



Novel minimally invasive treatments for lower urinary tract symptoms: a systematic review and network meta-analysis

Robertus Arnoldus Antonius van Kollenburg ¹, Luigi Antonio Maria Johannes Gerardus van Riel ¹, Daniel Martijn de Bruin ¹, Theodorus Maria de Reijke ¹, Jorg Reinier Ouddens ¹

¹ Department of Urology, Amsterdam UMC, University of Amsterdam, Biomedical Engineering and Physics, Netherlands

ABSTRACT

Purpose: To review and compare the effectivity of novel minimally invasive treatments (MITs) to transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms (LUTS) in men.

Methods: Medline, Embase, and Cochrane databases were searched from January 2010 to December 2022 for randomized controlled trials (RCTs) evaluating MITs, compared to TURP or sham, in men with LUTS. Studies were assessed by risk of bias tool, and evidence by GRADE. Functional outcomes by means of uroflowmetry and IPSS were the primary outcomes, safety and sexual function were secondary outcomes. As part of this review, a network meta-analysis (NMA) was conducted. MITs were ranked based on functional outcome improvement probability.

Results: In total, 10 RCTs were included, evaluating aquablation, prostatic urethral lift, prostatic artery embolization (PAE), convective water vapor thermal treatment or temporary implantable nitinol device. All MITs showed a better safety profile compared to TURP. Functional outcome improvement following aquablation were comparable to TURP. In the NMA, aquablation was ranked highest, PAE followed with the second highest probability to improve functional outcomes. Other novel MITs resulted in worse functional outcomes compared to TURP. Level of evidence was low to very low.

Conclusions: Five MITs for treatment of LUTS were identified. Aquablation is likely to result in functional outcomes most comparable to TURP. Second in ranking was PAE, a technique that does not require general or spinal anesthesia. MITs have a better safety profile compared to TURP. However, due to high study heterogeneity, results should be interpreted with caution.

ARTICLE INFO

 **J.R. Ouddens**

<https://orcid.org/0000-0002-6079-5613>

Keywords:

Systematic Review [Publication Type], Minimally Invasive Surgical Procedures, Prostate

Int Braz J Urol. 2023; 49: 411-27

Submitted for publication:
January 12, 2023

Accepted after revision:
April 19, 2023

Published as Ahead of Print:
May 20, 2023

INTRODUCTION

Bladder outlet obstruction is associated with lower urinary tract symptoms (LUTS) in men. If medical treatment fails to provide relief, a surgical procedure may be considered (1). Transurethral resection of the prostate (TURP) has proven its success in LUTS improvement and is considered the standard of care (1). However, it requires general or spinal anesthesia and hospital admission. Furthermore, it comes with side effects, such as retrograde ejaculation, and the risk of complications such as hematuria, clot retention, and urethral stricture (1).

Less invasive treatments such as transurethral microwave treatment, transurethral needle ablation, and interstitial laser coagulation treatments showed that minimally invasive procedures provided an improved safety profile, but functional outcomes were inferior to TURP (1-3). Therefore, they are not recommended in the 2021 EAU guidelines (1).

Recently, several novel minimal invasive treatments (MITs) have been developed using new approaches or energy sources for the treatment of LUTS. These MITs include the use of steam, waterjet, anchors, prostatic vascular embolization and temporarily implanted devices (4-8). Several studies have been performed to study the safety and functional outcomes of MITs, including randomized controlled trials (RCTs) (9-12). In these studies, MITs have been compared to either TURP or sham. However, there is a lack of direct or indirect comparisons between different MITs, challenging the determination of a preferred treatment.

This review aims to provide an overview of trials comparing MITs with TURP or sham. Using a network meta-analysis (NMA) approach, the comparative effectivity of these techniques and standard of care were analyzed.

METHODS AND METHODS

This systematic review is performed in accordance with the PRISMA guidelines (13). The review was registered at Prospero (CRD42020208039).

Eligibility criteria

A search was performed to identify randomized controlled trials that studies novel minimally invasive treatments as intervention and TURP or sham as control for men with lower urinary tract symptoms. The search was limited from January 2010 to the present to identify recent MITs. Earlier developed techniques are no longer recommended in the guidelines. Non-English articles were considered. The search was limited using the exclusion of female in the title or abstract, to improve the quality of the search.

Information sources

A systematic search was performed on MEDLINE (PubMed), Embase (Ovid), and Cochrane (Cochrane). Included records were screened for secondary interesting studies.

Search strategy

A systematic search was performed on December 7th 2022 using the following search: Randomized controlled trial OR randomi* OR trial (all title, abstract, keyword) AND Lower urinary tract symptom* OR benign prostat* (all title, abstract, keyword) AND Minimally invasive surgery OR minimally invasive procedure OR novel treatment OR Aquablation OR rezum OR urolift OR prostatic urethral lift OR emboli* OR surgical intervention OR laser OR new treatment (all terms) NOT female OR woman OR women (all title or abstract), limited to the period January 2010 to December 7th 2022.

Data management and selection

Records were managed in Endnote (version 20). Duplicates were removed by R.K. using EndNote's duplicate identification and removal tool. All identified records were independently reviewed by two reviewers (R.K. and L.R.). Any disagreements were settled by consensus and a third independent reader was consulted when necessary (J.O.).

Data extraction

Data extraction was performed independently by two reviewers (R.K. and L.R.) according to the prior established protocol. In case of missing

data, corresponding authors were contacted. Plot digitizer (version 2.6.9) was used to extract data from figures when outcomes were not explicitly mentioned in the full text of included articles (14).

Risk of Bias and quality of evidence assessment

The risk of bias was evaluated using the Cochrane Risk of Bias 2 tool (15). Two reviewers (R.K. and L.R.) performed the risk of bias assessment independently. Disagreement was solved by consensus and a third independent reader was consulted when necessary (J.O.). The quality of evidence was evaluated using GRADE.

Statistical Analysis

The baseline characteristics (e.g., age, prostate volume, Qmax, IPSS) and data of the included studies were descriptively summarized. The continuous outcomes (e.g., Qmax, IPSS) were summarized by the quantitative information provided by the included studies, including means plus standard deviations (SD). Dichotomous variables were examined in the descriptive analysis with proportions and event rates.

Network meta-analysis (NMA)

For each outcome, an NMA with a Bayesian approach was conducted using a random-effects model. In the absence of direct evidence for given comparisons, the indirect comparisons provided the estimates. In presence of both direct and indirect evidence, the NMA model provided a mixed-effect estimate (16). Since the NMA resulted in a star-shaped network, all the evidence of comparisons between the interventions was indirect, except for active treatments compared to the common comparator (i.e., TURP). Therefore, network consistency could not be assessed. We estimated the relative ranking of the different treatments using the distribution of the ranking probabilities and the surface under the cumulative ranking (SUCRA) curve (17). The larger the SUCRA for a specific treatment, the higher its ranking among the available treatment options. Direct and indirect meta-analysis was conducted in STATA, release 12 (StataCorp, College Station, Texas) using the network meta-analysis command (18).

