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Minimally Invasive Treatments for Benign Prostatic Obstruction: A Systematic Review and Network Meta-analysis

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Abstract

Context: Minimally invasive surgical therapies for male lower urinary tract symptoms secondary to benign prostatic obstruction were developed to be safer and more tolerable than standard ablative techniques. These treatments have not been compared with each other in a randomised fashion, and for some treatments, there are no trials against a reference technique.

Objective: To compare the efficacy, safety, and tolerability of water vapour thermal therapy (WVTT), prostatic urethral lift (PUL), prostatic arterial embolisation (PAE), temporary implantable nitinol device (iTIND), transurethral microwave thermotherapy (TUMT), and transurethral resection of the prostate (TURP).

Evidence acquisition: A systematic search of MEDLINE/PubMed, Embase, Cochrane Library, and grey literature for randomised controlled trials was performed. Trials meeting the selection criteria were assessed for the risk of bias using the Cochrane RoB2 tool. Treatments were compared, using a network meta-analysis, in terms of outcomes including symptom score, quality of life, maximum urinary flow rate, postvoid residual urine, International Index of Erectile Function (IIEF-5), and scales from the Male Sexual Health Questionnaire.

Evidence synthesis: The search identified 63 trials. Symptoms and quality of life for PAE, PUL, and WVTT appeared similar to those for TURP, whereas TURP was found to have the most clinically significant improvement in flow rate. TUMT was less efficacious than TURP but provided similar results on quality of life. Comparisons of ejaculatory function favoured WVTT and PUL compared with TURP. The relative efficacy of iTIND was less clear because of the risk of bias in the respective trial.

Conclusions: PAE, PUL, and WVTT appear favourable from a risk-benefit perspective despite probably having less efficacy than TURP for objective outcomes. These findings warrant confirmation through long-term randomised controlled trials.

Patient summary: This paper has summarised the evidence from 63 clinical trials on minimally invasive surgical therapies for men with symptoms of an enlarged prostate, including water vapour thermal therapy (WVTT), prostatic urethral lift (PUL), prostatic arterial embolisation (PAE), temporary implantable nitinol device, and transurethral microwave thermotherapy (TUMT). Improvement in symptoms for each of PAE, PUL, TUMT, and WVTT in short-term

follow-up was similar to that for the standard surgical treatment, although standard surgery appeared to provide the greatest increase in urine flow. Men who had WVTT or PUL were less likely to have problems with sexual function than those who had standard surgery.

1. Introduction

Lower urinary tract symptoms (LUTS) are highly prevalent in men older than 50 yr and represent a large epidemiological and financial burden in Western countries [1]. While aetiologies of male LUTS are multiple, benign prostatic obstruction (BPO) is recognised as the most frequent cause of voiding symptoms [2]. Initial management of LUTS/BPO is widely based on the use of alpha-blockers, 5-alpha-reductase inhibitors, and phosphodiesterase-5 inhibitors [3]. While no significant innovation has recently been introduced in novel medicines, the surgical armamentarium for LUTS/BPO management has rapidly enlarged in the past decade [4]. Minimally invasive surgical therapies (MISTs) that do not remove prostatic tissue at the time of the procedure have been proposed as alternatives to ablative surgery (eg, enucleation, resection, and vaporisation) with the aim of reducing adverse events, particularly bleeding and secondary sexual dysfunction [5]. These options include transurethral microwave thermotherapy (TUMT) [6] as a historic archetype, water vapour thermal therapy (WVTT, ie, Rezum) [7], prostatic urethral lift (PUL) [8], prostatic arterial embolisation (PAE) [9], and temporary implantable nitinol device (iTIND) [10], for which indications are presented in Table 1.

Inclusion of emerging therapies in clinical guidelines is conditioned upon strongly supportive evidence, as recommended by the European Association of Urology (EAU) guidelines panel [11]. Since currently available evidence supporting the use of MISTs is heterogeneous, only a couple

of options are included in the most recently released document on EAU guidelines [3]. Notably, WVTT and iTIND are still considered under investigation by the EAU guidelines because of the lack of randomised controlled trials (RCTs) against a recognised standard of care [3]. Further, attempts to indirectly compare MISTs with the reference surgical technique, transurethral resection of the prostate (TURP), have not provided evidence of sufficient certainty because of imprecision and inconsistency [12] and methodological limitations [13] in existing reviews.

For market approval in the USA, it is recommended that pivotal studies of new therapies are designed as randomised trials against a comparator such as TURP or sham treatment [14]. Use of sham control facilitates the assessment of treatments in a blinded fashion and the separation of treatment response from placebo effects and regression to the mean. Recent literature reviews reveal that WVTT as well as iTIND, PAE, PUL, and TUMT have been studied in sham-controlled trials, and some have been compared with TURP, but head-to-head trials of these MISTs are currently lacking. The availability of RCTs against common reference treatments offers the possibility of performing anchored comparisons between the MISTs and TURP that provide control for factors that may differ between trials.

The present systematic review with a network meta-analysis (NMA) was conducted to compare iTIND, PAE, PUL, TUMT, TURP, and WVTT with respect to effectiveness, safety, and tolerability.

2. Evidence acquisition

2.1. Systematic review methodology

A systematic review was performed on minimally invasive treatments for patients with LUTS/BPO. RCTs with comparative results for at least two of the following modalities were

included: WVTT (Rezum system), PUL, PAE, TUMT, iTIND, monopolar (mTURP) or bipolar (bTURP) TURP, and sham treatment. PAE was separated according to the largest microsphere size used (≤ 300 and >300 μm) because of potential differences in outcomes [15]. Trials were identified through searches of MEDLINE/PubMed, Embase, and Cochrane library, as well as grey literature and reference lists of systematic reviews through August 15, 2022. The search strategies used are provided in Supplementary Tables 1–3. Articles were screened and assessed for eligibility according to the inclusion and exclusion criteria (Supplementary Table 4) by two independent researchers (C.S. and C.T.), and disagreements were reconciled by discussion.

The outcomes included the International Prostate Symptom Score (IPSS) and associated quality of life measure (IPSS-QoL), Benign Prostatic Hyperplasia Impact Index (BPH-II), maximum urinary flow rate (Q_{max}), postvoid residual urine volume (PVR), erectile and ejaculatory function (including Male Sexual Health Questionnaire [MSHQ] and International Index of Erectile Function [IIEF-5] scores), bleeding complications, reintervention, and length of stay at the hospital. The mean (or median) postoperative value and change from baseline along with associated measures of dispersion or quartiles were extracted for continuous variables. Trial design, patient characteristics, and funding sources were also extracted. Priority was given to the intent-to-treat population. Data were extracted by one researcher and checked by a second (A.B., N.C., H.G., K.R., and C.T.), with disagreements resolved by a third (C.S. or A.M.).

2.2. Risk of bias in individual studies

The risk of bias at the trial level was assessed by two researchers (C.S. and C.T.) independently using the Cochrane RoB2 tool for RCTs [16], and differences were reconciled by discussion.

