up to 48 months for some participants). We also analysed multiple re-
23 interventions using the Andersen-Gill model. Time to recurrence was analysed using a Cox regression
24 adjusting for minimisation variables and centre.

25

26 Subgroup analyses explored the possible modification of treatment effect by including a treatment-
27 by-factor interaction in models. Factors were: time since last procedure (<12 months or >= 12
28 months) as a global measure of stricture severity, age (≤ 50 years old or >50), stricture length (≤ 2 cm
29 or >2 cm) and number of previous interventions (one or more than one). Adverse and serious
30 adverse events are presented by intervention received.

31

32 Analyses were carried out in StataCorp. 2015. Stata Statistical Software: Release 14. College Station,
33 TX: StataCorp LP. The study was overseen by independent Trial Steering and Data Monitoring
34 Committees.

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Results

A total of 222 men were randomised between 27/02/2013 and 23/12/2015, out of 1,262 identified by study sites (Figure 1 & Supplementary Table 1). There were two post-randomisation exclusions because further assessment prior to intervention showed them to have been ineligible. Recorded patient characteristics were balanced at baseline, including important clinical characteristics such as length of stricture and number of previous interventions such as previous urethrotomies (Table 1). Table 2 presents results for the primary and secondary clinical outcomes. In the primary as-randomised analysis we included 69/108 allocated to the urethroplasty group (63% of those randomised) and 90/112 allocated to urethrotomy (81% of those randomised). Of the 39 participants excluded in the urethroplasty group and the 22 participants excluded in the urethrotomy group, 15 and 8 respectively had no surgery at all (Supplementary Table 2). Supplementary Table 3 presents baseline characteristics by randomised arm and inclusion or exclusion from the primary analysis status. Participants were similar in most characteristics, although the proportion of participants never using intermittent self-dilatation at baseline was higher for those that provided the primary outcome compared with those that did not but balanced across groups. Participants allocated to the urethrotomy arm and excluded from the analysis had a higher PROM score at baseline than those included in the analysis.

Primary outcome

The PROM profile mean (SD) over 24 months after randomisation on a scale from 0 (no symptoms) to 24 (worst symptoms) was 7.4 (3.8) in the urethroplasty group and 7.8 (4.2) in the urethrotomy group, a mean (95% CI) difference of -0.36 (-1.74 to 1.02; p=0.6). Sensitivity analysis using multiple imputation (intention-to-treat analysis) gave a mean difference of -0.33 (95% CI -1.74 to 1.09; p=0.6); the modified intention-to-treat analysis gave a mean difference of -0.52 (95% CI -2.0 to 0.96; p=0.5). The estimate of the primary outcome was robust to sensitivity analyses using pattern mixture models for missing data for all but unrealistic, extreme scenarios (Supplemental Figure 1). There was no evidence of treatment effect heterogeneity by subgroup (Figure 2).

Secondary patient reported outcomes

The impact of urinary symptoms profile mean (SD) over 24 months for impact of urinary symptoms was 1.1 (0.8) for the urethroplasty group versus 1.0 (0.7) in the urethrotomy group. The adjusted mean (95% CI) difference between treatments was 0.06 (-0.19 to 0.30; p = 0.6). The satisfaction with sexual function profile mean (SD) over 24 months was 2.9 (1.2) in the urethroplasty group versus 2.5

1 (1.2) in the urethrotomy group. The adjusted mean (95% CI) difference between treatments was
2 0.35 (-0.06 to 0.75), p=0.090.

3 *Re-interventions and other secondary clinical outcomes*

4 In total, 44 participants had at least one re-intervention and there were 52 re-interventions overall.
5 Between randomisation and end of follow-up (participants were followed up to 4 years), 15 men in
6 the urethroplasty group required a re-intervention 474 (399-577) days after initial surgery compared
7 to 29 men allocated to the urethrotomy group 308 (211-448) days after surgery (median
8 (interquartile range)). The hazard ratio for time until first re-intervention (95% CI) was 0.52 (0.31 to
9 0.89), p=0.017 representing a 48% lower risk of re-intervention with urethroplasty. Calculation
10 including multiple re-interventions per participant gave a similar hazard ratio (95% CI) of 0.49 (0.30
11 to 0.82), p=0.006. A secondary analysis only involving men who underwent the allocated
12 intervention (per-protocol) showed a hazard ratio (95% CI) for time to re-intervention of 0.28 (0.15
13 to 0.55), p<0.001 (Figure 3).