RESULTS

Systematic search

The literature search identified 2150 unique records. Based on title and abstract 2018 records were excluded. The remaining 132 records underwent full-text assessment for eligibility. Finally, 13 articles covering ten studies were included (9-11, 19-28) (Figure-1). Five MITs were identified: Aquablation, prostatic urethral lift (PUL), convective water vapor thermal therapy (CWVTT), prostatic artery embolization (PAE), and temporary implantable nitinol device (TIND). Six studies compared MIT with TURP, and four studies compared MIT with sham (Table-1, Figure-2). For the primary outcomes at three months, all identified studies were included for analysis. At twelve months, only six trials were included, since sham group cross-over was at three months (9, 20, 27, 28).

Working mechanisms of the identified minimally invasive techniques.

Aquablation uses a high-velocity water jet to ablate prostate tissue. The technique has a trans-urethral approach and is automated using ultrasound image-guidance (4). Hemostasis following ablation is accomplished by bipolar coagulation.

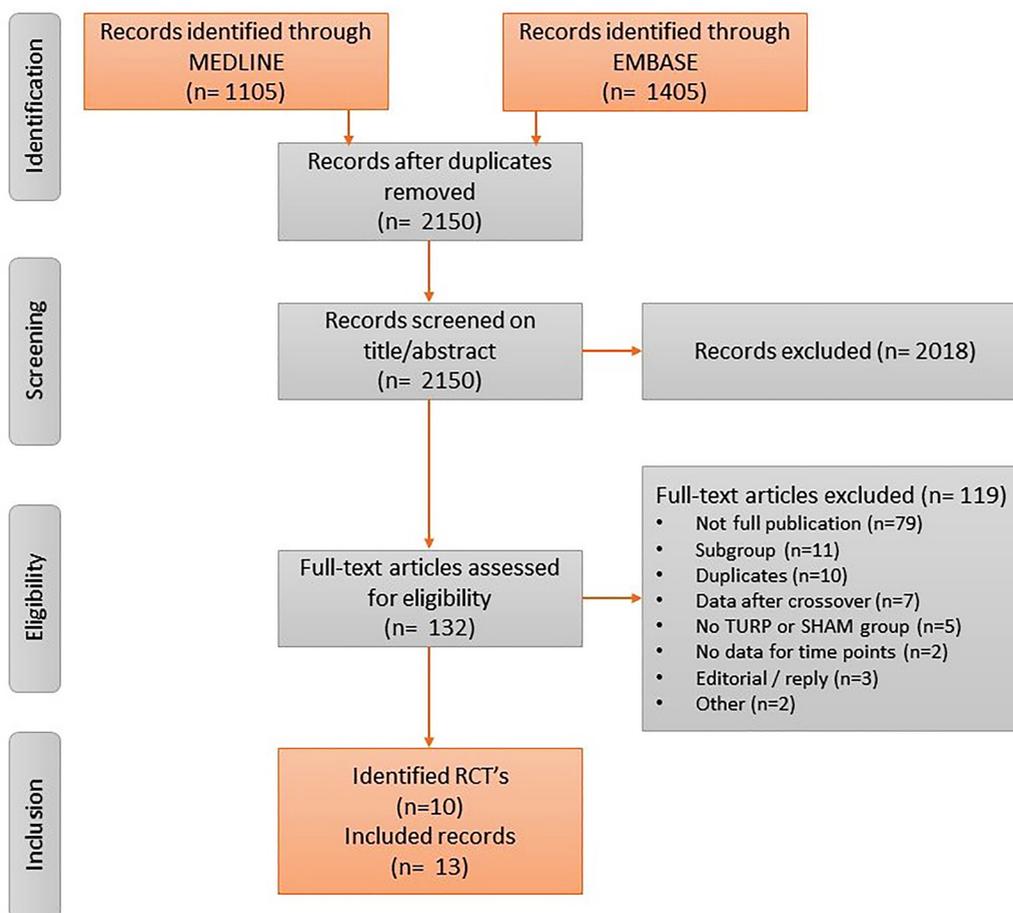
PUL uses anchor shaped implants that are introduced through the lobe until the capsule. Under compression of the lobe an end-piece is placed on the monofilament, reducing the obstruction without tissue removal (6).

CWVTT is based on water vapor injection in the prostatic lobes. Water vapor is introduced in the lobe during multiple nine second treatments, using a specific cystoscope with puncture needle. Due to the convective properties of water vapor, the treatment is naturally limited to the prostate capsule (5).

PAE is based on artery embolization. A sheath is placed in the common femoral artery. The prostate artery supply is identified using angiography. When identified microspheres are introduced, various sizes are used in the included studies. The procedure is repeated on the contralateral side (7).

TIND is a device that is inserted into the urethra and expanded. By exerting pressure on the prostatic tissue, ischemic necrosis is induced, incising the

Figure 1 - Screening overview, based on the PRISMA method.



prostate, and reshaping it. The device is generally removed after over the period of five to seven days (8).

Characteristics of the identified studies

-1 lists the included studies and their main characteristics. A total of 117, 185, 136, 183, 128, and 247 patients were included for treatment with Aquablation, PUL, CWVTI, PAE, TIND, or TURP, respectively. There were no substantial differences in baseline characteristics of included patients (Table-1). The only notable difference was seen in study by Abt et al. as IPSS and QoL were slightly better compared to other studies (25). However, Qmax and PVR of the same patients were worse than most other studies, which is contradictory. Inclusion and exclusion criteria did not substantially differ between studies, ex-

cept for a median lobe as exclusion criteria for PUL (see supplementary Table-1).

Risk of Bias

The risk of bias for the included studies was evaluated separately for objective outcomes (Qmax and post-void residual), subjective outcomes (IPSS and QoL) and adverse events (see supplementary Table-2). Among the included studies, two studies scored "low risk" on all domains and outcomes (9,10). While two studies scored "high risk" on the objective and subjective outcomes (26, 27). In the study by Insausti et al. prostates up to 120cc were included. However, data of patients with a prostate of >100cc were excluded during analyses,

Table 1 - Details and baseline patient characteristics of included studies.