2.3. Network meta-analysis

The trial network was displayed in a graph, with arc thickness representing the number of trials. Data synthesis was performed for the postoperative value based on the within-trial pairwise mean differences (MDs) between arms. A frequentist NMA with random effects was performed using the graph-theoretic approach of Rücker [17] assuming a common between-study variance estimated by the method of moments [17], as implemented in the R package netmeta [18]. Moore-Penrose inverse and downweighting were applied for multiarm studies, which yield results identical to those from a linear mixed model approach [19]. Missing means and standard deviations were imputed from the within-trial medians, quartiles, and ranges using the approximations of Wan et al [20]. Heterogeneity was assessed and quantified using the Q-statistic and tau, respectively. Treatments were ranked on the p score, a frequentist analogue of the surface under the cumulative ranking curve [21]. Bayesian results based on an uninformative prior distribution for the between-trial variance were also computed as a conservative analysis.

2.4. Assessment of inconsistency

An assumption of an NMA is that the treatment effect for any pair of treatments, say, A versus B, is the same (in distribution) across the trials. For example, the treatment effect in a trial of A versus B would be the same as that obtained if A and B were inserted into a trial of C versus D. Such exchangeability of trials implies that treatment effects may be calculated indirectly and will be consistent with those from direct (head-to-head) comparisons. Exchangeability was assessed by checking the similarity of the designs and subject characteristics across trials. In addition, consistency between direct and indirect estimates of the treatment effects was assessed using a

design-by-treatment interaction test [22] and net heat plot [23] as well as by node splitting in closed loops [24], when feasible. Evidence of violation of exchangeability was addressed through network meta-regression as well as partitioning of the network.

2.5. Certainty assessment

The certainty of evidence on each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework for NMA [25].

3. Evidence synthesis

Disposition of articles identified by the search is summarised in Figure 1. Sixty-three unique RCTs were identified from the 84 articles that met the selection criteria; full-length articles were available for 56 of these trials.

3.1. Study characteristics

Characteristics of the included trials are summarised in Supplementary Table 5. Ten of the studies were double blinded, 16 single blinded, five open label, and one with only the outcome assessor blinded, while 31 did not report blinding information. All sham-controlled trials were blinded for the follow-up ranging from 3 to 6 mo, after which control individuals could cross over to the active treatment. Sham procedures involved urethral insertion of a catheter or cystoscope (18–21F) with the exception that prostatic artery catheterisation was performed in the trial of PAE.

The main selection criteria are provided in Supplementary Table 4. No trial planned to include prostates over 100 ml. Baseline characteristics are summarised in Table 2 by intervention, and by trial in Supplementary Table 6. Mean patient age was similar across trials. Mean prostate volume was larger in the trials of PAE and varied significantly between the trials of bTURP and mTURP, but was reasonably similar across the trials comparing other modalities. However, the mean prostate-specific antigen values for most studies were well matched, with the majority of studies averaging between 2 and 4 ng/ml. Most trials were similar with respect to the mean IPSS as well as IPSS-QoL, Qmax, and PVR at baseline; however, a few studies with outlying values of these characteristics were noted most frequently among the trials of bTURP versus mTURP (Supplementary Table 6 and Supplementary Fig. 3–5).

The change in IPSS score was the most common primary outcome (18 studies), although the primary outcome was not specified in most articles. Few articles specified whether the purpose was to assess superiority (six studies), noninferiority (two studies), or both (one study). The bias was assessed to be of low risk for 26 trials, some concern for 36, and high risk for one trial (Supplementary Table 5).

3.2. NMA results

For each included study, the outcome data from the earliest reported time point inside 3–6-mo follow-up were used for the main analysis. Of the 63 unique trials, 34 reported comparative data that were included in the NMA; the reasons the other trials did not contribute data included a lack of dispersion data or data outside the time period considered (Supplementary Table 7).

There was evidence of heterogeneity in outcomes between trials ($p \leq 0.001$) except for IIEF-5 ($p = 0.7$). The results of the main analyses are shown in Figure 2, including the network diagram,

forest plots of treatment comparisons, GRADE certainty of estimate, and P scores. Improvement of IPSS was deemed similarly high after TURP, WVTT, PAE, and PUL. Less important change was seen after iTIND or TUMT. Similar results were seen for IPSS-QoL improvement. Objective outcomes (PVR and Qmax) reflecting BPO relief were improved to the greatest extent after TURP, with moderate improvement after WVTT and TUMT, and less improvement after PUL and iTIND. The results of PAE varied widely among studies. Ejaculatory function was maintained after WVTT or PUL, while TURP led to significant and bothersome ejaculatory dysfunction. An analysis of the BPH-II composite score favoured PAE followed by PUL and WVTT compared with other options.

The length of stay was reported for few trials of MISTs, and comparisons were contraindicated because of dissimilarity between trials in the times reported for TURP arms (and discharge criteria were unstated). An assessment of reintervention from the articles reporting trial results was infeasible. Complications were rarely defined as well as heterogeneous in terms of completeness and time point of reporting. Thus, these outcomes were not meta-analysed.

Consistency between the direct and indirect comparisons was rejected for each of IPSS (design-by-treatment interaction $p = 0.002$), Qmax ($p = 0.023$), and PVR ($p = 0.019$), but not for IPSS-QoL ($p = 0.5$). The inconsistency was greatest in the comparisons that included PAE (Fig. 3).

An additional definitive analysis was thus conducted to split the studies into two groups: one excluding PAE studies (Fig. 4) and the other containing only PAE studies (Fig. 5).

For the subnetwork without PAE, consistency of the comparisons of the direct and indirect treatments was not rejected for any of the outcomes (p values ranging from 0.2 to >0.9). WVTT and PUL again appeared to achieve similar results regarding IPSS improvement, which was comparable with that of TURP. WVTT achieved better results for Qmax improvement than PUL

but less than that with TURP. Finally, PUL and WVTT had a very low impact on ejaculatory dysfunction with a favourable profile on the BPH-II trade-off score. An NMA of the PAE subnetwork was possible for IPSS, IPSS-QoL, Qmax, and PVR, but some lack of consistency was still evident; short-term results were comparable with TURP for IPSS but weaker for Qmax. The subnetwork results were similar to those of network meta-regression adjusting for baseline prostate volume (Supplementary Fig. 6–9). The results of one trial of PAE >300 µm versus bTURP (Insausti 2020) were inconsistent with those of other trials; on excluding this trial from the PAE subnetwork, comparisons with mTURP were less favourable for PAE on IPSS (MD 3.9; 95% confidence interval [CI] 2.2–5.6) and IPSS-QoL (MD 0.3; 95% CI –0.1 to 0.7).

3.2.1. Outcomes at 12 mo

The NMA was repeated at 12 mo for the treatments with available data (PAE, PUL, and TUMT). For IPSS, results were similar for PAE and mTURP (MD –0.4; 95% CI –1.6 to 0.9); compared with mTURP, IPSS appeared greater for TUMT (MD 2.4; 95% CI 1.2–3.6) and PUL (MD 3.4; 95% CI –0.01 to 6.9) but was not statistically different for the latter. However, the fractions of patients who had received retreatment for LUTS/BPO (either procedure or pharmacotherapy) by 12 mo were 11.1% for PAE, 6.8% for PUL, 8.1% for TUMT, and only 3.1% for TURP. Compared with mTURP, Qmax was less for each of PAE (MD –2.9; 95% CI –4.8 to –1.1), PUL (MD –9.6; 95% CI –14.4 to –4.8), and TUMT (MD –4.9; 95% CI –7.0 to –2.7).