14

15 Participants in the urethroplasty group had twice the odds of experiencing an improvement \geq
16 10mL/s in their maximum flow rate at 3 months compared with participants in the urethrotomy
17 group (OR 95% CI 2.1 (1.05,4.12), p=0.035). At 12 or 24 months the 44 participants in the
18 urethroplasty group had 2.6 times greater odds of experiencing an improvement of \geq 10mL/s in their
19 maximum flow rate compared with the 63 participants in the urethrotomy group (OR 95% CI 2.6 (1.1
20 to 6.1), p=0.024).

21

22 At the end of follow-up, there were 19 recurrences in the urethroplasty group and 39 in the
23 urethrotomy group (Hazard ratio 0.46 95% CI (0.29 to 0.72), p=0.001).

24

25 *Adverse events*

26 There were 88 adverse events reported during trial with 80 participants suffering at least one
27 adverse event. Out of those: 43 vs 30 suffered one event in the group receiving urethroplasty vs
28 urethrotomy (treatment received); 6 vs 0 suffered 2 events and 1 vs 0 suffered 3 events during the
29 trial. See Table 3 for more information. 22 serious adverse events were reported during the trial with
30 2 related to the trial intervention. During the trial 17 participants were reported to have experienced
31 at least one serious adverse event (7 vs 10 in the group that received urethroplasty versus
32 urethrotomy respectively): 14 participants suffered one serious adverse event (6 vs 8); 1 participant
33 had 2 (0 vs 1) and 2 participants had 3 events (1 vs 1).

34

1 **Discussion**

2 The OPEN trial is the first multi-centre randomised controlled trial comparing the effectiveness and
3 cost-effectiveness (not reported in this paper) of the two choices available for men suffering
4 recurrence of bulbar urethral stricture: endoscopic urethrotomy vs urethroplasty. We found that at
5 24-months, participants in both groups had similarly improved symptom scores compared to
6 baseline. Clinical outcomes, including time to re-intervention, and urinary flow rate (the most
7 frequently used clinical outcome (10)) favoured urethroplasty on average. These results were
8 homogeneous across different subgroups.

9 The OPEN trial design followed best practice for surgical trials in a pragmatic setting: participants
10 and clinicians could not be blinded, but central trial staff entering and analysing results were masked
11 where possible. Use of a remote computerised randomisation system ensured allocation
12 concealment. We set the trial in the UK NHS recruiting from both specialist and general units. The
13 trial's primary outcome focused on patients' symptoms since men with recurrent stricture are most
14 concerned about their poor and prolonged voiding which threatens urinary retention, a problem
15 they find distressing and which negatively impacts on their lives (13). A further strength of the study
16 is that both randomised groups were evenly balanced with respect to stricture length, aetiology,
17 number of prior recurrences and their prior experience of self-dilatation. The outcomes from both
18 arms ought to be representative of a "typical" patient with a recurrent bulbar stricture with similar
19 values to recent published cohorts of men undergoing urethroplasty or urethrotomy.

20 We faced difficulties in recruiting and retaining participants. This could be due to several reasons.
21 The two treatments are very different in complexity and short-term patient experience; participants
22 will have had treatment failure to enter the trial. Furthermore, we embedded qualitative work and
23 made changes to the design as a result of that (14). To help improve retention, we provided different
24 communication options, including to complete outcome questionnaires online (used by 30% of
25 participants). We used automated alerts to monitor and chased overdue outcome data from
26 participants and sites. Despite these efforts, we could only include 159/220 (72%) participants in the
27 primary analysis; 69 (63%) allocated to urethroplasty and 90 (81%) allocated to urethrotomy. This is
28 a common experience in studies of urethroplasty with number of patients attending clinics declining
29 with time. The reasons for the differential drop-out between randomised arms are unknown,
30 however they could be related to more participants receiving their allocated treatment in the
31 urethrotomy arm or the shorter waiting time for that intervention. Due to this observed difference,
32 an additional statistical analysis plan was prepared by the trial team's statistical experts not involved
33 in the data analysis of the trial. We conducted several sensitivity analyses as a result, including

1 multiple imputation assuming a missing at random mechanism and pattern mixture models
2 assuming missing not at random. The OPEN trial results were robust to all but unrealistic scenarios.
3 The percentage of SAEs was similar in both the urethroplasty and urethrotomy groups (10.9% vs
4 11.3%). Given the increased complexity of urethroplasty, a greater proportion of SAEs in that group
5 would have been expected. However, the serious adverse events rate for urethroplasty is similar to
6 the 30-day complication rate recently reported in the UK national database (15). One possible
7 explanation is that there were a total of four re-admissions following urethrotomy, typically
8 performed as a day case, for bleeding and/or retention.

