Title

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

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Abstract

Background

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

Objectives

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

Design, Setting and Participants

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

Interventions

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

Main outcome measures

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

Results

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

Conclusion

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

Patient summary

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

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Main Report

Introduction

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

Methods

Study design

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

Participants

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

Randomisation and masking

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

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

Procedures

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

Outcomes

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

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

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

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

Sample size

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

Statistical analysis

The statistical analysis plans are available from 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 and using all available measurements (starting a baseline which was measured immediately prior to randomisation) to then construct the area under the curve using the trapezoid rule, was analysed using linear regression adjusted for minimisation covariates.

The primary analysis included all participants who had any surgery and completed at least three voiding scores: one baseline measure, one early measure (up to 12 months after intervention), and one later measure (18 or 24-months post-randomisation). We analysed as randomised, i.e. participants were analysed according to their allocated group regardless of the intervention received. Given the pragmatic nature of the trial we planned sensitivity analysis to account for missing data and non-compliance. We did a full intention-to-treat analysis using multiple imputation to include all

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

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

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

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

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

Re-interventions and other secondary clinical outcomes

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

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

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

Adverse events

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

Discussion

The OPEN trial is the first multi-centre randomised controlled trial comparing the effectiveness and cost-effectiveness (not reported in this paper) of the two choices available for men suffering

recurrence of bulbar urethral stricture: endoscopic urethrotomy vs urethroplasty. We found that at 24-months, participants in both groups had similarly improved symptom scores compared to baseline. Clinical outcomes, including time to re-intervention, and urinary flow rate (the most frequently used clinical outcome (10)) favoured urethroplasty on average. These results were homogeneous across different subgroups.

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

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

The percentage of SAEs was similar in both the urethroplasty and urethrotomy groups (10.9% vs 11.3%). Given the increased complexity of urethroplasty, a greater proportion of SAEs in that group would have been expected. However, the serious adverse events rate for urethroplasty is similar to the 30-day complication rate recently reported in the UK national database (15). One possible explanation is that there were a total of four re-admissions following urethrotomy, typically performed as a day case, for bleeding and/or retention.

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

Conclusion

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

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Tables and figures

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).) Variable	Urethroplasty (N=108)	Urethrotomy (N=112)
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