3.3. Discussion

The introduction of contemporary MISTs (PUL, then PAE and WVTT) has been the most recent paradigm shift in the field of LUTS/BPO management. MISTs were originally highlighted as potential competitors of conventional ablative surgical options with similar efficacy, leading to potentially fewer complications and decreased sexual adverse effects (especially regarding ejaculatory dysfunction) [26]. However, MISTs are associated with a significantly lower amount of tissue ablation (if any) and a lower impact on prostatic volume. This raises the hypothesis of lower efficacy of MISTs than TURP for BPO relief. It has been proposed that MIST be considered as an intermediate option between medical treatment, especially combination therapies, and ablative BPO surgery [27], especially for patients who accept the trade-off between better sexual outcomes and potentially less effective or durable treatment. However, while potential indications increase and the use of MISTs expands rapidly in current clinical practice, the amount of evidence remains heterogeneous and insufficient to strongly support the widespread use of all MIST techniques [11].

To overcome this limitation, the present work combined all available evidence from RCTs into an NMA in order to compare treatment options, despite the absence of head-to-head trials between some options. TURP was found to provide the greatest increase in Qmax, followed by WVTT and then TUMT, iTIND, and PUL. However, changes in IPSS and IPSS-QoL appeared to be comparable for mTURP, WVTT, and PUL, suggesting that symptoms and quality of life improvement were not strictly correlated to Qmax. This might also be due to the use of MISTs in less symptomatic patients or the inclusion of patients with mixed symptoms. However, baseline IPSS values appeared comparable for all treatment options (Supplementary Table 6 and Supplementary Fig. 3). Short-term efficacy for symptoms was possibly worse for iTIND than for

mTURP, but the certainty of evidence on iTIND was graded as low, partly because the respective trial has a risk of bias from considerable subject attrition and noncompliance to follow-up.

Adverse effects on sexual function, in particular ejaculatory disorders, clearly favoured PUL and WVTT compared with TURP, with a very small impact on MSHQ scores in particular. In accordance with this, the BPH-II score (reflecting the balance between efficacy and adverse events) was possibly better after WVTT and PUL than after TURP. Those results were in line with the clinical approach described above, suggesting that WVTT and PUL in men with middle-size prostates provide less BPO relief than TURP, but lead to a similar IPSS improvement without impairing sexual function. These data are of utmost importance as patient care in the field of male LUTS is increasingly focused not only on symptoms and bother, but also on patient values, preferences, fears, and expectations [5]. The role of MISTs is probably about to change, with these becoming not only direct competitors of ablative surgeries, but also potentially relevant tools to improve symptoms and quality of life before the patient would normally be considered for surgical management.

PAE was studied separately in our definitive analysis for several reasons. First, major inconsistencies among the comparisons involving PAE were observed in our initial analysis. A preplanned assessment of the network model validity has shown a significant difference between indirect comparisons (coming from the NMA) and direct comparisons (coming from the RCTs themselves) for the primary outcomes (namely Qmax and IPSS). A second reason was the heterogeneity of the PAE technique. In addition to bead size variability, other differences among PAE techniques were frequently highlighted in the literature, such as surgeon experience, vascular approach, vascular check during the procedure, and sequence of embolisation (distal vs proximal arteries) [15]. Finally, patient profiles proposed for PAE are not the same as those for

WVTT, PUL, iTIND, or TURP. PAE has widely been proposed in patients unsuitable for surgery, in particular, elderly or frail patients, and sometimes those with an indwelling urinary catheter.

In the set of RCTs analysed in the present work, prostate volume was significantly different at baseline between the trials of PAE and trials of other treatments. Removal of PAE from the main network has improved consistency while leaving enough data on PAE to conduct a separate analysis (Fig. 5). This has shown results similar to the existing literature on PAE, which suggests short-term IPSS improvement comparable with that of TURP but less effect on Qmax. Ejaculatory function following PAE could not be assessed because of insufficient data.

Short-term outcomes were emphasised owing partly to the very limited number of patients for whom long-term follow-up is available. Longer-term outcomes also have a relatively greater risk of bias from noncompliance to follow-up. Treatment responses of MISTs will be realised by the 3–6-mo period considered in the present review and must be adequate for the therapy to have long-term benefit. Therefore, the short-term outcomes are meaningful and allow a comparison of MISTs before sufficient long-term data may become available.

An NMA of available data on IPSS and Qmax for PAE, PUL, and TUMT suggested durability of the respective short-term comparisons through 12 mo. Some insight into the durability of iTIND, PUL, and WVTT is available from 12-mo follow-up of the active arms of the respective sham-controlled trials. In these trials, the proportions of patients re-treated for LUTS/BPO from 3 to 12 mo were 6.3%, 8.8%, and 2.2% for iTIND, PUL, and WVTT, respectively; in the individuals free of retreatment, evolution of the mean IPSS from 3 to 12 mo was 12.6–12.7 for iTIND, 11.0–11.1 for PUL, and 10.6–10.3 for WVTT; the same for Qmax was 13.6–11.9 for iTIND, 12.4–12.1 for

PUL, and 16.1–15.1 for WVTT. These results indicate the stability of the short-term outcomes but are from an uncontrolled study.

The present work differs from existing reviews of MISTs with respect to the treatment modalities, outcomes, or methodology. A recent Cochrane Collaboration review by Franco et al [12] compared similar treatments and selected a similar set of trials. The main differences from the present work relate to the outcomes considered and network model formulation. Franco et al [12] included each of PAE and TURP as a single modality in the network; thus, trials comprising only mTURP and bTURP arms, for example, were not eligible. In regard to outcomes, uroflowmetry measurements were not analysed by Franco et al [12], and ejaculatory dysfunction was assessed through adverse events reported, whereas existing scales were used in the present work. Tallman et al [28] performed an anchored indirect comparison of PUL and WVTT on IPSS, quality of life, and uroflowmetry, and obtained results consistent with those of the present work. Tanneru et al [13] compared Aquablation, PUL, and WVTT with TURP by pooling and comparing arms from different studies as if these arms were from the same trial. Such an approach breaks the randomisation and control provided by the original trials and is prone to a bias [29] from imbalance in participant characteristics and other trial differences.

A limitation of the present work is the small number of trials available for some MISTs. The availability of only a single trial for each of iTIND and WVTT was addressed in the NMA by assuming that the variation in treatment effect across trials would be the same as that of the other treatments in the network, that is, common between-trial variance. This assumption corresponds to the different MISTs being similarly reproducible, which would seem reasonable among therapies with standardised techniques performed in similar patient populations; moreover, this assumption enables the scenario of treatment effects varying for all the modalities to be reflected in the comparisons of the NMA. The NMA was used to make indirect treatment comparisons,

which are valid if the trials are exchangeable. Exchangeability is supported by the fact that the trials of MISTs had similar designs, selection criteria, and participant characteristics with few exceptions (eg, larger prostates in the PAE trials). Empirical tests of exchangeability were performed, and the results of the NMA were interpreted accordingly. Finally, treatment comparisons were reported only for outcomes that were assessed using the same instrument across trials. These considerations increase confidence in the comparisons made.