9 A systematic literature review, including data from trial registries, which was updated just prior to
10 trial completion did not identify further relevant trials published or in progress to compare with our
11 design and results. However, clinical guidance suggests that urethroplasty is the better option, but
12 this advice has been based on low-level published evidence and expert opinion so far. Outcomes for
13 participants of our randomised trial were similar to data from non-randomised cohorts of patients
14 undergoing urethroplasty or urethrotomy in Europe and the USA. The proportion of recurrences
15 following urethrotomy and the improvement in measured low rate found in the urethrotomy group
16 was also similar to that found in recent published cohorts (2,16) as well as in a previous randomised
17 controlled trial of internal urethrotomy versus dilation for male urethral stricture disease (17).

18

19 **Conclusion**

20 Our study will help clinicians worldwide to provide more accurate information on the comparative
21 benefit of urethroplasty and urethrotomy for their male patients with recurrent bulbar urethral
22 stricture. Our study shows that either procedure is likely to improve symptoms from baseline
23 without risking significant harms and therefore both should be available. The duration of that
24 benefit is longer with urethroplasty. Patients, informed by their clinician, will need to balance these
25 factors in the light of their individual circumstances, values and preferences to decide which
26 procedure to undergo. It appears that urologists are discouraged from referring men to
27 urethroplasty, if it will mean a travelling time of longer than 45 minutes for the patient (18). In order
28 to successfully implement urethroplasty in health care systems, there is a need for robust clinical
29 pathways that ensure specialist services with sufficient resources in terms of theatre time and
30 ongoing specialist surgeon availability. It is likely that this will have implications for training needs
31 within the urology speciality.

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1 **Tables and figures**

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Table 1 - Participant clinical characteristics and reported symptoms at baseline (Data are mean (SD), count or median (p25 – p75), count for continuous variables . Binary and categorical data are presented as frequency (% out of randomised).)	Urethroplasty (N=108)	Urethrotomy (N=112)
Variable		
Age (years)	49.4 (14.3); 108	48.5 (15.4); 112
Length of stricture (cm)	2.0 (1.4); 67	1.7 (1.1); 63
Duration of disease (years)	7.3 (9.7); 78	9.9 (11.7); 80
Previous interventions (any type)	1.9 (2.0); 108	1.8 (1.7); 112
Previous dilatation –	0.4 (0.8);80	0.5 (1.8);83
Previous urethroplasty	0.1 (0.4);76	0.1 (0.3);82
Previous urethrotomy	1.6 (1.8);106	1.4 (1.0);109
Time since last intervention		
< 12 months	36 (33.3)	36 (32.1)
≥ 12 months	72 (66.7)	76 (67.9)
Predominant site of stricture in bulbar urethra		
Proximal	30 (27.8)	24 (21.4)
Mid	34 (31.5)	41 (36.6)
Distal	17 (15.7)	17 (15.2)
Unknown	6 (5.6)	14 (12.5)
Missing	21 (19.4)	16 (14.3)
Cause of stricture		
Unknown	76 (70.4)	81 (72.3)
Trauma	11 (10.2)	11 (9.8)
Infection	5 (4.6)	6 (5.4)
Other	12 (11.1)	7 (6.3)
Missing	4 (3.7)	7 (6.3)
Use of intermittent self-dilatation		
Never	60 (55.6)	66 (58.9)
Previously	25 (23.1)	31 (27.7)
Currently	23 (21.3)	14 (12.5)
Missing	0 (0)	1 (0.9)
Maximum urinary flow rate (mL/s)	10.0 (6.0); 83	9.7 (5.2); 90
Urethrogram performed	70 (64.8)	62 (55.4)
Urethroscopy performed	34 (31.5)	42 (37.5)
PROM		
Total voiding score mean (standard deviation), 0 (no symptoms) to 24 (symptoms all the time)	13.5 (4.5); 104	13.2 (4.7); 109
Impact of urinary symptoms on daily activities 0 (none) to 3 (a lot)	2.0 (1.0-3.0); 107	2.0 (1.0-3.0); 110
Satisfaction with sexual function 1 (very satisfied) to 5 (very dissatisfied)	3.0 (2.0-4.0); 97	3.0 (2.0-4.0); 100

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1 Table 2 – Clinical and patient reported outcomes (mean (SD), count or % (n/N) or n as appropriate)