Studies	Inclusion period	Region (n of centers)	Intervention (n)	Control (n)	Age (years±SD)	Prostate volume (mL±SD)	Qmax (mL/s±SD)	PVR (mL±SD)	IPSS (±SD)	QoL (±SD)	IIEF-5 (±SD)
Aquablation, Gilling et al. (4)	2015-2016	International (17)	Aquablation (117)	TURP (67)	66.0±7.3	51.4±16.2	9.4±3.0	97±79	22.9±6.0	4.8±1.1	17.2±6.5
PUL, Roehrborn et al. (2)	2011	International (19)	PUL (140)	Sham (66)	67±8.6	44.5±12.4	8.9±2.2	85.5±69.2	22.2±5.4	4.6±1.1	13.0±8.4
PUL, Sønksen et al. (11)	2012-2013	International (10)	PUL (45)	TURP (35)	63±6.8	38±12	9.2±3.5	86±72	22±5.7	4.7±1.1	20±4.9
CWVTT, McVary et al. (23)	2013-2014	USA (15)	CWVTT (136)	Sham (61)	63.0±7.1	45.8±13.0	9.9±2.3	82.0±51.5	22.0±4.8	4.4±1.1	NR
PAE, Insausti et al. (26)	2014-2017	Spain (1)	PAE (23)	TURP (22)	72.4±6.2	60.0±4.5	7.7±0.54	82.2±41.9	26.6±0.3	4.5±0.2	15.7±7.2
PAE, Abt et al. (25)	2014-2017	Switzerland (1)	PAE (48)	TURP (51)	65.7±9.3	51.2±16.5	7.5±4.1	168.5±183	19.4±6.4	4.0±1.0	15.15
PAE, Gao et al. (21)	2007-2012	China (1)	PAE (57)	TURP (57)	67.7±8.7	64.7±19.7	7.8±2.5	126.9±68.8	22.8±5.9	4.8±0.8	NR
PAE, Pisco et al. (28)	2014-2018	Portugal (1)	PAE (40)	Sham (40)	63.9±5.83	83.1±47.7	7.5	139.2±105.4	25.9±3.9	4.4±0.5	NR
PAE, Carnevale et al. (24)	2010-2012	Brazil (1)	PAE (15)	TURP (15)	63.5±8.7	63.0±17.8	7.0±3.6	127±99.9	25.3±3.6	4.7±0.6	14.3±6.8
TIND, Chughtai et al. (27)	2015-2018	US (14) and Canada (2)	TIND (128)	Sham (57)	61.5±6.5	43.4±15.5	8.7±3.3	61.6±55.5	22.1±6.8	4.6±1.3	NR

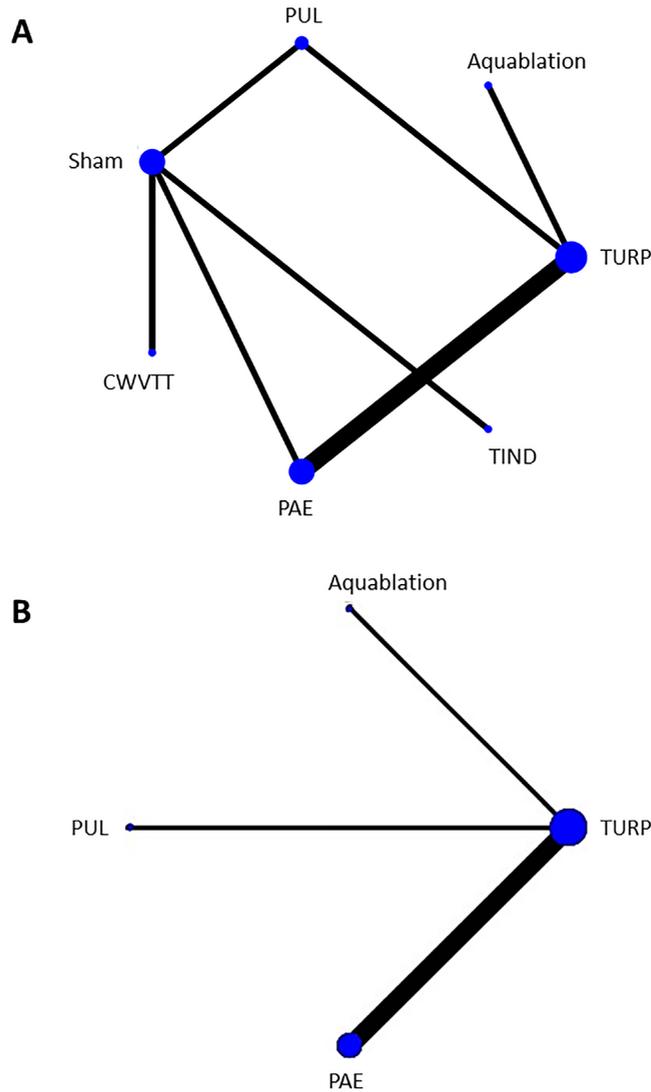
CWVTT = Convective Water Vapor Thermal Therapy; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; NR = Not Reported; PAE = Prostatic Artery Embolization; PVR = Post-Void Residual; PUL = Prostatic Urethral Lift; Qmax = Peak Urinary Flow; QoL = Quality of Life; SD = standard deviation

as TURP is only indicated for prostates ≤ 100 cc according to guidelines. This exclusion might have introduced reporting bias, as outcomes in the intervention group might have been worse. In the study by Chughtai et al. a 29-30% loss of follow-up was seen in both arms during the first three months, which might have impacted outcomes, as the reason behind the lost to follow-up is unknown. Therefore, the study may have resulted in less reliable outcomes. The remaining studies had some concerns in one or multiple domains and/or outcomes.

Peri-operative outcomes

Aquablation is performed under general or spinal anesthesia (Table-2) (4). PUL, CWVTT, PAE and TIND are performed under local anesthesia of the prostate or puncture site (11, 20, 21, 24-29). Procedure times were 32.8 ± 16.5 minutes for Aquablation, 55 ± 17 to 66.2 ± 23.8 for PUL, and 75 (60-90) to 144 ± 50.1 minutes for PAE. Procedural time for TIND was not reported. All Aquablation procedures required hospital admission, with an average stay of 1.4 days, while about half of the PAE procedures required hospital admission for 2.2 days. PUL, CWVTT, TIND,

Figure 2 - Network diagrams showing the network at A) three and B) 12 months. The dots indicate each included treatment. The lines that connect the dots indicate the direct comparisons between treatment groups. Thickness of the lines represents the available number of trials.



and about half of the PAE treatments were performed in an outpatient setting or day-care admission.

Functional outcomes

Q_{max}

An indirect comparison of MITs with TURP showed that Aquablation provided the greatest Q_{max} improvement compared to the other MITs, with Q_{max} improvement following Aquablation being compara-

ble to TURP at both 3- and 12-months follow-up, with a mean difference (MD) of 0.80; (95%CI: -4.25,5.88) and an MD of -0.40 (95% CI: -13.85, 13.05) (Figures 3A and B). At 3 months, PAE, CWVTT, and PUL resulted in significantly worse Q_{max} when compared to TURP. TIND and PUL had the lowest Q_{max} change compared to TURP at 3 and 12 months, respectively (MD -9.94; 95%CI: -15.54, -4.33 and MD -9.60; 95%CI: -23.40, 4.20).

Table 2 - Peri-operative characteristics.