Most comparisons of MISTs with TURP made in the present review were rated using the GRADE framework to be of low to moderate certainty, primarily reflecting the risk of bias from an open-label study and imprecision owing to a small number of trials for some MISTs. These limitations, in turn, reflect challenges of TURP-controlled trials, including patient consent and blinding. Notably, low certainty was assigned to the comparisons on IPSS for some MISTs. This is partly because the imprecision admits the possibility of inferiority to TURP of 3.2 and 5.1 points or less for PUL and WVTT, respectively. These amounts, however, approximately correspond to patient perception of only slight and moderate improvement, respectively [30], implying that any inferiority would be of limited relevance. Similar comments apply to some comparisons for PAE on the IPSS-QoL.

Our results, of necessity, have mixed all types of patients included in the underlying RCTs and may be not transferrable for every case in clinical practice. In spite of this review providing insight into how MISTs compare, personalised treatment of LUTS/BPO requires a specific evaluation and specific goals of treatment to be agreed for each patient.

4. Conclusions

The present systematic review highlighted the potential role of MISTs for LUTS/BPO. It emphasised the status of WVTT, PUL, and PAE as alternatives to ablative surgery, with probably less short-term efficacy for urinary flow, but similar improvement in IPSS and quality of life. Sexual function is better for PUL and WVTT than for TURP. TUMT is less efficacious than TURP but provides similar improvement in quality of life. The relative efficacy of iTIND is less clear. Evidence was synthesised from a small number of trials for some of the MISTs and would be strengthened by further RCTs. Long-term comparative evidence is sparse, and filling of this gap remains necessary to refine patient counselling.

Author contributions: Jean-Nicolas Cornu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cornu, Zantek, Burt, A. Martin, Springate.

Acquisition of data: A. Martin, Springate.

Analysis and interpretation of data: Cornu, Chughtai.

Drafting of the manuscript: Cornu, Zantek, C. Martin, A. Martin.

Critical revision of the manuscript for important intellectual content: Burt, Chughtai, Springate.

Statistical analysis: Zantek, C. Martin.

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Fig. 1 – Flow-chart of literature search and article selection.

Fig. 2 – Main outcome of the network meta-analysis results. Each row is dedicated to one of the outcomes studied in the main analysis. The graph represents the network characteristics, including the number of available head-to-head comparisons in randomised controlled trials. The forest plot with squares and bars is issued from a random-effect model using a frequentist approach. Certainty of estimated treatment difference was rated using the GRADE framework. Table at right lists the P score of each option based on the frequentist analysis.

bTURP = bipoplar TURP; CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; iTIND = implantable nitinol device; mTURP = monopoplar TURP; PAE = prostatic arterial embolisation; PUL = prostatic urethral lift; TUMT = transurethral microwave thermotherapy; TURP = transurethral resection of the prostate; WVTT = water vapour thermal therapy.

Certainty was downgraded for the ^a risk of bias (trial limitations), ^b contributing direct evidence of low quality, ^c contributing direct evidence of moderate quality, ^d imprecision, and ^e intransitivity.

Fig. 3 – Assessment of consistency of the main NMA analysis. The forest plots (left side) display the direct treatment comparison from the head-to-head trial(s) versus the indirect comparison derived from splitting the network. The net heat plot (right side) contains rectangles representing the contribution of the direct treatment comparison corresponding to the column to the network estimate of the treatment comparison shown in the row. The colours on the diagonal of the net heat plot indicate inconsistency between the direct and indirect estimates of the treatment comparison. Off-diagonal colours indicate the change in inconsistency between the direct and indirect estimates of the treatment comparison shown in the row after the trial(s) corresponding to the column are removed from the network; warm colours indicate a decrease, whereas blue colours indicate an increase. bTURP = bipoplar TURP; CI = confidence interval; IPSS = International Prostate Symptom Score; IPSS-QoL = International Prostate Symptom Score-associated quality of life measure; MD = mean difference; mTURP = monopoplar TURP; NMA = network meta-analysis; PAE = prostatic

arterial embolisation; PUL = prostatic urethral lift; PVR = postvoid residual urine volume; Qmax = maximum urinary flow rate; TUMT = transurethral microwave thermotherapy; TURP = transurethral resection of the prostate.

Fig. 4 – Additional network meta-analysis results excluding PAE studies. Organisation of the display is identical to that in Figure 2.

CI = confidence interval; iTIND = implantable nitinol device; mTURP = monopolar TURP; PAE = prostatic arterial embolisation; PUL = prostatic urethral lift; TUMT = transurethral microwave thermotherapy; TURP = transurethral resection of the prostate; WVT = water vapour thermal therapy.

Certainty was downgraded for the ^c risk of bias (trial limitations), ^a contributing direct evidence of low quality, ^b imprecision, ^c risk of bias (trial limitations), and ^d contributing direct evidence of moderate quality.

Fig. 5 – Additional network meta-analysis of studies including PAE and TURP only. Organisation of the display is identical to that in Figure 2.

bTURP = bipolar TURP; CI = confidence interval; mTURP = monopolar TURP; PAE = prostatic arterial embolisation; TURP = transurethral resection of the prostate.

Certainty was downgraded for the ^a risk of bias (trial limitations), ^b contributing direct evidence of moderate quality, ^c imprecision, and ^d intransitivity.