Analysis	Urethroplasty (n=108)	Urethrotomy (112)	Effect size (95% CI)	p-value
Patient reported outcomes				
			Mean difference	
Profile Void score	7.4 (3.8), 69	7.8 (4.2), 90	-0.36 (-1.74 to 1.02)	0.6
Profile impact of urinary symptoms	1.1 (0.8), 69	1.0 (0.7), 90	0.06 (-0.19 to 0.30)	0.6
Profile satisfaction with sexual function	2.9 (1.2), 63	2.5 (1.2), 87	0.35 (-0.06 to 0.75)	0.090
Clinical outcomes				
			Odds ratio	
Q _{max} Improved at 12 or 24-mo from baseline ¹	19% (18/93)	13% (13/104)	2.64 (1.14 to 6.15)	0.024
			Hazard ratio	
Any recurrence	19	39	0.46 (0.29 to 0.72)	0.001
Re-intervention	15	29	0.52 (0.31 to 0.89)	0.017

2 The effect sizes presented differ by outcome and are all adjusted to minimisation variables; all effect
3 sizes are urethroplasty vs urethrotomy.

4 ¹Improvement defined as an increase in the flow rate of 10 mL/s or more

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Table 3 Frequency of adverse events by treatment received

	Urethroplasty (n=82)	Urethrotomy (n=115)
No. of adverse events		
0	32 (39.0)	85 (73.9)
1	43 (52.4)	30 (26.1)
2	6 (7.3)	0 (0)
3	1 (1.2)	0 (0)
Adverse events during the perio-operative period		
Mouth pain	^a 12 (14.6)	2 (1.7)
Wound infection	4 (4.9)	0 (0)
Bladder 'spasm' requiring treatment	2 (2.4)	1 (0.9)
Urinary infection	3 (3.7)	0 (0)
Initial failed trial without catheter	0 (0)	1 (0.9)
Adverse events during the re-intervention perio-operative period		
Mouth pain	0 (0)	2 (1.7)
Wound infection	0 (0)	1 (0.9)
Urinary infection	0 (0)	2 (1.7)
Urinary retention	0 (0)	1 (0.9)
Constipation	0 (0)	1 (0.9)
Adverse events during follow-up		
Erectile dysfunction	4 (4.9)	3 (2.6)
Mouth pain	4 (4.9)	0 (0)
UTI	5 (6.1)	6 (5.2)
Urinary symptom outcome	^b 7 (8.5)	6 (5.2)
Wound infection	1 (1.2)	1 (0.9)
Wound pain	5 (6.1)	1 (0.9)
Numb testicles	2 (2.4)	0 (0)
Issues related to climax	^c 1 (1.2)	0 (0)
Other ^d	1 (1.2)	3 (2.6)
Erectile dysfunction and wound infection	1 (1.2)	0 (0)
Erectile dysfunction and wound pain	1 (1.2)	0 (0)
Wound infection, UTI and fistula	1 (1.2)	0 (0)

a – 2 people had 2 events of mouth pain

b- 1 person had 2 new urinary symptoms

c- 1 person had 2 reports of issues related to climax

d- Upper respiratory tract infection, swollen ankles, haematuria and dysuria, falls.

Table 4 Frequency of serious adverse events by treatment received

	Urethroplasty (n=82)	Urethrotomy (n=115)
No. of serious adverse events		

0	75 (91.5)	105 (91.3)
1	6 (7.3)	8 (7.0)
2	0 (0)	1 (0.9)
3	1 (1.2)	1 (0.9)
Serious adverse events		
Readmission to hospital	0 (0)	^a 2 (1.7)
Diverticular perforation	0 (0)	1 (0.9)
UTI	3 (3.7)	1 (0.9)
Haematuria	1 (1.2)	1 (0.9)
New urinary symptom	1 (1.2)	1 (0.9)
Wound infection	1 (1.2)	1 (0.9)
Wound pain	1 (1.2)	0 (0)
Wound infection and fistula	1 (1.2)	0 (0)
Death	0 (0)	^b 1 (0.9)
Other ^c	1 (1.2)	3 (2.6)

a- 1 person had 3 readmissions to the hospital

b- Event unrelated to the trial intervention. Death by deep vein thrombosis and pulmonary embolism

c- Urethral bleeding following a urethrogram, posterior circulation cerebral infarct, left hemianopia, chest pain, cholecystitis. Two events related to the trial intervention and expected

