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Minimally-Invasive Treatments for Lower Urinary Tract Symptoms in People with Benign Prostatic Hyperplasia: A Review of Clinical Effectiveness

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Abbreviations

BPH	benign prostatic hyperplasia or hypertrophy
BPHII	BPH impact index
IIEF	international index of erectile function
IPSS	international prostate symptoms score
ISI	Incontinence severity index
LUTS	lower urinary tract symptoms
MSHQ-EjD	men's sexual health questionnaire for ejaculatory dysfunction
PAE	prostatic artery embolization or embolotherapy
PUL	prostatic urethral lift
PVR	post-void residual urine volume
Qmax	maximum urinary flow
QoL	quality of life
QoR	quality of recovery
RCT	randomized controlled trial
SHIM	sexual health inventory for men
TURP	transurethral resection of the prostate
WVTT	water vapour thermal therapy

Context and Policy Issues

Benign prostatic hyperplasia or hypertrophy (BPH) refers to the enlargement of the prostate gland in men due to an overgrowth of cells.[1] Although it is not a life-threatening condition, BPH causes serious morbidity in the form of lower urinary tract symptoms (LUTS) in an estimated 50% of men older than 75 years.[2] As the prostate gland grows, it presses against the urethra and may partially obstruct the flow of urine from the bladder causing dribbling or a weak urine stream, the urge to urinate, and incomplete voiding or urine retention.[2]

The first line of treatment for LUTS involves lifestyle changes.[1] Drinking less fluids, avoiding fluids that contain caffeine or alcohol, reducing the intake of certain medications, and conducting specific exercises may alleviate some mild BPH symptoms.[1] If symptoms progress, alpha-blockers, 5-alpha-reductase inhibitors, phosphodiesterase-5 inhibitors, or muscle relaxants may be offered.[1]

For moderate to severe cases of LUTS that are unresponsive to medical management, surgery is the primary choice of treatment, the most common form being transurethral resection of the prostate (TURP).[3] Prostatectomy (or a complete removal of the prostate) may be considered if the urethra is completely blocked or the prostate is extremely enlarged.[1]

Side effects of surgery such as bleeding, infection, retrograde ejaculation, erectile dysfunction, and incontinence have been reported.[1] To limit the occurrence of side effects, several minimally-invasive treatments have been developed.[1] They include, but are not limited to, aquablation, prostatic artery embolization or embolotherapy (PAE), prostate urethral lift (PUL), and water vapour thermal therapy (WVTT).[1] Each of these techniques is based on a unique technology. Aquablation for example, uses water under high pressure to resect tissue from the prostate under ultrasound image guidance.[4,5] Also under image guidance, PAE entails injecting an embolizing agent or pharmaceutical into prostatic arteries via a catheter to block blood flow to the prostate, cause tissue death and consequently reduce the size of the prostate.[6] PUL involves the use of a needle-shaped

probe to deliver permanent or temporary mechanical implants into the urethra to relieve obstructions.[7] The implants pull back the lateral lobes of the urethra causing the latter to widen and lower resistance to the flow of urine.[8] Another water-based technique, WVTT, uses a radiofrequency system to generate and deliver water vapour to the transition zone of the prostate.[8] Through convection, heat from the steam transfers to the prostate tissue and gradually causes cell death.[8] Other minimally-invasive options involve the use of lasers to resect prostate tissue.[9]

This review aims to summarize evidence regarding the clinical effectiveness of select minimally-invasive techniques for the treatment of LUTS associated with BPH.

Research Question

What is the clinical effectiveness of select minimally-invasive treatments for the management of lower urinary tract symptoms in people with benign prostatic hyperplasia?

Key Findings

Four recent systematic reviews, two randomized controlled trials, and one retrospective comparative study were identified that addressed the clinical effectiveness and safety of minimally invasive surgical techniques in treating lower urinary tract symptoms in patients with benign prostatic hyperplasia.

The systematic reviews were well-conducted and comprehensive, reporting on numerous outcome measures evaluating prostatic artery embolization, prostatic urethral lift, and transurethral resection of the prostate. However, there was substantial overlap in the populations that were included and bias in some of the primary studies was apparent. One randomized controlled trial on aquablation was covered by four articles. There was some evidence of patient selection bias and discrepancy in the reporting of results among these studies. While the authors of the systematic reviews may have had no conflicts of interest, authors of the randomized controlled trials were sponsored by the manufacturer of a technology that was under evaluation. For these and other reasons, considerable caution must be taken in making inferences from the results presented in this report.