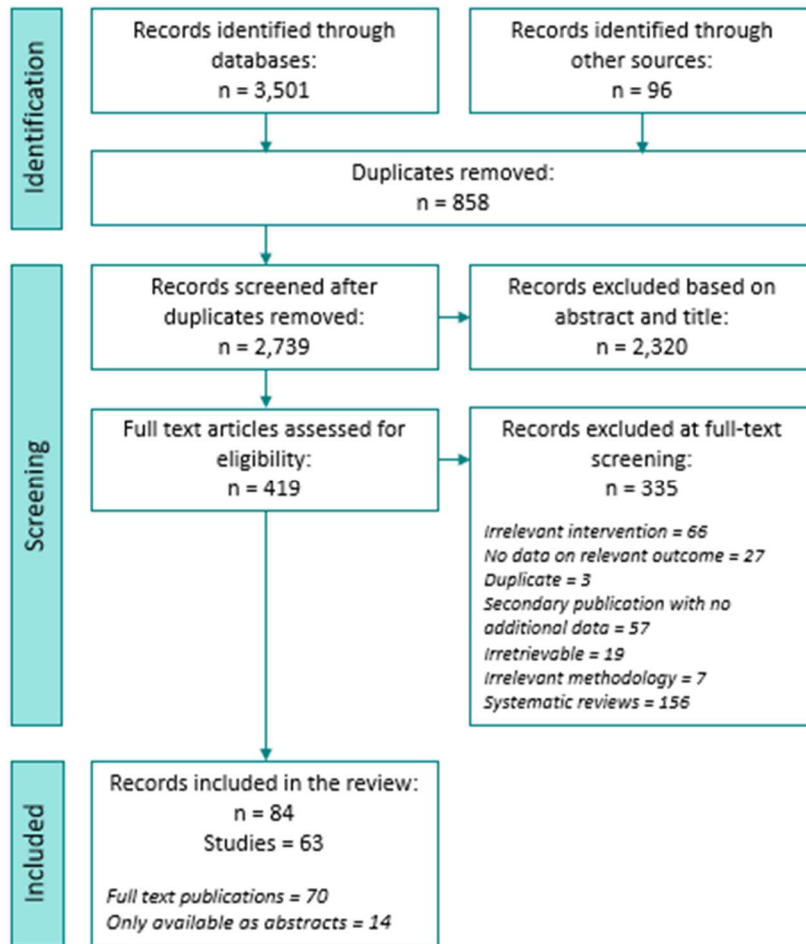
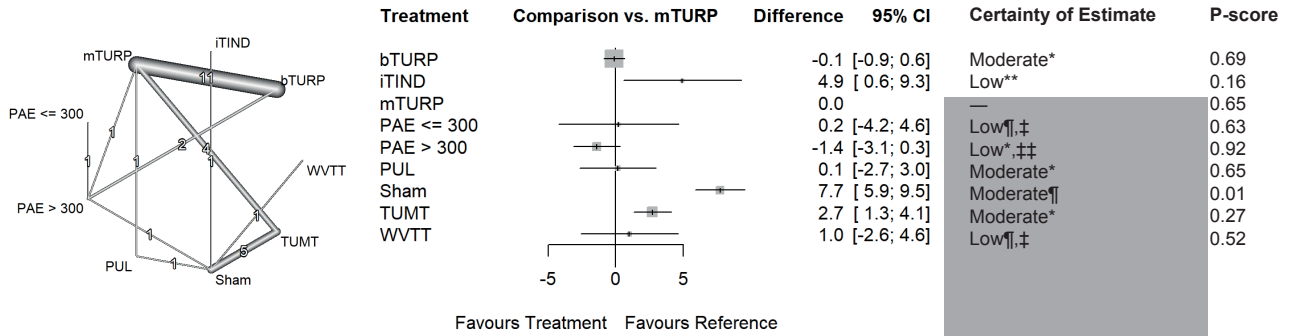
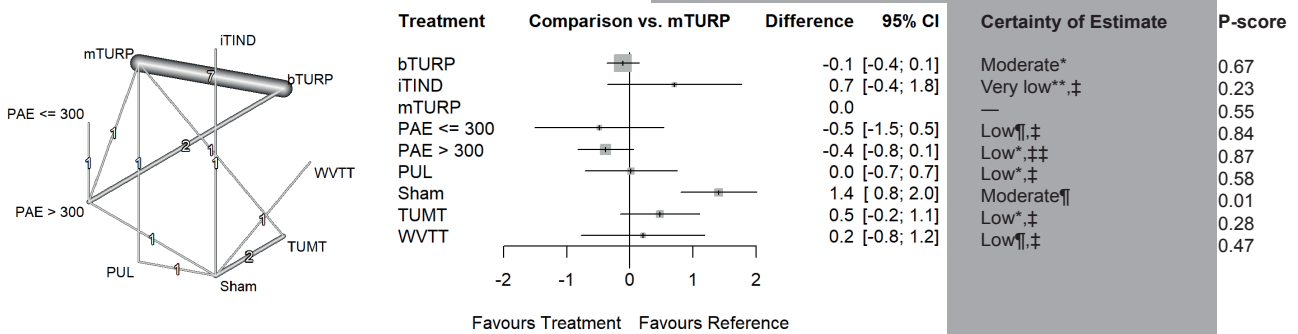


Figure 1. Flow of literature through the review

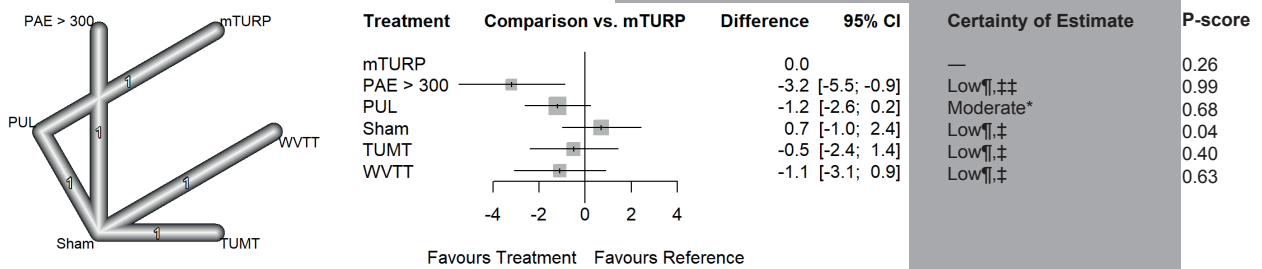
International Prostate Symptom Score (IPSS)



International Prostate Symptom Score Quality of Life (IPSS-QoL)



Benign Prostatic Hyperplasia Impact Index (BPHII)



Maximum Urinary Flow Rate (Qmax)

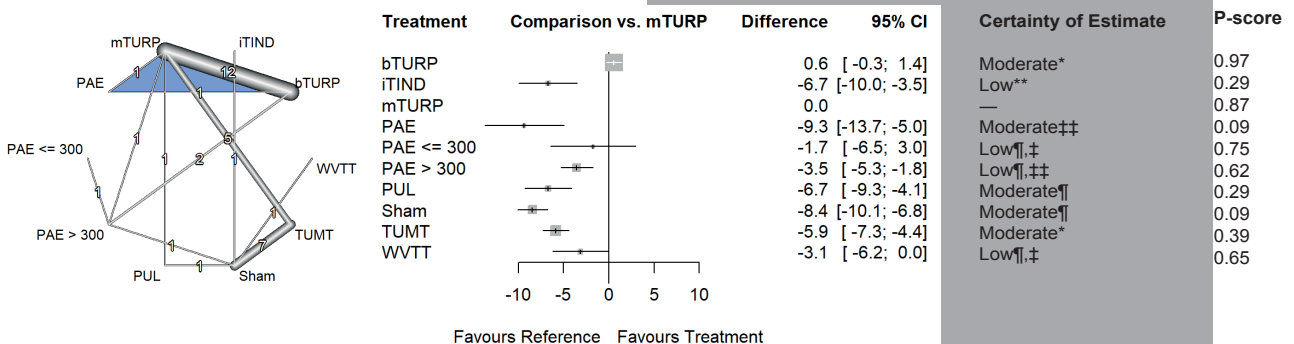
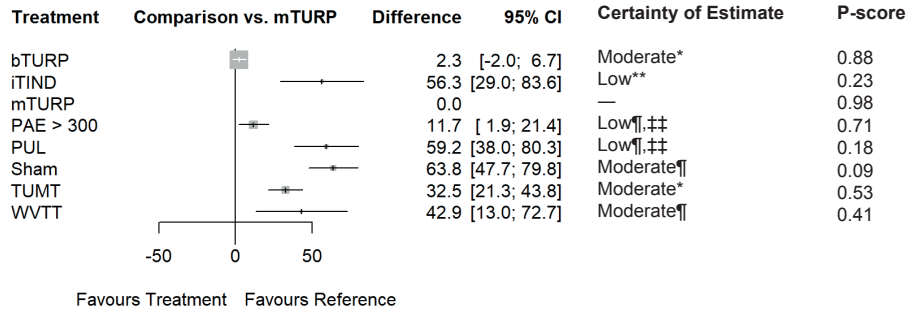
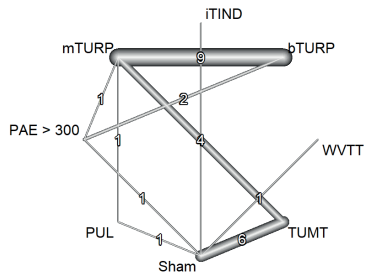
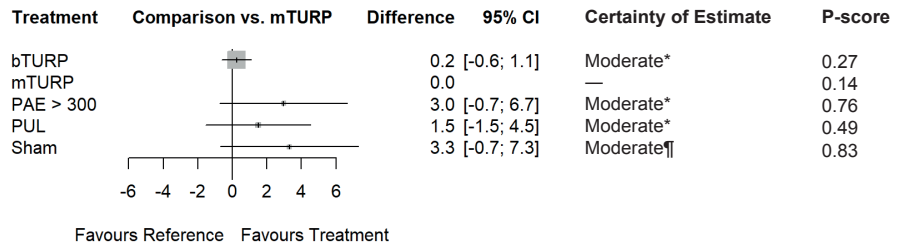
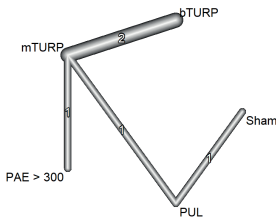