Studies	Anesthesia	Setting	Procedural time (min), mean±SD	Hospital stays (days), mean±SD	Spontaneous voiding or bladder catheter (days), mean±SD	Median lobe treatment possible
Aquablation, Gilling et al. (4)	General (94%) and spinal (6%)	Operating room	32.8±16.5	1.4±0.7	Bladder catheter, median of 1 day	Yes
PUL, Roehrborn et al. (2)	168/169 local using diazepam and Lidocaine gel in 164 and prostatic block in 4, general anesthesia in 37#	Outpatient	66.2±23.8	NR	68% spontaneous void, 32% bladder catheter with a mean duration 0.9 days	No
PUL, Sønksen et al. (11)	General (86%), spinal (13%), topical (1%)	Operating room	55±17	1.0±0.9	45% bladder catheter > 24h	No
CWVTT, McVary et al. (23)	Oral sedation (68.9%), prostate block (20.9%), conscious intravenous (10.2%)	Outpatient	NR	NR	90.4% bladder catheter 3.4±3.2 days	Yes
PAE, Insausti et al. (26)	Local (skin)	NR	138.7±51.9	1±0	No, if spontaneous void pre-PAE	Yes
PAE, Abt et al. (25)	Local (skin)	Clinical	122.2±25.8	2.2±0.6	Bladder catheter, 1.3±1.4	Yes
PAE, Gao et al. (21)	Local (skin)	NR	89.7±17.1	2.9±1.6	35.2% bladder catheter	NR
PAE, Pisco et al. (28)	Local (skin)	NR	75 (60-90)*	NR	NR	NR
PAE, Carnevale et al. (24)	Local (skin)	Outpatient	144.8±50.1	0±0.25	NR	NR
TIND, Chughtai et al. (27)	Local (27%), IV sedation (66%), or general anesthesia (7%)	Outpatient/clinical	NR	Same day discharge	No bladder catheter	Exclusion criteria

Australian cohort received general anesthesia as standard of care, * Median time, NR = not reported

CWVTT = Convective Water Vapor Thermal Therapy; NR = Not Reported; PAE = Prostatic Artery Embolization; PUL = Prostatic Urethral Lift; SD = standard deviation; TURP = Transurethral Resection of the Prostate

Ranking of MITs, TURP, and sham groups using the surface under the cumulative ranking (SUCRA) showed that Aquablation had the highest probability to improve Qmax (92.6%), followed closely by TURP (89.6%) at 3 months (Table-3). PAE, CWVTT, and PUL followed Aquablation and TURP, with TIND having the lowest probability of improving Qmax (23.1%). At 12 months, TURP had the highest probability to improve Qmax, followed by Aquablation, PAE and PUL, with probabilities of 79.0%, 69.9%, 31.7% and 19.4%, respectively. The

certainty of evidence scored by GRADE is very low for TIND due to the high risk of bias and indirect comparison to TURP and low for all other MITs.

Post Void Residual (PVR)

PVR improvement following Aquablation was most comparable to TURP at 3 and 12 months (MD 7.00; 95%CI: -32.14, 46.14 and MD -8.00; 95%CI: -53.17, 37.17) (Figures 3 C and D). PAE demonstrated a similar trend with a mean difference of 14.10; 95%CI: -7.75, 35.95 and

Figure 3 - Network meta-analysis outcomes comparing MIT with TURP for Qmax, PVR, IPSS and QoL at three and twelve months. On the right side of each graphs the mean difference and 95% confidence interval of the specific outcome are shown. The arrow under each graph shows per technique whether the MIT or TURP is favored.

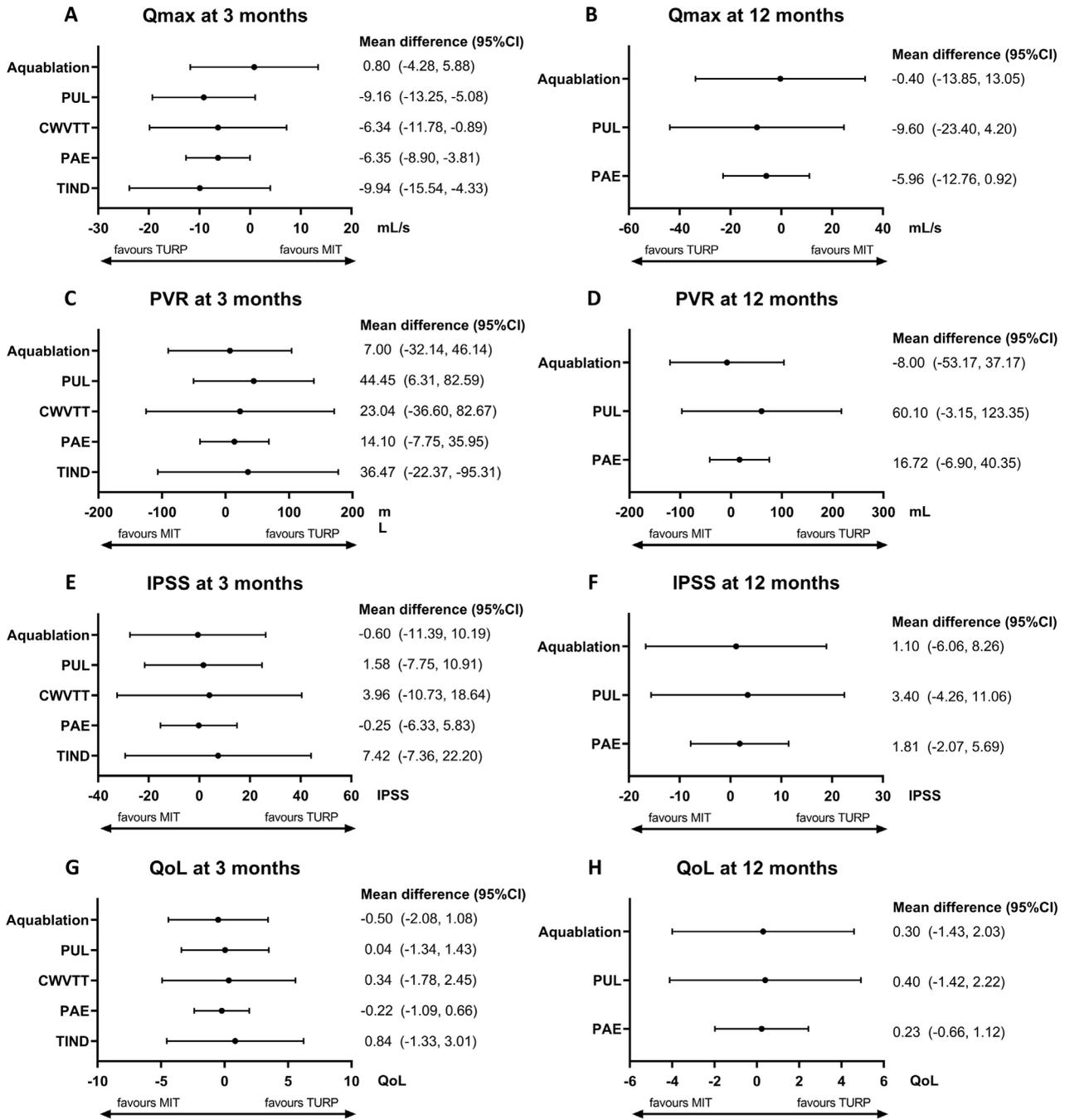


Table 3 - SUCRA outcomes.