Treatment effect was assessed with numerous outcomes ranging from symptom relief, quality of recovery, quality of life, and safety. Overall, based on findings from four studies that covered one randomized controlled trial, there was no difference in the changes in symptom relief between aquablation and transurethral resection at six and 12 months, except for men with prostates that were 50 mL or larger. In this sub-population, the difference in the change in maximum urinary flow from baseline to six months favoured aquablation over transurethral resection. Findings on prostatic artery embolization and prostatic urethral lift were mixed. Based on results from one meta-analysis, the difference in maximum urinary flow at post-treatment and the difference in the change of ejaculatory function scores favoured embolization over transurethral resection. Conversely, the difference in post-treatment quality of life scores and prostate volume, as well as the difference in symptom relief favoured transurethral resection and prostatectomy over embolization. Similarly, while changes in ejaculatory function at 12 months and quality of recovery at 12 and 24 months favoured prostate urethral life over transurethral resection, improvement in symptom relief at 12 months and 24 months favoured transurethral resection over prostatic urethral lift.

Overall, safety outcomes favoured minimally invasive surgical techniques over transurethral resection. Evidence from three primary studies reporting on the same randomized controlled trial suggested that for up to six months, men who were treated with aquablation had a lower mean incidence of complications compared to those who had transurethral resection. One primary study involving the same randomized controlled trial reported similar findings at 12 months. Evidence from two systematic reviews favoured both prostatic artery embolization and prostatic urethral lift over transurethral resection up to 12 months after treatment. Additionally, one randomized controlled trial favoured prostatic urethral lift over transurethral resection up to 24 months after treatment.

No comparative evidence on recovery time following surgery was found, nor was there comparative evidence on water vapour thermal therapy. None of the studies compared minimally invasive surgical techniques with lifestyle changes, watchful waiting, or medical management, and none were conducted in Canada

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were minimally invasive treatments such as embolization, aquablation, and urethral lift, and lower urinary tract symptoms in benign prostatic hyperplasia. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, and randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and July 29, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People with benign prostatic hyperplasia (or hypertrophy) who have lower urinary tract symptoms
Intervention	The following minimally-invasive treatment options Urolift system Prostatic artery embolization or embolotherapy Aquablation with the Aquabeam system Rezum transurethral thermal therapy system
Comparator(s)	A different minimally invasive surgical treatment option Lifestyle changes and watchful waiting Drug therapies (e.g. NX-1207, PRX-302, botulinum toxin A, ethanol) Surgical reduction of prostate tissue

Outcome(s)	Recovery time following surgery, improvement or resolution of lower urinary tract symptoms Adverse effects (e.g., sexual disfunction and urinary incontinence due to nerve damage from the procedures)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicates. One additional reference of interest is listed in Appendix 6.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist,[10] and the comparative studies were critically appraised using the Downs and Black checklist.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 408 citations were identified in the literature search. Following screening of titles and abstracts, 359 citations were excluded and 49 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search and other sources for full text review. Of these 50 potentially relevant articles, 10 publications met the inclusion criteria for this report and 40 publications were excluded for various reasons. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2.

Study Design

Four systematic reviews,[13-16] two randomized controlled trials (RCTs) covered by five articles,[17-21] and one retrospective, non-randomized comparative study were included in this review.[22] As shown in Appendix 5, there was considerable overlap in the populations that were included in the various articles. Three systematic reviews[13,15,16] reported on different sets of outcomes from the same study population as one or more primary studies that are also included in this review.[21,22] Two systematic reviews[13,14] included three overlapping primary studies. Four of articles[17-20] reported on different sets of outcomes from a single randomized controlled trial – three articles reported on the full population who were recruited across four countries[17-19] while one reported on a sub-group of men who were treated in one of the countries.[20] Patients in the RCT were enrolled in a 2:1 ratio into the intervention and comparator groups, respectively.