Figure 4.1

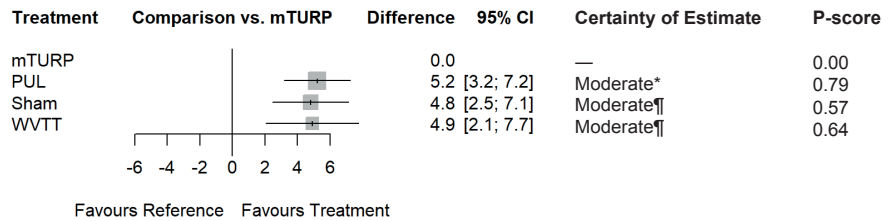
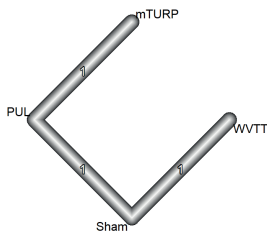
Post Void Residual Volume (PVR)



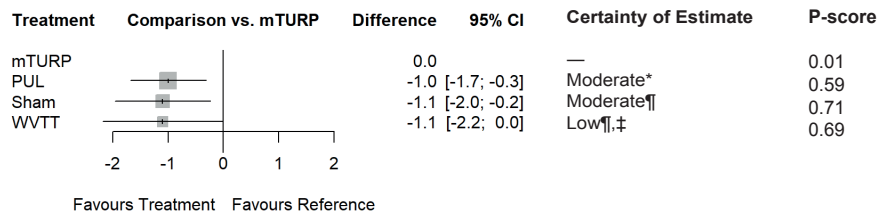
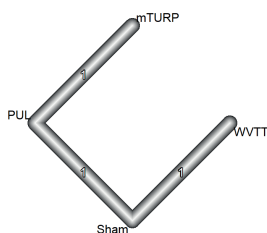
International Index of Erectile Function 5 (IIEF-5)



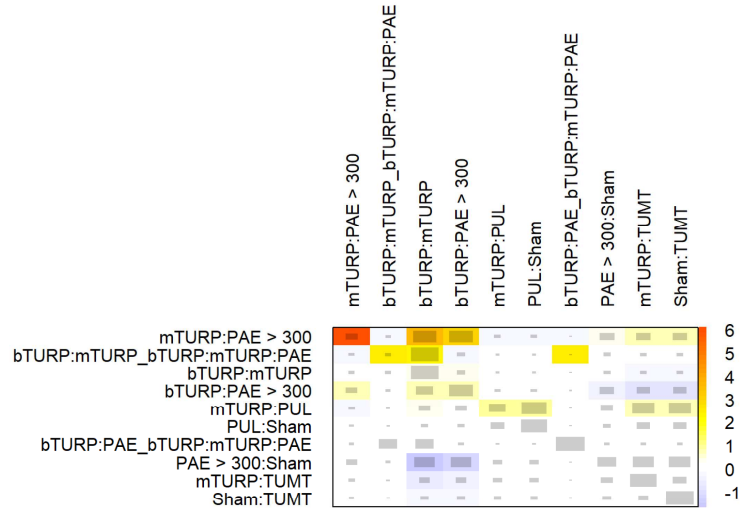
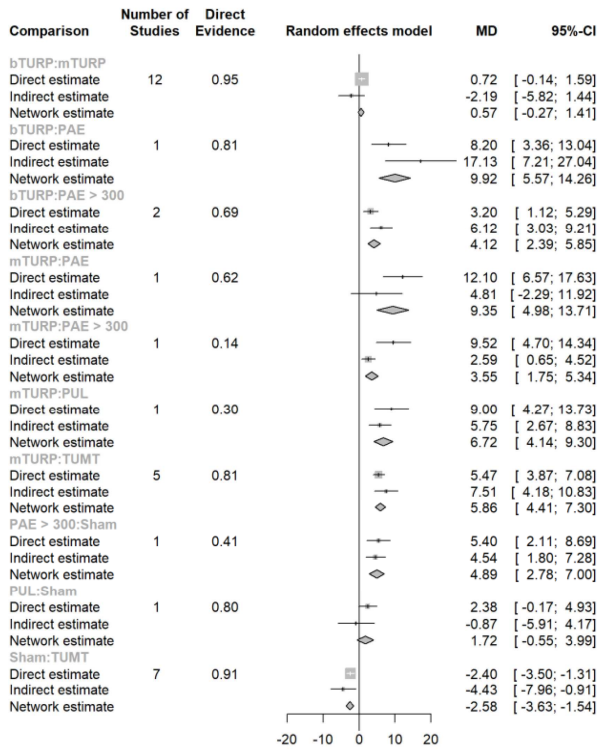
Mens' Sexual Health Questionnaire Function Domain (MSHQ-SF)