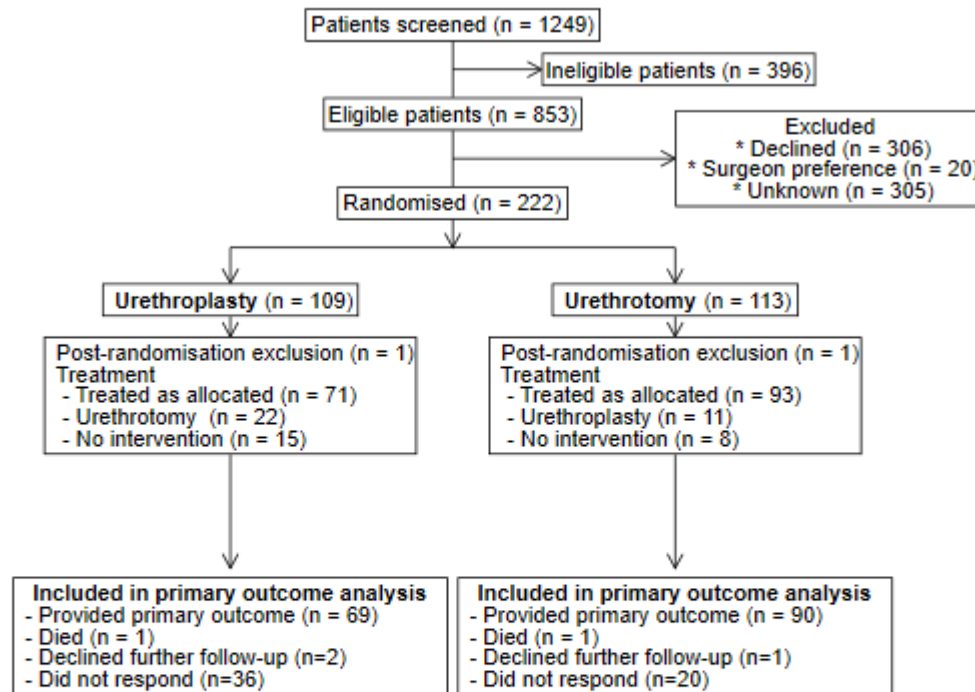


Figure 1 - CONSORT diagram showing progress of participants through the study

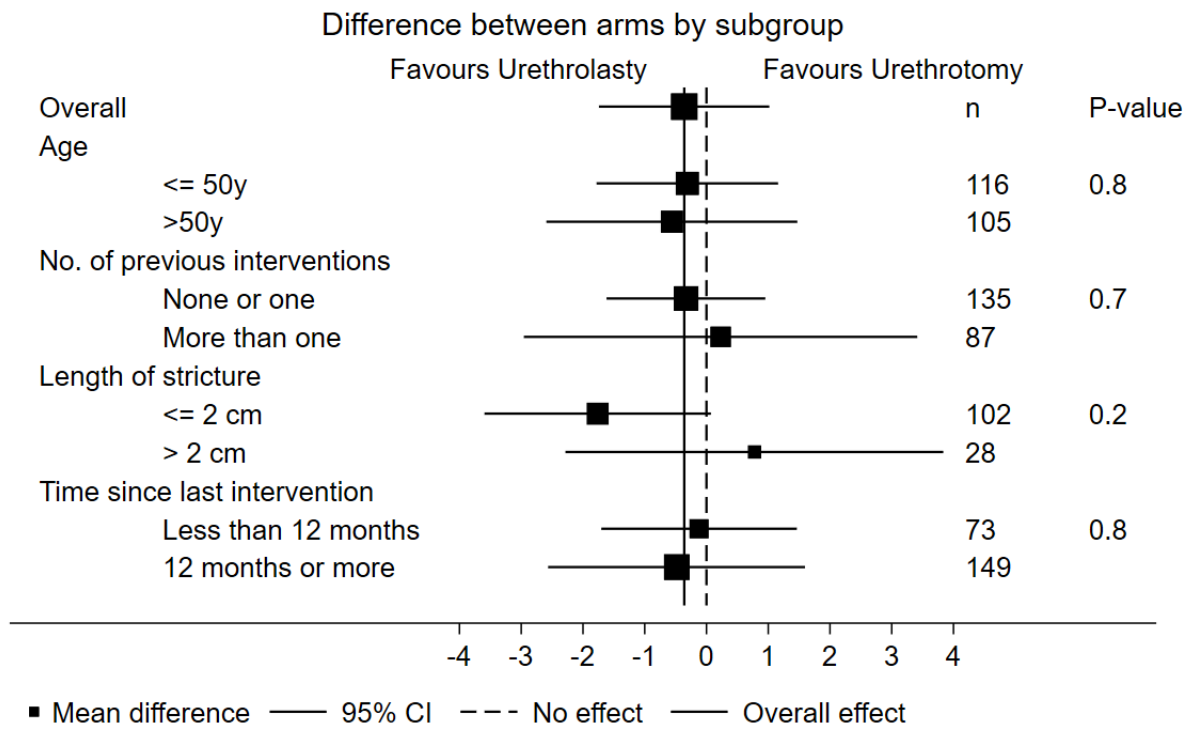


Figure 2 Subgroup analyses for the PROM voiding score area under the curve (calculated by including a treatment-by-factor interaction in models)