The systematic reviews were published in 2019[13,15] and 2018.[14,16] One systematic review[13] conducted meta-analyses that involved two RCTs, a retrospective registry-based observational study, along with a retrospective non-randomized comparative study.[22]

Another[14] conducted meta-analyses that included three RCTs, one prospective propensity score matched-pair analysis, and one retrospective, registry-based observational study and propensity score matched-pair analysis. Both sets of meta-analyses included a test for heterogeneity and evaluated the treatment effect between two interventions based on the weight mean differences and 95% confidence intervals of continuous data, and the odds ratio and 95% confidence intervals of binary data. The authors of all four systematic reviews assessed the quality and potential likelihood of bias of individual RCTs using elements of the Cochrane Collaboration's tool[13,14] or the Jadad scale.[15,16] One set of authors evaluated non-randomized studies using a modified Newcastle-Ottawa Quality Assessment Scale[13] while another used the Risk of Bias in Non-randomised Studies of Interventions tool.[14] In the latter review, a risk of bias assessment was conducted on the body of evidence for each clinical outcome using the Grading of Recommendations Assessment, Development and Evaluation methodology.[14]

The five articles that reported on the two RCTs were published in 2019,[17,18] 2018,[19,20] and 2017;[21] while the non-randomized study was published in 2017.[22] Randomization blocks were stratified by baseline symptom scores[17-20] or study site.[21] Differences in outcomes between the interventions and comparators were assessed using an independent *t*-test following treatment.[17-22] Differences in outcome measurements were considered statistically significant when the calculated *P* value was less than 0.05.

Country of Origin

The systematic reviews were conducted by authors in Brasil,[16] China,[13] Germany and Italy,[15] and Germany and Switzerland.[14]

The primary authors of the articles that covered the RCTs were based in Germany, [21] New Zealand,[17,19] the United Kingdom,[20] and the United States.[18] The retrospective non-randomized study was conducted and written by authors in China.[22]

Patient Population

All the studies reported on the treatment of patients with LUTS secondary to BPH. The first systematic review[13] reported on 506 men and the second[14] reported on 708 men. Between the two systematic reviews, there was an overlap of approximately 450 patients from three studies.[13,14] The two remaining systematic reviews[15,16] reported on the same population of 80 men that were included in one of the RCTs.[21]

Four articles reported on a subset or the full cohort of an RCT that included 184 men aged 45 to 80 years with prostate sizes 30 to 80 cc, moderate-to-severe LUTS as indicated by an International Prostate Symptoms Score (IPSS) of at least 12 and maximum urinary flow (Qmax) lower than 15 mL/s.[17-20] Patients were excluded if they had a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence, post-void residual urine volume (PVR) greater than 300 mL or urinary retention, use of self-catheterization, prior prostate surgery, on anticoagulants or bladder anticholinergics, or with severe cardiovascular disease. At the six month follow-up, data was collected from 114 patients in the intervention arm and from 62 in the comparator arm.[19] Twelve months after treatment, 115 men from the intervention arm were available whereas 61 from the comparator arm were available.[17] The second RCT that is included in this review enrolled 80 men aged at least 50 years and with LUTS as indicated by IPSS higher than 12 and Qmax of 15 mL/s or lower.[21] Each patient's prostate had to be 60 cc or

smaller in volume and had to be eligible for transurethral resection of the prostate (TURP).[21] The authors of the non-randomized study retrospectively enrolled patients who had been treated at a single site.[22] In the intervention arm were 17 selected men (ranging in age from 68 to 87 years) in whom medical treatment had failed and surgery was contraindicated whereas in the comparator arm were 40 men with no serious cardiovascular or cerebrovascular disease.[22] The men in the intervention arm were selected by a urologist, anesthesiologist and an interventional radiologist. These men had to have been treated with α-receptor blocker and 5α-reductase inhibitors without success, diagnosed with severe cardiovascular and cerebrovascular diseases, on life-time anticoagulants and could not lie in position for lithotomy.[22] The severity of urethral stricture prevented insertion of a resectoscope and the men were unwilling to undergo surgery.[22]

Interventions and Comparators

The interventions of interest in the included studies were aquablation,[17-20] PAE,[13,14,22] and PUL.[15,16,21]

Aquablation was delivered with the AquaBeam® System (PROCEPT BioRobotics, Redwood Shores, CA) which is a surgeon-operated robotic system that produces a high velocity water jet that resects unwanted prostate tissue.[17-20] The resection volume was identified by a surgeon under transrectal ultrasound guidance.[19] Following ablation, hemostasis was facilitated with either low-pressure inflation of a Foley balloon catheter in the prostatic fossa or through focal electrocautery.[19] Catheterization and bladder irrigation were completed at the discretion of the surgeon.[19]