3 months	Qmax (%)	PVR (%)	IPSS (%)	QoL (%)
TURP	89.6	86.0	67.5	58.5
Aquablation	92.6	70.4	66.2	75.4
PUL	29.3	21.6	58.6	58.0
CWVTT	54.5	53.9	48.1	47.9
PAE	56.0	61.0	69.8	72.4
TIND	23.1	35.8	30.6	31.8
Sham	4.5	21.3	9.1	5.9
12 months	Qmax	PVR	IPSS	QoL
TURP	79.0	76.2	74.5	65.6
Aquablation	69.9	80.1	54.6	45.3
PUL	19.4	4.2	28.3	40.6
PAE	31.7	39.5	42.6	48.6

SUCRA = the surface under the cumulative ranking curve. The SUCRA is a calculation of the overall ranking in a single number. The higher the SUCRA the higher the chance that the treatment is in a high rank (equals a good outcome). The lower the SUCRA, the higher the chance that the treatment is in a low rank (equals a worse outcome).

-16.72; 95%CI: -6.90, 40.35 at 3 and 12 months, respectively. At 3 months, PVR following PUL was found to be significantly higher, indicating worse outcomes, compared to TURP (MD 44.45; 95%CI: 6.31, 82.59) (Figure-3C). However, at 12 months, there were no significant differences in PVR outcomes between MITs and TURP, although the mean difference between TURP and PUL was 60.10 (Figure-3D).

When ranking the treatments based on PVR change, TURP had the highest probability (86%) of improving PVR at 3 months (Table-3), followed by Aquablation with a probability of 70.4%. In contrast, PUL and the sham group were the least likely to improve PVR with probabilities of 21.6% and 21.3%, respectively. At 12 months, Aquablation had the highest probability (80.1%) to improve PVR, closely followed by TURP (76.2%). PUL was found to be the least likely to result in the best PVR improvement (4.2%). The certainty of evidence is very low for TIND and low for all other MITs.

IPSS

There were no significant differences in IPSS between MITs and TURP at 3 or 12 months (Figures 3E and F). However, at three months, the mean difference varied from -0.60 and -0.25 for Aquablation and PAE, respectively, to 3.96 and 7.42 for CWVTT and TIND, respectively. At 12 months, the mean difference for MITs varied between 1.10 and 3.40, compared to TURP (Figure-3F).

Ranking the treatments based on IPSS improvement did not show a clear preference (Table-3). The probabilities for best IPSS improvement by PAE, TURP and Aquablation were 69.8%, 67.5%, and 66.2%, respectively, at three months. Among the MITs, TIND (SUCRA 30.6%) was the least likely to improve IPSS. At 12 months, TURP had the highest probability to improve IPSS (74.5%). Of the MITs, Aquablation had the highest probability to improve IPSS (54.6%). The certainty of evidence is very low for TIND and low for all other MITs.

QoL

There were no significant differences in QoL scores between MITs and TURP at 3 and 12 months (Figures 3G and H). At three months, Aquablation and PAE showed a slightly lower mean difference than TURP (MD -0.50; 95%CI: -2.08, 1.08, MD -0.22; 95%CI: -1.09, 0.66). However, these differences were no longer present at 12 months (Figures 3G and H).

At three months, Aquablation and PAE had the highest probability of improving QoL, with 75.4% and 72.4%, respectively (Table-3). TURP, PUL, CWVTT and TIND followed. At 12 months, TURP had the highest probability of improving QoL (65.6%). The probability of PAE, Aquablation and PUL to result in the best QoL improvement was between 48.6% and 40.6%. The certainty of evidence is very low for TIND and low for all other MITs.

Sexual function

The incidence of erectile dysfunction *de novo* following PAE and TURP was 1% (n=2) and 3% (n=8), respectively, while no such cases were reported following any of the other MITs (Table-4). Retrograde ejaculation occurred in 14 (8%), 8 (7%), 4 (3%) and 67 (28%) patients following PAE, Aquablation, CWVTT, and TURP, respectively. Reduced ejaculate volume was reported in 3 (2%), 4 (3%) and 1 (0%) patient following PAE, CWVTT, and TURP, respectively.

Adverse events

Serious adverse events (SAE) were reported following Aquablation, PUL, CWVTT, PAE, TIND, and TURP in 7 (6%), 2 (1%), 3 (2%), 5 (3%), 5 (4%), and 19 (8%) patients, respectively. An overview of (serious) adverse events following MITs and TURP is shown in Table-4. The most frequently occurring SAE following Aquablation and TURP were urethral stricture and bleeding. Technical failure was reported in only 3 (2%) PAE procedures due to iliac artery tortuosity or atherosclerotic changes (21). Urinary tract infection or sepsis incidence were more common following TIND (2%) (27).

Comparison of adverse events following MIT revealed that dysuria and hematuria occurred more

frequently following PUL. The incidence of urine retention was two times higher in patients treated by Aquablation and PAE compared to PUL and CWVTT. In general, the number of adverse events following MITs was lower compared to TURP.

Retreatment rates

At one year follow-up, the retreatment rates were 3% (n=3), 3% (n=5), 0% (n=0), 4% (n=7), 2% (n=3), and 2% (n=4) for Aquablation, PUL, CWVTT, PAE, TIND, and TURP, respectively (Table-4).

DISCUSSION

This review provides an overview of several MITs that have become commercially available in the last 13 years and have been studied in RCTs. It presents treatment characteristics and safety outcomes, as well as functional outcomes compared to standard of care TURP, using an NMA at 3- and 12-months follow-up.

The MITs described in this review all have different approaches to improve voiding with subsequent varying side effects. The techniques vary in balance between the least invasive approach and best functional outcomes.

The results of this NMA showed that the functional outcomes following Aquablation were most comparable to TURP. This was seen in both objective outcomes by means of the Qmax and PVR as well as subjective outcomes by PROMs. PAE closely followed with slightly less improvement compared to TURP. PUL and TIND had the least voiding improvement compared to TURP. CWVTT outcomes fall between these groups for Qmax and PVR and are comparable with PUL and TIND for IPSS and QOL. SUCRA analysis confirmed the ranking of treatments described above.

Preservation of sexual function is one of the advantages of MITs, as mentioned in the included studies.

For some patient's preservation of sexual function is of great importance and could be an important reason to choose an MIT over TURP. However, the variation in PROMs used by the included studies for sexual function evaluation, hampers outcome comparison by statistical analyses. Direct comparison

Table 4 - Adverse events, sexual function and treatment failure.