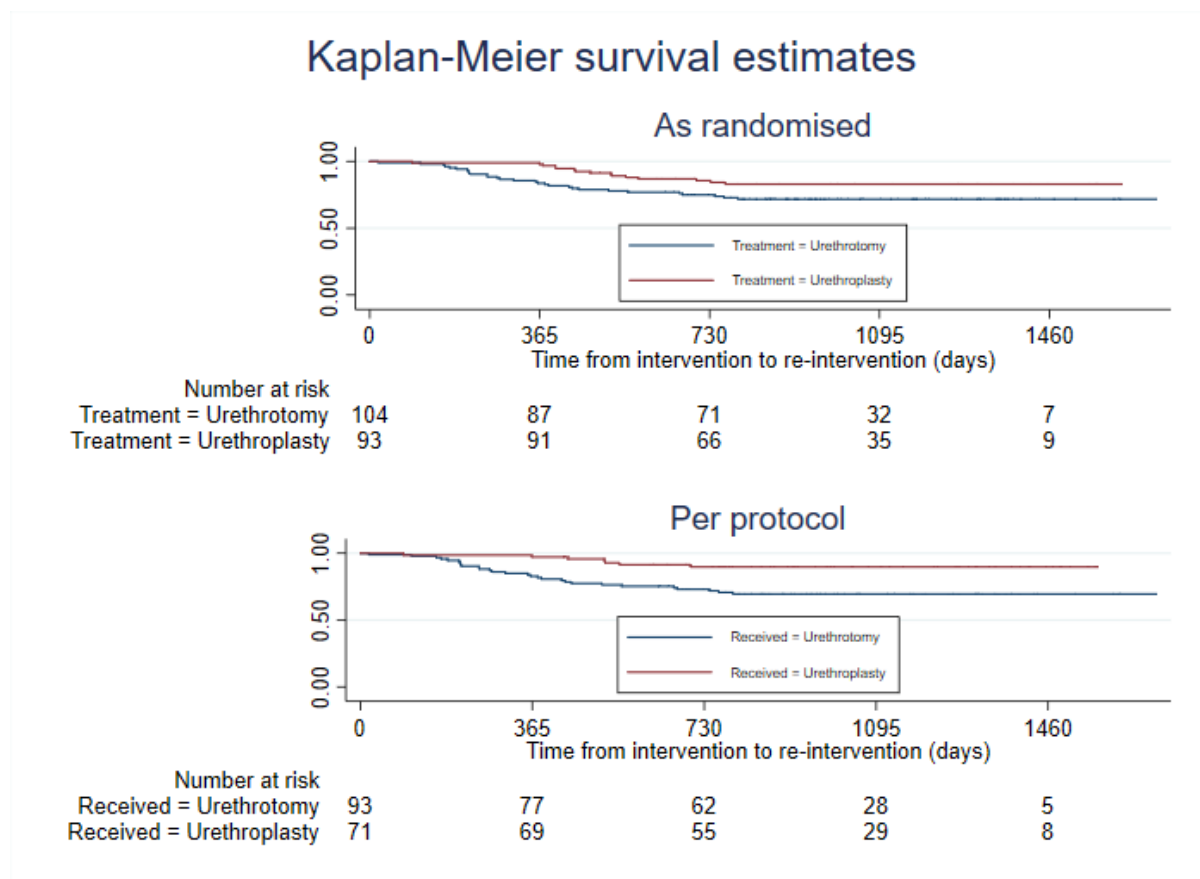


Figure 3 Hazard curves for re-intervention by randomised or treatment received group up to 4 years after initial intervention. Analysis of participants that had surgery according to their randomised allocation (as randomised) or restricted to men who underwent procedure allocated at randomisation (per-protocol)

Supplementary tables (OPEN)

Table 1: Reasons for non-participation in participants approached to take part in OPEN

		Total = 1249
Ineligible		396 (32)
Reasons for ineligibility	Age less than 16y	4 (0.3)
	Stricture in penile urethra	66 (5.3)
	No previous intervention for stricture	101 (8.1)
	Intervention not required	65 (5.2)
	Unwilling to have 2w catheterisation	1 (0.1)
	Unable to give consent	13 (1.0)
	Perineal sepsis or fistula	7 (0.6)
	Previous participation in OPEN	5 (0.4)
	Unable to have 3 hour	22 (1.8)

	anesthetic	
	Inability to adhere to trial protocol	11 (0.9)
	Ineligible, no reason stated	101 (8.1)
Patient declined participation		306 (24.5)
Reason patient declined participation	Preference for open urethroplasty	185 (14.8) 60% of those who declined
	Preference for endoscopic urethrotomy	79 (6.3) 26% of those who declined
	Potential adverse effects of urethroplasty	6 (0.5)
	Potential adverse effects of urethrotomy	1 (0.1)
	Need for urethrogram for urethroplasty	2 (0.2)
	Unable to fulfil protocol commitments	19 (1.5) 6% of those who declined
	Patient did not attend	14 (1.1)
Surgeon preference		20 (1.6) 7% of those who declined
Unknown		305 (24.4)