In the single nonrandomized primary study that reported on PAE, the procedure was conducted under local anesthesia.[22] Guided by contrast-enhanced pelvic angiography and prostatic substance staining, the prostatic artery on one side of the body was catheterized and Embosphere microspheres (90 to 180 µm in diameter) were injected slowly until blood flow was detected only in the proximal part of the prostatic artery.[22] Care was taken to avoid reflux of the embolic agent into other arteries.[22] The embolization procedure was repeated on the contralateral side.[22] Each patient was treated with infection prophylaxis within three days following the procedure, and the urethral catheter was removed after seven days.[22] The systematic reviews[13,14] , included studies with microspheres sizes that were approximately two and a half to three times larger than those used in the nonrandomized study;[22] the microscpheres were 250 to 400 µm, 300 to 500 µm, and 355 to 500 µm in diameter.

PUL with the UroLift® system involved inserting small permanent implants through the urethra to compress tissue and widen the urethral lumen.[21] The relevant systematic reviews did not describe the system that was used in their included studies.[15,16]

TURP was the comparator of interest in all studies. In one systematic review,[14] one of the five studies that were included enrolled patients who had been treated with suprapubic transvesical/open protastectomy (OP) in the comparator arm. The prostatectomy procedure was not described. In the remaining studies, TURP was performed according to facility standards. One example suggests that the procedure involved transurethral electrocision under television monitoring.[22] First, the extent of hyperplasia was verified with a standard Olympus iso-ionic resectoscope inserted with a balloon catheter.[22] Then layers of the prostate were resected from the bladder neck to the prostatic capsule with a bipolar generator.[22] Following hemostasis by electrocoagulation, the resectoscope was removed and the balloon catheter was extracted three days later.[22]

Outcomes

The clinical effectiveness of aquablation, PAE, and PUL relative to TURP was assessed through numerous measures that reflected symptom relief, quality of recovery, and quality of life outcomes. Safety was assessed through procedure-related adverse effects such as erectile and ejaculatory dysfunction. The outcomes and reported measures were as follows:

Clinical effectiveness: symptom relief

- International Prostate Symptoms Score[13,14,16-22] was assessed with a validated questionnaire. A decrease in IPSS indicated symptom relief.

Clinical effectiveness: quality of recovery

- Qmax[13,14,16-22] was measured using uroflowmetry.[22] An increase in Qmax values suggested better quality of recovery.
- Post-void residual urine volume (PVR)[14,17-21] was measured under image-guidance. A decrease in PVR indicated better quality of recovery.
- Prostate volume[13,14,22] was calculated using the prostate ellipsoid formula which multiplies the true volume as measured with transrectal ultrasound by 0.52.[22] A smaller prostate volume indicated better quality of recovery.
- Quality of recovery (QoR) score was reported on a scale from 0 to 100 where recovery was defined by a score of at least 70 points[21]

Clinical effectiveness: quality of life

- IPSS-quality of life (QoL) score[13,14,17-20,22] was assessed with a validated questionnaire. A decrease in QoL scores indicated improvement.
- BPH impact index (BPHII)/Sexual Health Inventory for Men (SHIM) score,[21] International Index of Erectile Function (IIEF)-5 score,[14,15,19] and male sexual health questionnaire for ejaculatory function (MSHQ-EjD) score[15,19,21] were assessed with validated questionnaires. Decreases in the scores suggested improvement.
- Incontinence Severity Index (ISI)[19,21] was assessed with a validated questionnaire. An ISI score greater than 4 indicated incontinence.

Safety

- Adverse events or procedure-related complications[13-15,17-22] The safety outcome measures were reported as complications,[13,14,18-20,22] erectile dysfunction,[15,20,21] ejaculatory dysfunction,[20,21] anejaculation/loss of ejaculation,[16,18,19] incontinence,[17,20,21] sexual dysfunction,[17] dysuria,[19] hypogastralgia (i.e., pain in the perineum, retropubic space, and/or urethra)[22] and fever.[22]

Follow-up periods

Outcomes were reported over a wide range of follow-up periods. The systematic reviews primarily included studies that followed patients for at least 12 months,[13-16] with one including a study that reported IPSS and prostate volume following 3 months of treatment.[14] The authors of the primary studies measured or reported outcomes after three months,[19] six months,[17,18,22] and 12 months[17,20,22] following treatment.