	Aquablation (n=116)	PUL (n=184)	CWVTT (n=134)	PAE (n=183)	TIND (n=128)	TURP (n=241)
Time period	90 days	NR	90 days	30-365 days	90 days	30-365 days
Serious Adverse Events	7 (6%)	2 (1%)	3 (2%)	5 (3%)	5 (4%)	19 (8%)
Bleeding	3 (3%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	5 (2%)
(Clot) retention	1 (1%)	1 (1%)	2 (1%)	0 (0%)	2 (2%)	1 (0%)
UTI/sepsis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)
Technical failure	0 (0%)	0 (0%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)
Urethral stricture	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)
Ischemia bladder wall	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
TUR syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)
Other	0 (0%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
Adverse Events	83	286	138	305	83	317
Post-embolization syndrome	0 (0%)	0 (0%)	0 (0%)	7 (4%)	0 (0%)	0 (0%)
Frequency	0 (0%)	0 (0%)	8 (6%)	15 (8%)	8 (6%)	0 (0%)
Dysuria	12 (10%)	82 (45%)	23 (17%)	18 (10%)	27 (21%)	63 (26%)
Haematuria	13 (11%)	53 (29%)	16 (12%)	10 (5%)	16 (16%)	67 (28%)
Haematospermia	0 (0%)	0 (0%)	10 (7%)	4 (2%)	0 (0%)	0 (0%)
Urgency	6 (5%)	10 (5%)	8 (6%)	0 (0%)	6 (5%)	4 (2%)
(Urge) incontinence	0 (0%)	6 (3%)	0 (0%)	0 (0%)	0 (0%)	16 (7%)
(Pelvic floor) pain	6 (5%)	25 (14%)	4 (3%)	21 (11%)	1 (1%)	34 (14%)
UTI	11 (9%)	7 (4%)	10 (7%)	12 (7%)	3 (2%)	33 (14%)
Epididymitis	0 (0%)	0 (0%)	4 (3%)	0 (0%)	0 (0%)	2 (1%)
Retention	11 (9%)	5 (3%)	5 (4%)	19 (10%)	8 (6%)	14 (6%)
Other	16 (13%)	15 (8%)	42 (31%)	180 (98%)	1 (1%)	29 (12%)
Sexual function:						
Erectile dysfunction	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	8 (3%)
Retrograde ejaculation	8 (7%)	0 (0%)	4 (3%)	14 (8%)	0 (0%)	67 (28%)
Reduced ejaculate volume	0 (0%)	0 (0%)	4 (3%)	3 (2%)	0 (0%)	1 (0%)
Treatment failure at 1 year:	3 (3%)	5 (3%)	0 (0%)	7 (4%)	3 (2%)	4 (2%)

CWVTT = Convective Water Vapor Thermal Therapy; NR = Not Reported; PAE = Prostatic Artery Embolization; PUL = Prostatic Urethral Lift; TURP = Transurethral Resection of the Prostate; UTI = Urinary Tract Infection

of outcomes, although it should be interpreted with caution, seems to indicate a relation between the functional outcomes of a treatment and the chance of retrograde ejaculation. Consequently, TIND and PUL might be favored for sexual function preservation.

The improved safety profile is another often discussed advantage of MITs. The majority of MITs can be performed under local anesthesia or sedation, which eliminates potential general anesthesia side effects and makes them available for patients unfit for general anesthesia. Moreover, the majority of included MITs could be performed in an office-based setting or intervention room. This review confirms that MITs have a better safety profile than TURP, with TURP having the highest percentage of SAE's, followed by Aquablation. The other MITs had lower SAE percentages, and AE rates were lower following MITs compared to TURP, except PUL which noted higher percentages for dysuria and hematuria, potentially due to the transurethral approach and insertion of material. Overall, the included MITs have a better safety profile than TURP.

The findings in this review are in line with findings of other recent MIT reviews, although it is the first to include PAE and compared to TURP. Tanneru et al. included CWVTT, Aquablation and PUL in their systematic review and NMA and their findings were similar to those of this review (30). The Cochrane review by Franco et al. focused on PROM and adverse event outcomes, which indicated that IPSS for PAE and PUL were similar to TURP (31). However, the current review is unique as it covers all MITs including PAE and compared them to TURP for both objective and subjective outcomes. Therefore, this review provides a comprehensive overview and comparison of the novel MITs that have been investigated by RCT so far.

Our review has several limitations as a consequence of the scarcity of available literature. Since the included treatments are relatively new, only a limited number of RCT's were available, subsequently leading to wide confidence intervals. Furthermore, the patient characteristics of the included patients showed some variation. Abt et al. included patients with better IPSS and QoL scores but worse Qmax and PVR, the impact of these contradictive baseline characteristics remains unclear. Furthermore, included studies had comparable inclusion and exclusion criteria, except for PUL

that excluded median lobes. However, as baseline differences were limited, we assumed that in case there were effect modifiers that influenced the outcomes, these were distributed equally over the studies, and therefore transitivity is assumed. The network geometry showed that some comparisons were only based on a single study with limited patients, affecting the reliability of the network outcomes. Moreover, TURP outcome varied between PAE studies, suggesting heterogeneity between studies. In addition, the certainty of evidence is low to very low. For TIND the certainty of evidence is rated very low as the outcomes are only indirectly compared to TURP using the sham control group. Furthermore, the study had a high risk of bias. For the other studies, the outcomes were rated low due to the limited number of available studies with limited number of included patients. Therefore, the outcomes should be interpreted with caution. This review has not been able to provide high quality evidence to choose one MIT over another or over standard of care. As RCT's are expensive additional RCT's will be unfeasible. For these reasons, the overview of the currently available recent MITs for LUTS with their treatment effect and side effects provided by this review is the best achievable at the moment.

CONCLUSIONS

Based on the findings in this review, it can be concluded that not all new minimally invasive treatments are equally effective in LUTS improvement. Of the reviewed MITs, Aquablation results in the best voiding improvement, outcomes are comparable to TURP. However, Aquablation is also the most invasive as it requires general or spinal anesthesia and hospitalization. If the desired technique can be performed under local anesthesia, PAE ranked as highest. These outcomes should be interpreted with caution due to the heterogeneity and low certainty of evidence of included studies.