Table 2: Treatment received in the trial by randomised group, n(%)

Allocated intervention	Urethroplasty (N=108)	Urethrotomy (N=112)
Intervention performed		
Urethroplasty	71 (66)	11 (9.8)
• Anastomotic without transection	9 (8.3)	4 (3.6)
• Anastomotic with transection	9 (8.3)	1 (0.89)
• Ventral graft urethroplasty	7 (6.5)	2 (1.8)
• Dorsal graft urethroplasty	45 (42)	4 (3.6)
• Perineal urethrostomy	1 (0.93)	0 (0)

Urethrotomy	22 (20)	93 (83)
• Optical urethrotomy cold knife	15 (14)	90 (80)
• Optical urethrotomy hot knife	0 (0)	1 (0.89)
• Dilatation	7 (6.5)	2 (1.8)
Commenced regimen of intermittent self-dilatation (ISD)	9 (8.3)*	29 (26)
No intervention performed	15 (14)	8 (7.1)

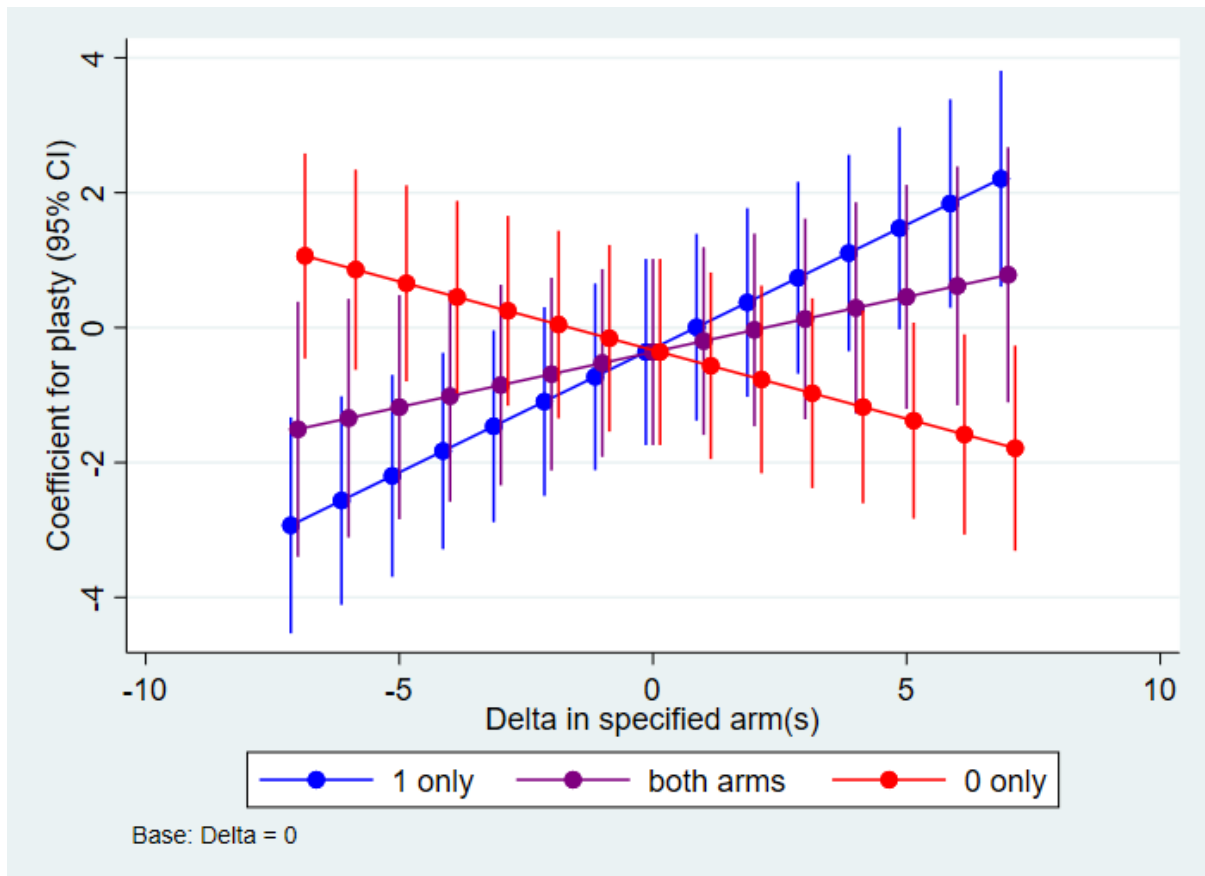
*All had crossed over and received urethrotomy