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

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

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

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

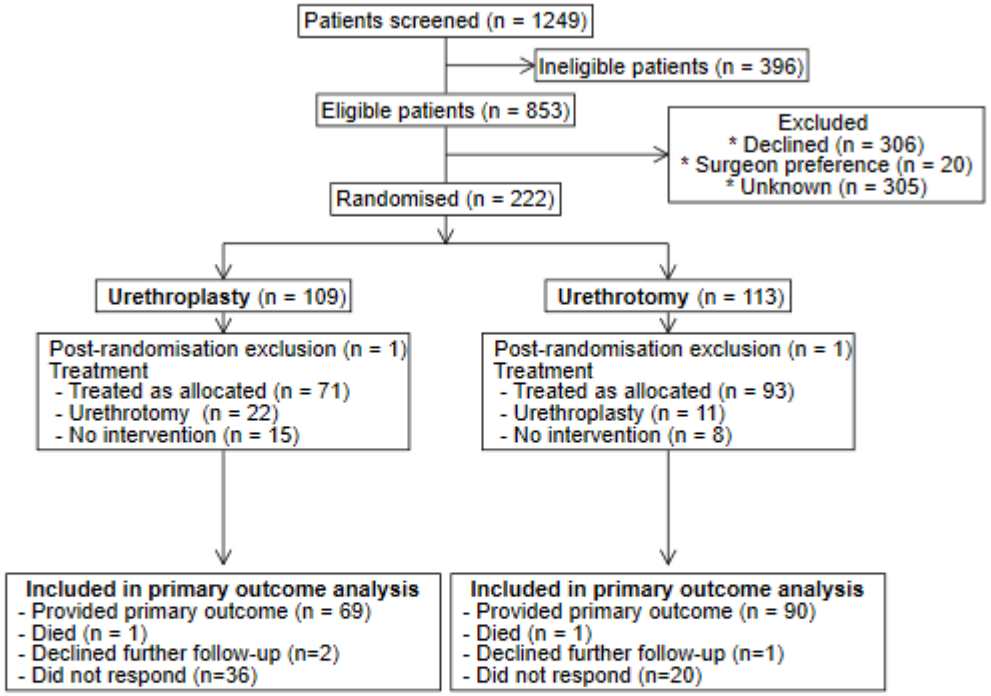

Figure 1 - CONSORT diagram showing progress of participants through the study

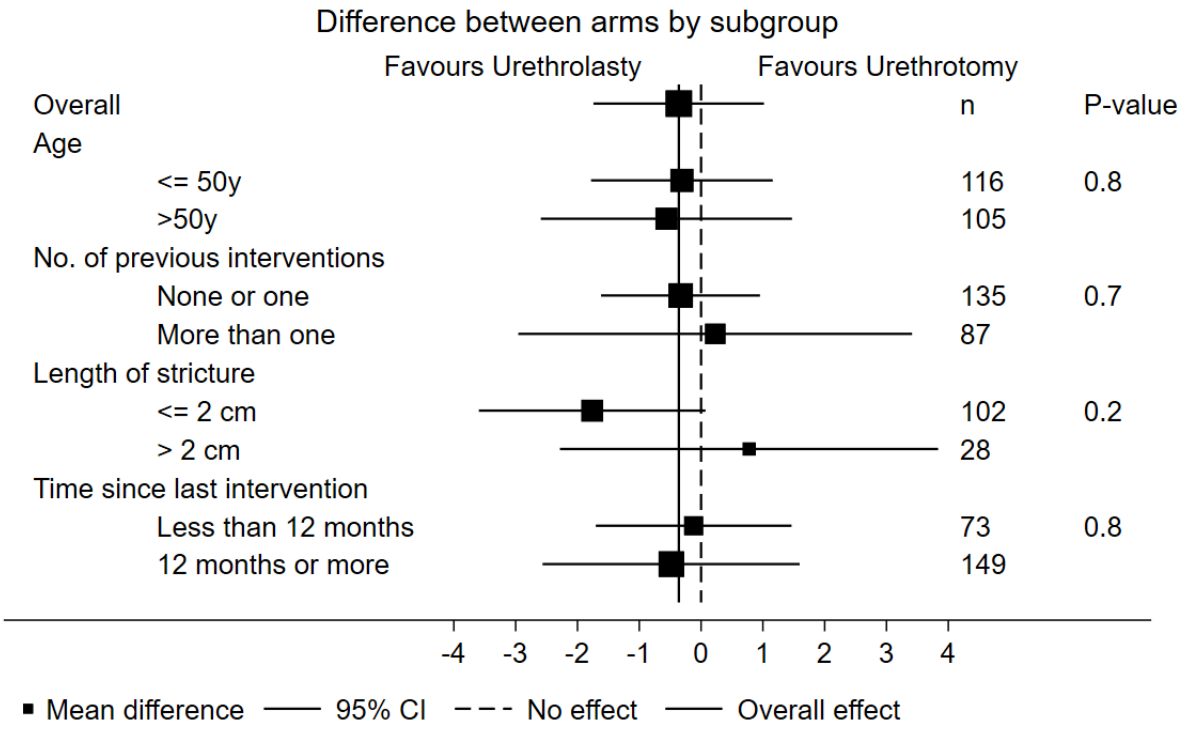

Figure 2 Subgroup analyses for the PROM voiding score area under the curve (calculated by including a treatment-by-factor interaction in models)

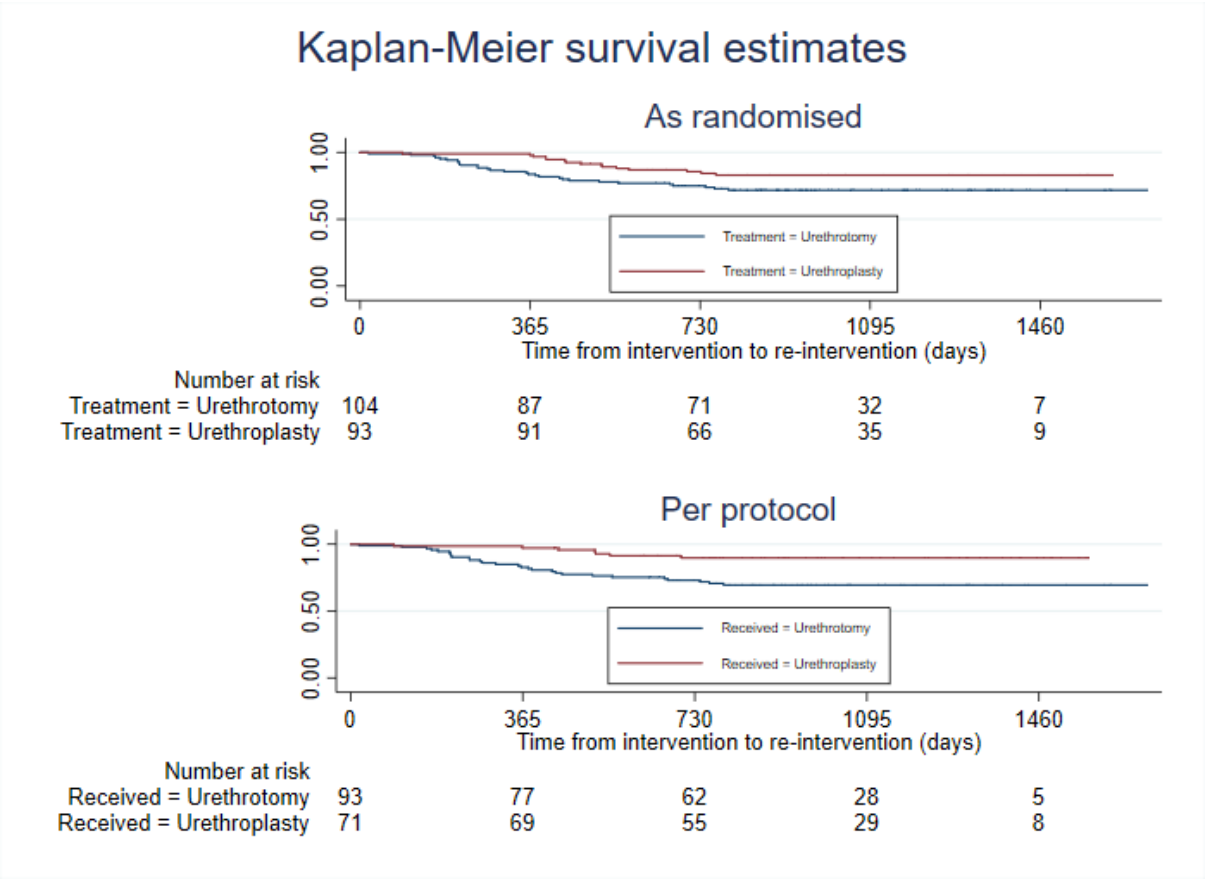

Figure 3 Hazard curves for re-intervention by randomised or treatment received group up to 4 years after initial intervention. Analysis of participants that had surgery according to their randomised allocation (as randomised) or restricted to men who underwent procedure allocated at randomisation (per-protocol)