ABBREVIATIONS

BPH = Benign prostatic hyperplasia

CI - Confidence Interval

CWVTT = Convective Water Vapor Thermal Therapy

IIEF = International Index of Erectile Function

IPSS = International Prostate Symptom Score
 LUTS = Lower Urinary Tract Symptoms
 MIT = Minimally Invasive Treatment
 NMA = Network Meta-Analysis
 NR = Not Reported
 PAE = Prostatic Artery Embolization
 PUL = Prostatic Urethral Lift
 PV = Prostate volume
 PVR = Post-Void Residual
 Qmax = Peak Urinary Flow
 QoL = Quality of Life
 RCT = Randomized Controlled Trial
 SD = Standard deviation
 SUCRA = Surface under the cumulative ranking
 TIND = Temporary implantable nitinol device
 TURP = Transurethral Resection of the Prostate
 UTI = Urinary Tract Infection

ACKNOWLEDGMENT

Robin Vernooij and Manon Kappelhof for their support in the STATA analyses. Mitra Almasian for the critical review of the final manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

- Cornu JN, Gacci M, Hashim H, Herrmann TRW, Malde S, Netsch C, et al. EAU guidelines on Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO). [Internet] Eur. Assoc. Urol., 2023. Available at. <<https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Non-Neurogenic-Male-LUTS-2022.pdf>>
- Hoffman RM, MacDonald R, Monga M, Wilt TJ. Transurethral microwave thermotherapy vs transurethral resection for treating benign prostatic hyperplasia: a systematic review. *BJU Int.* 2004;94:1031-6.
- Laguna MP, Alivizatos G, De La Rosette JJ. Interstitial laser coagulation treatment of benign prostatic hyperplasia: is it to be recommended? *J Endourol.* 2003;17:595-600.
- Gilling P, Reuther R, Kahokehr A, Fraundorfer M. Aquablation - image-guided robot-assisted waterjet ablation of the prostate: initial clinical experience. *BJU Int.* 2016;117:923-9.
- Dixon CM, Rijo Cedano E, Mynderse LA, Larson TR. Transurethral convective water vapor as a treatment for lower urinary tract symptomatology due to benign prostatic hyperplasia using the Rezm(®) system: evaluation of acute ablative capabilities in the human prostate. *Res Rep Urol.* 2015;7:13-8.
- McNicholas TA, Woo HH, Chin PT, Bolton D, Fernández Arjona M, Sievert KD, et al. Minimally invasive prostatic urethral lift: surgical technique and multinational experience. *Eur Urol.* 2013;64:292-9.
- Pisco JM, Rio Tinto H, Campos Pinheiro L, Bilhim T, Duarte M, Fernandes L, et al. Embolisation of prostatic arteries as treatment of moderate to severe lower urinary symptoms (LUTS) secondary to benign hyperplasia: results of short- and mid-term follow-up. *Eur Radiol.* 2013;23:2561-72.
- Amparore D, De Cillis S, Volpi G, Checcucci E, Manfredi M, Morra I, et al. First- and Second-Generation Temporary Implantable Nitinol Devices As Minimally Invasive Treatments for BPH-Related LUTS: Systematic Review of the Literature. *Curr Urol Rep.* 2019;20:47.
- McVary KT, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Minimally Invasive Prostate Convective Water Vapor Energy Ablation: A Multicenter, Randomized, Controlled Study for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. *J Urol.* 2016;195:1529-38.
- Gilling P, Barber N, Bidair M, Anderson P, Sutton M, Aho T, et al. WATER: A Double-Blind, Randomized, Controlled Trial of Aquablation® vs Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia. *J Urol.* 2018;199:1252-61.
- Sønksen J, Barber NJ, Speakman MJ, Berges R, Wetterauer U, Greene D, et al. Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. *Eur Urol.* 2015;68:643-52.
- Kuang M, Vu A, Athreya S. A Systematic Review of Prostatic Artery Embolization in the Treatment of Symptomatic Benign Prostatic Hyperplasia. *Cardiovasc Intervent Radiol.* 2017;40:655-63.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
- [No Authors] Plot digitizer. [Internet]. Available at. <<http://plotdigitizer.sourceforge.net>> Accessed in may 2023.
- Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev.* 2019;10:ED000142.

16. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914.
17. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol*. 2011;64:163-71.
18. White IR. Network Meta-analysis. *The Stata Journal*, 20215;15:951–85.
19. McVary KT, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, et al. Erectile and Ejaculatory Function Preserved With Convective Water Vapor Energy Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Randomized Controlled Study. *J Sex Med*. 2016;13:924-33.
20. Roehrborn CG, Gange SN, Shore ND, Giddens JL, Bolton DM, Cowan BE, et al. The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. *J Urol*. 2013;190:2161-7.
21. Gao YA, Huang Y, Zhang R, Yang YD, Zhang Q, Hou M, et al. Benign prostatic hyperplasia: prostatic arterial embolization versus transurethral resection of the prostate--a prospective, randomized, and controlled clinical trial. *Radiology*. 2014;270:920-8.
22. Gilling PJ, Barber N, Bidair M, Anderson P, Sutton M, Aho T, et al. Randomized Controlled Trial of Aquablation versus Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia: One-year Outcomes. *Urology*. 2019;125:169-73.
23. McVary KT, Gange SN, Shore ND, Bolton DM, Cowan BE, Brown BT, et al. Treatment of LUTS secondary to BPH while preserving sexual function: randomized controlled study of prostatic urethral lift. *J Sex Med*. 2014;11:279-87.
24. Carnevale FC, Iscaife A, Yoshinaga EM, Moreira AM, Antunes AA, Srougi M. Transurethral Resection of the Prostate (TURP) Versus Original and PERFECTED Prostate Artery Embolization (PAE) Due to Benign Prostatic Hyperplasia (BPH): Preliminary Results of a Single Center, Prospective, Urodynamic-Controlled Analysis. *Cardiovasc Intervent Radiol*. 2016;39:44-52.
25. Abt D, Hechelhammer L, Müllhaupt G, Markart S, Güsewell S, Kessler TM, et al. Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. *BMJ*. 2018;361:k2338.
26. Insausti I, Sáez de Ocáriz A, Galbete A, Capdevila F, Solchaga S, Giral P, et al. Randomized Comparison of Prostatic Artery Embolization versus Transurethral Resection of the Prostate for Treatment of Benign Prostatic Hyperplasia. *J Vasc Interv Radiol*. 2020;31:882-90.
27. Chughtai B, Elterman D, Shore N, Gittleman M, Motola J, Pike S, et al. The iTind Temporarily Implanted Nitinol Device for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Multicenter, Randomized, Controlled Trial. *Urology*. 2021;153:270-6.
28. Pisco JM, Bilhim T, Costa NV, Torres D, Pisco J, Pinheiro LC, et al. Randomised Clinical Trial of Prostatic Artery Embolisation Versus a Sham Procedure for Benign Prostatic Hyperplasia. *Eur Urol*. 2020;77:354-62.
29. McVary KT, Rogers T, Roehrborn CG. Rez m Water Vapor Thermal Therapy for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia: 4-Year Results From Randomized Controlled Study. *Urology*. 2019;126:171-9.
30. Tanneru K, Jazayeri SB, Alam MU, Kumar J, Bazargani S, Kuntz G, et al. An Indirect Comparison of Newer Minimally Invasive Treatments for Benign Prostatic Hyperplasia: A Network Meta-Analysis Model. *J Endourol*. 2021;35:409-16.
31. Franco JV, Jung JH, Imamura M, Borofsky M, Omar MI, Escobar Liquitay CM, et al. Minimally invasive treatments for lower urinary tract symptoms in men with benign prostatic hyperplasia: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;7:CD013656.