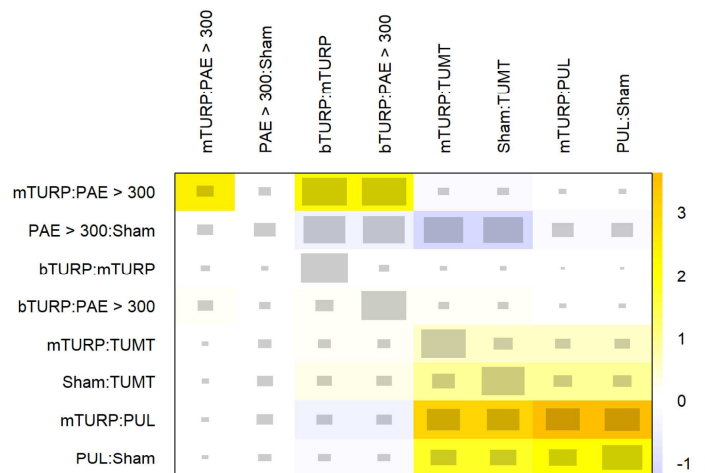
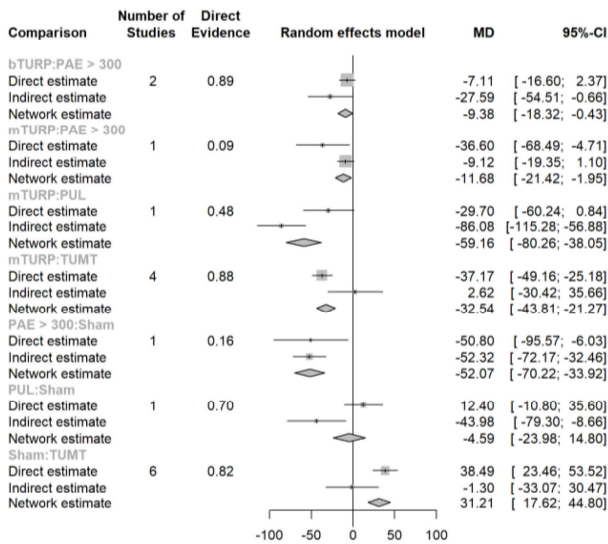
Mens' Sexual Health Questionnaire Bother Domain (MSHQ-SF)



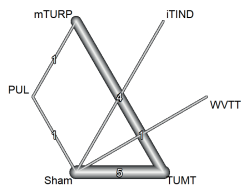
Qmax



PVR



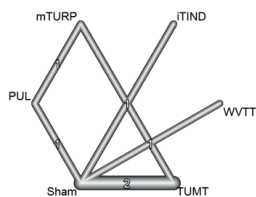
International Prostate Symptom Score (IPSS)



Treatment	Comparison vs. mTURP	Difference	95% CI
iTIND		4.0	[-1.5; 9.6]
mTURP		0.0	
PUL		-0.4	[-4.0; 3.2]
Sham		6.8	[4.2; 9.5]
TUMT		2.3	[0.3; 4.3]
WVTT		0.1	[-4.8; 5.1]

Treatment	Certainty of Estimate	P-score
iTIND	Very low**, ‡	0.28
mTURP	—	0.77
PUL	Low*, ‡	0.80
Sham	Moderate¶	0.03
TUMT	Moderate*	0.40
WVTT	Low¶, ‡	0.72

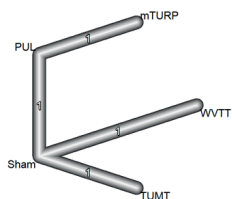
International Prostate Symptom Score Quality of Life (IPSS-QoL)



Treatment	Comparison vs. mTURP	Difference	95% CI
iTIND		0.5	[-0.3; 1.3]
mTURP		0.0	
PUL		-0.1	[-0.7; 0.5]
Sham		1.2	[0.6; 1.7]
TUMT		0.3	[-0.2; 0.8]
WVTT		-0.0	[-0.7; 0.7]

Treatment	Certainty of Estimate	P-score
iTIND	Very low**, ‡	0.32
mTURP	—	0.72
PUL	Low*, ‡	0.82
Sham	Moderate¶	0.00
TUMT	Moderate*	0.40
WVTT	Low¶, ‡	0.75

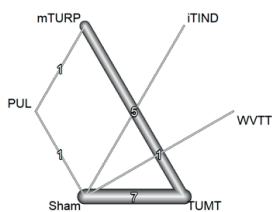
Benign Prostatic Hyperplasia Impact Index (BPHII)



Treatment	Comparison vs. mTURP	Difference	95% CI
mTURP		0.0	
PUL		-1.2	[-2.6; 0.2]
Sham		0.7	[-1.0; 2.4]
TUMT		-0.5	[-2.4; 1.4]
WVTT		-1.1	[-3.1; 0.9]

Treatment	Certainty of Estimate	P-score
mTURP	—	0.32
PUL	Moderate*	0.84
Sham	Low¶, ‡	0.05
TUMT	Low¶, ‡	0.51
WVTT	Low¶, ‡	0.78

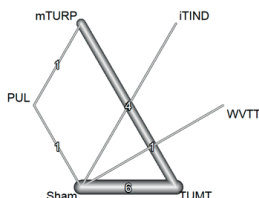
Maximum Urinary Flow Rate (Qmax)



Treatment	Comparison vs. mTURP	Difference	95% CI
iTIND		-6.7	[-10.3; -3.0]
mTURP		0.0	
PUL		-6.7	[-9.6; -3.9]
Sham		-8.4	[-10.3; -6.4]
TUMT		-5.8	[-7.4; -4.1]
WVTT		-3.1	[-6.6; 0.5]

Treatment	Certainty of Estimate	P-score
iTIND	Low**	0.35
mTURP	—	0.99
PUL	Moderate¶	0.33
Sham	Moderate¶	0.05
TUMT	Moderate*	0.50
WVTT	Low¶, ‡	0.78

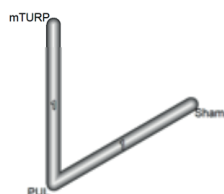
Post Void Residual Volume (PVR)



Treatment	Comparison vs. mTURP	Difference	95% CI
iTIND		63.5	[-7.2; 134.2]
mTURP		0.0	
PUL		57.9	[9.9; 105.9]
Sham		71.0	[33.6; 108.3]
TUMT		33.3	[4.3; 62.2]
WVTT		50.1	[-21.7; 121.8]

Treatment	Certainty of Estimate	P-score
iTIND	Very low**, ‡	0.33
mTURP	—	0.97
PUL	Moderate*	0.37
Sham	Moderate¶	0.19
TUMT	Moderate*	0.67
WVTT	Low¶, ‡	0.47

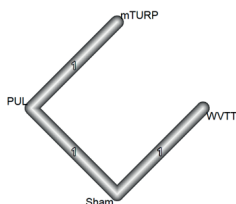
International Index of Erectile Function 5 (IIEF-5)



Treatment	Comparison vs. mTURP	Difference	95% CI
mTURP		0.0	
PUL		1.5	[-1.5; 4.5]
Sham		3.3	[-0.7; 7.3]

Treatment	Certainty of Estimate	P-score
mTURP	—	0.11
PUL	Moderate*	0.46
Sham	Moderate¶	0.93

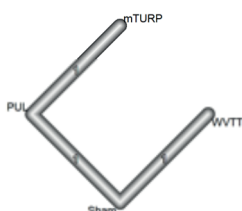
Mens' Sexual Health Questionnaire Function Domain (MSHQ-SF)



Treatment	Comparison vs. mTURP	Difference	95% CI
mTURP		0.0	
PUL		5.2	[3.2; 7.2]
Sham		4.8	[2.5; 7.1]
WVTT		4.9	[2.1; 7.7]

Treatment	Certainty of Estimate	P-score
mTURP	—	0.00
PUL	Moderate*	0.79
Sham	Moderate¶	0.57
WVTT	Moderate¶	0.64

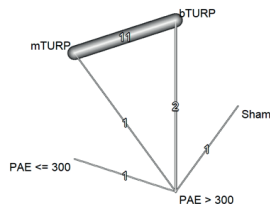
Mens' Sexual Health Questionnaire Bother Domain (MSHQ-SB)