Table 3 – Baseline characteristics by randomised arm and inclusion in primary analysis

	Urethroplasty (N=108)		Urethrotomy (N=112)	
	Has PROM profile (n=69)	Doesn't have PROM profile (n=39)	Has PROM profile (n=90)	Doesn't have PROM profile (n=22)
Age – mean(SD), count	50.6 (13.3),69	47.2 (16.0),39	48.1 (15.7),90	49.8 (14.3),22
Length of stricture (cm) – mean(SD), count	1.9 (1.5),40	2.1 (1.2),27	1.7 (1.2),53	1.6 (0.8),10
Duration of disease (years) – mean(SD), count	5.4 (5.4),55	12.0 (15.0),23	10.4 (12.4),62	8.4 (9.0),18
Previous interventions – mean(SD), count	1.5 (1.1),69	2.6 (2.9),39	1.8 (1.8),90	1.6 (1.3),22
Previous dilatations – mean(SD), count	0.4 (0.8),52	0.5 (0.6),28	0.5 (1.9),66	0.5 (1.2),17
Previous urethroplasty – mean(SD), count	0.0 (0.2),52	0.3 (0.7),24	0.1 (0.3),65	0.1 (0.3),17
Previous urethrotomy – mean(SD), count	1.2 (0.7),69	2.2 (2.8),37	1.4 (1.0),87	1.2 (0.9),22
Time since last procedure [n (%)]				
Less than 12 months	24 (35)	12 (31)	29 (32)	7 (32)
12 months or more	45 (65)	27 (69)	61 (68)	15 (68)
Estimated main site of bulbar stricture [n (%)]				
Proximal	19 (28)	11 (28)	22 (24)	2 (9.1)
Mid	19 (28)	15 (39)	33 (37)	8 (36)
Distal	13 (19)	4 (10)	12 (13)	5 (23)
Unknown	2 (2.9)	4 (10)	13 (14)	1 (4.5)
Missing	16 (23)	5 (13)	10 (11)	6 (27)
Cause of stricture [n (%)]				
Unknown	48 (70)	28 (72)	66 (73)	15 (68)
Trauma	3 (4.3)	8 (21)	10 (11)	1 (4.5)
Infection	5 (7.2)	0 (0)	5 (5.6)	1 (4.5)
Other	9 (13)	3 (7.7)	6 (6.7)	1 (4.5)
Missing	4 (5.8)	0 (0)	3 (3.3)	4 (18)
Use of intermittent self-dilatation [n (%)]				
Never	43 (62)	17 (44)	56 (62)	10 (46)
Previously	12 (17)	13 (33)	23 (26)	8 (36)
Currently	14 (20)	9 (23)	10 (11)	4 (18)
Missing	0 (0)	0 (0)	1 (1.1)	0 (0)
Maximum urinary flow rate (mL/s) – mean(SD), count	10.0 (6.1),51	10.1 (6.0),32	9.7 (5.2),75	9.7 (5.4),15
Urethrogram performed [n (%)]	49 (71)	21 (54)	52 (58)	10 (46)
Urethroscopy performed [n (%)]	21 (30)	13 (33)	34 (38)	8 (36)
PROM				
Total voiding score mean (standard deviation), 0 (no symptoms) to 24 (symptoms all the time) – mean(SD), count	13.6 (4.4), 67	13.2 (4.8), 37	12.7 (4.7), 87	15 (4.1), 22
Impact of urinary symptoms on	2.0 (1.0-	2.0 (1.0-	2.0 (1.0-	2.5 (2.0-

daily activities 0 (none) to 3 (a lot)	3.0),69	3.0),38	3.0),88	3.0),22
Satisfaction with sexual function 1 (very satisfied) to 5 (very dissatisfied)	2.0 (1.0-3.0),66	2.0 (1.0-4.0),31	1.0 (1.0-3.0),82	2.0 (1.0-4.0),18

Data are median (p25 – p75), count unless indicated otherwise. Binary and categorical data are presented as frequency (% out of randomised).



Supplemental Figure 1 – Pattern mixture model results