Correspondence address:

Rob Arnoldus Antonius van Kollenburg, MD
Department of Urology,
Amsterdam University Medical Centres
Meibergdreef 9 Amsterdam
1105 AZ Netherlands
E-mail:r.a.vankollenburg@amsterdamumc.nl

APPENDIX

Supplementary 1 - Inclusion and exclusion criteria of patients per study.

Studies	Inclusion criteria	Exclusion criteria
Aquablation, Gilling et al. (4)	Men 45-80 years, Qmax \leq 15, Prostate 30 - 80 cc by TRUS, IPSS \geq 12	PVR >300 mL, Prostate/bladder cancer, Prior prostate surgery
PUL, Roehrborn et al. (2)	Men \geq 50 years, Flow rate \leq 12, VV \geq 125 cc, AUASI \geq 13, Prostate 30-80 cc, no prior surgical treatment for BPH, washouts of 2 weeks for α -blocker, 3 months for 5 α -reductase inhibitor and 3 days for anticoagulants	Obstructive median lobe, PVR >250 mL, Active UTI, PSA >10 ng/mL (unless negative biopsy)
PUL, Sønksen et al. (11)	Male \geq 50 years, Qmax \leq 15 mL/s for 125 mL voided volume, IPSS >12, PVR <350 mL Prostate volume \leq 60 cc, Incontinence Severity Index score \leq 4	Median lobe, Active UTI, Urinary retention, Prior prostate surgery
CWVTT, McVary et al. (23)	Male \geq 50 years, Qmax 5 - 15 mL/s for 125 mL voided volume, IPSS \geq 13, Prostate volume 30 – 80cc, No prior invasive prostate intervention	PVR \geq 250 mL, PSA \geq 2.5 ng/mL, Active UTI
PAE, Insausti et al. (26)	Male >60 years, Qmax \leq 10 mL/s or urinary retention, IPSS was \geq 8, (QoL) related to LUTS was \geq 3, TURP was indicated, BPH-related LUTS refractory to medical treatment for at least 6 months or the patient could not tolerate medical treatment	Advanced atherosclerosis, Tortuosity of the iliac arteries, GFR <30 mL/min, Neurogenic bladder, Prostate cancer
PAE, Abt et al. (25)	Male \geq 40 years, Qmax <12 mL/s or urinary retention, IPSS was \geq 8, Prostate 25 – 80 cc, QoL related to LUTS was \geq 3, TURP indicated, refractory to medical treatment or not willing to undergo or continue medical treatment.	Advanced atherosclerosis, Tortuosity of the iliac arteries, GFR <60 mL/min, Neurogenic bladder, Prostate cancer

PAE, Gao et al. (21)	<p>Qmax ≤15, (IPSS) >7, Prostate 20-100cc, Failed medical therapy with a washout period of 2 or more weeks.</p>	<p>Detrusor hyperactivity or hypocontractility at urodynamic study, Prostate cancer, Prior prostate surgery, PSA >4 ng/mL</p>
PAE, Pisco et al. (28)	<p>Male >45 yr old, Qmax <12 mL/s; IPSS of ≥ 20 and a QoL score of ≥ 3 PV ≥ 40 cc;</p>	<p>Prostatic arteries not feasible for PAE, Active UTI, Prior prostate surgery,</p>
PAE, Carnevale et al. (24)	<p>Male >45 yr old, IPSS >19, Prostate 30-90cc, bladder outlet obstruction (BOO) confirmed by urodynamic examination</p>	<p>Renal failure, suspected prostate cancer, neurogenic bladder disorder</p>
TIND, Chughtai et al. (27)	<p>Male ≥ 50 yr old, Qmax ≤ 12 mL/s, with 125mL voided volume, IPSS of ≥10, PV 25-75 cc;</p>	<p>PVR > 250mL, obstructive median lobe, PSA >10ng/mL or free PSA < 25% without a subsequent negative biopsy, previous prostate surgery.</p>

CWVTT = Convective Water Vapor Thermal Therapy; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; NR = Not Reported; PAE = Prostatic Artery Embolization; PV = prostate volume; PUL = Prostatic Urethral Lift; PVR = Post-Void Residual; Qmax = Peak Urinary Flow; QoL = Quality of Life; UTI = Urinary Tract Infection

Supplementary 2 – Risk of Bias

Qmax and post-void residual outcomes.

Studies	Intervention	Control	D1	D2	D3	D4	D5	O
Aquablation, Gilling et al. (4)	Aquablation	TURP	L	L	L	L	L	L
PUL, Roehrborn et al. (2)	PUL	Sham	L	L	S	L	S	S
PUL, Sønksen et al. (11)	PUL	TURP	L	S	S	L	L	S
CWVTT, McVary et al. (23)	CWVTT	Sham	L	L	L	L	L	L
PAE, Insausti et al. (26)	PAE	TURP	L	S	H	L	H	H
PAE, Abt et al. (25)	PAE	TURP	L	S	L	S	L	S
PAE, Gao et al. (21)	PAE	TURP	S	S	S	L	S	S
PAE, Pisco et al. (28)	PAE	Sham	L	L	L	S	S	S
PAE, Carnevale et al. (24)	PAE	TURP	S	S	L	S	S	S
TIND, Chughtai et al. (27)	TIND	Sham	L	H	H	L	S	H

IPSS and QoL outcomes.

Studies	Intervention	Control	D1	D2	D3	D4	D5	O
Aquablation, Gilling et al. (4)	Aquablation	TURP	L	L	L	L	L	L
PUL, Roehrborn et al. (2)	PUL	Sham	L	L	L	L	S	S
PUL, Sønksen et al. (11)	PUL	TURP	L	S	S	L	L	S
CWVTT, McVary et al. (23)	CWVTT	Sham	L	L	L	L	L	L
PAE, Insausti et al. (26)	PAE	TURP	L	S	H	L	H	H
PAE, Abt et al. (25)	PAE	TURP	L	S	L	S	L	S
PAE, Gao et al. (21)	PAE	TURP	S	L	S	S	S	S
PAE, Pisco et al. (28)	PAE	Sham	L	L	L	S	S	S
PAE, Carnevale et al. (24)	PAE	TURP	S	S	S	S	S	S
TIND, Chughtai et al. (27)	TIND	Sham	L	S	H	S	S	H

Adverse event outcomes

Studies	Intervention	Control	D1	D2	D3	D4	D5	O
Aquablation, Gilling et al. (4)	Aquablation	TURP	L	L	L	L	L	L
PUL, Roehrborn et al. (2)	PUL	Sham	L	L	L	L	S	S
PUL, Sønksen et al. (11)	PUL	TURP	L	S	S	L	L	S