Treatment	Comparison vs. mTURP	Difference	95% CI
mTURP		0.0	
PUL		-1.0	[-1.7; -0.3]
Sham		-1.1	[-2.0; -0.2]
WVTT		-1.1	[-2.2; 0.0]

Treatment	Certainty of Estimate	P-score
mTURP	—	0.01
PUL	Moderate*	0.59
Sham	Moderate¶	0.71
WVTT	Low¶, ‡	0.69

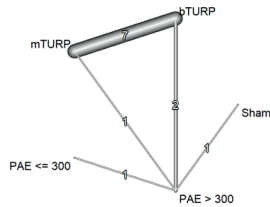
International Prostate Symptom Score (IPSS)



Treatment	Comparison vs. mTURP	Difference	95% CI
bTURP		-0.0	[-0.8; 0.7]
mTURP		0.0	
PAE <= 300		1.0	[-3.4; 5.4]
PAE > 300		-0.6	[-2.4; 1.2]
Sham		12.1	[8.0; 16.2]

Treatment	Certainty of Estimate	P-score
bTURP	Moderate*	0.62
mTURP	—	0.60
PAE ≤ 300	Low [†] , _‡	0.47
PAE > 300	Low [†] , _‡	0.82
Sham	Moderate [¶]	0.00

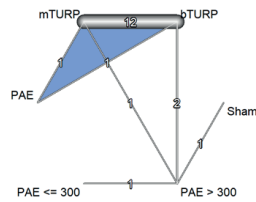
International Prostate Symptom Score Quality of Life (IPSS-QoL)



Treatment	Comparison vs. mTURP	Difference	95% CI
bTURP		-0.1	[-0.4; 0.2]
mTURP		0.0	
PAE <= 300		-0.4	[-1.5; 0.7]
PAE > 300		-0.3	[-0.8; 0.2]
Sham		1.8	[0.8; 2.7]

Treatment	Certainty of Estimate	P-score
bTURP	Moderate*	0.56
mTURP	—	0.41
PAE ≤ 300	Low [†] , _‡	0.76
PAE > 300	Moderate*	0.77
Sham	Moderate [¶]	0.00

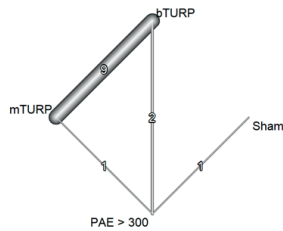
Maximum Urinary Flow Rate (Qmax)



Treatment	Comparison vs. mTURP	Difference	95% CI
bTURP		0.5	[-0.3; 1.4]
mTURP		0.0	
PAE		-9.4	[-13.7; -5.0]
PAE <= 300		-1.9	[-6.7; 2.9]
PAE > 300		-3.7	[-5.7; -1.7]
Sham		-9.1	[-13.0; -5.3]

Treatment	Certainty of Estimate	P-score
bTURP	Moderate*	0.95
mTURP	—	0.78
PAE	Moderate [¶]	0.10
PAE ≤ 300	Low [†] , _‡	0.63
PAE > 300	Low [†] , _‡	0.44
Sham	Moderate [¶]	0.11

Post Void Residual Volume (PVR)



Treatment	Comparison vs. mTURP	Difference	95% CI
bTURP		1.5	[-1.9; 4.9]
mTURP		0.0	
PAE <= 300		9.0	[0.8; 17.3]
Sham		59.8	[14.9; 104.8]

Treatment	Certainty of Estimate	P-score
bTURP	Moderate*	0.72
mTURP	—	0.93
PAE > 300	Low [†] , _‡	0.34
Sham	Moderate [¶]	0.01

Table 1 – Indications for minimally invasive surgical therapies

Treatment	Prostate volume	Details
iTIND	–	Medi-Tate temporary implantable nitinol device system (iTIND) is designed for the treatment of male patients suffering from symptoms from the lower urinary tract as a result of BPH.
PAE (per Naidu et al.)	–	It is used for the treatment of symptomatic benign prostatic hypertrophy in men.
PUL	≤100 ml	The UroLift system is indicated for the treatment of symptoms due to urinary outflow obstruction secondary to BPH in men 50 yr of age or older.
TUMT	20–80 ml	The ProLieve Thermodilatation system is a transurethral microwave therapy device for the treatment of symptomatic BPH in men with a prostate size of 20–80 g and prostatic urethra length between 1.2 and 5.5 cm, and in whom drug therapy (finasteride or Proscar) is typically indicated.
WVTT	≥30 ml	The Rezūm system is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH. It is indicated for men with a prostate volume of ≥30 cm ³ . The Rezūm system is also indicated for the treatment of prostate with hyperplasia of the central zone and/or a median lobe.

BPH = benign prostatic hyperplasia; iTIND = implantable nitinol device; PAE = prostatic arterial embolisation; PUL = prostatic urethral lift; TUMT = transurethral microwave thermotherapy; WVTT = water vapour thermal therapy.

Table 2 – Baseline characteristics of participants by treatment^a

Treatment	Number of trials	Number of participants	Age (yr), mean/range	Prostate volume (ml), range of means	IPSS (range of means)	Qmax (ml/s), range of means	PVR (ml), range of means
WVTT	1	136	63	45.8	22	9.9	82
mTURP	45	>2938	61–73.1	27.9–82.4 (42.5–50.3 g)	16.7–30.0	4.19–10.9	47.4–230.7
bTURP	38	>2701	59–73.8	24.1–82.6 (39.5–57.9 g)	17.6–30.4	4.37–10.9	43.7–172.5
PAE (any bead size) ^b	9	>408	63.1	59.3	25.2–26.8	8.6–9.5	NA
PAE 100–300 µm	3	99	67.5	63.8–87.9	22.6–23	0.14–5.2 ^c	120.7
PAE 250–400 µm	1	51	65.7	51.2	19.38	7.47	168.5
PAE 300–500 µm	6	187	63.5–72.4	60–89	17.2–25.8	0.13–7.7 ^c	34.5–127
PAE 355–500 µm	1	57	67.7	64.7	22.8	7.8	126.9
TUMT	17	1046	63.7–70.0	33–51.1	18.3–21	7.3–12.3	56.4–147
PUL	2	186	63–67	38–44.5	22–22.3	7.9–9.2	85.9–86
iTIND	1	128	61.5	43.4	22.1	8.7	61.6
Sham	14	605	60.1–67.1	35.4–51	21.9–24.6	7.4–10.8	52.6–145.2

bTURP = bipolar TURP; IPSS = International Prostate Symptom Score; iTIND = implantable nitinol device; mTURP = monopolar TURP; NA = not available; PAE = prostatic arterial embolisation; PUL = prostatic urethral lift; PVR = postvoid residual urine volume; Qmax = maximum urinary flow rate; TUMT = transurethral microwave thermotherapy; TURP = transurethral resection of the prostate; WVTT = water vapour thermal therapy.

^a The table reports range of mean values across all trials for participants within each treatment arm; number of participants was not reported for some trials of bTURP, mTURP, and PAE.

^b Includes two trials that compared different PAE bead sizes and two trials where bead size was not reported.

^c Data converted from ml/min to ml/s.