Treatment effect

In all but one study,[13] the clinical treatment effect between interventions and comparators was assessed as the difference in the change in outcome measures due to treatment. First, the changes in the outcome measures from baseline to the follow-up period were calculated separately for both arms, then a *t*-test was used to assess the statistical significance of the differences between those changes. In the systematic review that did not assess changes in outcome measures, authors reported the treatment effect as the difference in the absolute values of the outcome measures between the interventions following treatment. The change in outcome measures was not calculated. All studies reported on the difference in the incidence of safety outcomes as a treatment effect.

Summary of Critical Appraisal

The critical appraisal of the studies is summarized below and details are available in Appendix 3.

Systematic Reviews

Common strengths of the systematic reviews were that their authors described their populations, interventions, comparators, and outcomes of interest as part of their objectives, multiple databases were searched, and keywords for the literature searches, and search strategies were provided.[13-16] The authors also critically assessed the quality of the individual included studies and declared that they had no conflicts of interest.[13-16] One set of authors further performed study selection and data extraction in duplicate;[13] and included the population, intervention, study types, outcomes, and minimum length of follow-up in the study eligibility criteria[13]. Three sets of authors critically assessed the quality of the body of evidence for each outcome.[13,14,16] One limitation of importance was that authors of one systematic review[15] opened up their assessment to all minimally invasive surgical intervention, indicating that their approach may have been less focused than the others.

Randomized controlled trials

All articles that reported on RCTs clearly described the population and main findings; however they described their objectives, interventions, potential confounders, and outcomes with varying levels of detail.[17-21] Registration of the RCTs on a publicly-accessible database suggests that the authors were transparent in their research and minimized patient selection and reporting biases.[17-21] However, there were differences across the studies in the number of patients with reported results, in three of the articles on aquablation.[17-19] At 12 months[17] there was one more patient in the aquablation arm and one less in the TURP arm than at six months.[19] Also, at the 6 month follow-up a third article[18] reported on two more patients in the aquablation arm and three more in the TURP arm than were reported in its companion article.[19] Regarding external validity, given the low loss-to-follow up rate of 8 out of 184 patients in the trial, it appears that the patients who enrolled in the study were representative of the population from which they were recruited.[17-19] It does appear however that patients who met the study inclusion criteria were selected to have moderate symptoms – those with serious comorbidities such as neurogenic bladder, diagnosed urethral stricture, stress urinary incontinence, urinary retention, or cardiovascular diseases were excluded.[17-19] The apparent use of stringent inclusion criteria, means the generalizability of the results may be limited because the patients may not be representative of the general population of patients with BPH. There was no evidence of risk to internal validity given that patients and outcome assessors were blinded to the treatment options, the main outcome measures that were used were accurate, patients

were recruited from the same population over the same time frame, and randomization was documented. Authors of two articles suggested that part of their analyses may not have been sufficiently powered to detect a clinically meaningful effect.[18,21] The remaining studies did not report on whether their analyses were sufficiently powered to detect a clinically important effect in their primary analyses.[17,20]

Non-randomized comparative study

The authors of the non-randomized comparative study clearly described their objectives, patient characteristics, the interventions, main outcome measures, and findings.[22] Appropriate statistical tests were used to assess the main outcomes. There was a risk to external validity given that both groups of patients were selected and not representative of the general population. There was a high risk to internal validity as no attempt was made to blind study participants and outcome assessors and no adjustments were made for potential differences in follow-up times. It is worth highlighting that in this retrospective comparison, patients in the intervention group were enrolled separately from patients in the comparator group. Surgery was contraindicated in those treated with PAE whereas patients with serious cardiovascular or cerebrovascular disease were excluded from the TURP group. This patient criteria suggested that the group of patients who were treated with PAE had worse symptoms than those who were treated with TURP. Therefore, it is possible that symptom relief may be easier to obtain in the PAE group, introducing bias. Furthermore, the number of patients in the comparator arm more than doubled the number of patients in the intervention arm. It is unclear what effect the unevenness in study sizes might have had on the results given that information on the skewness of the distribution of the outcome measures was unavailable.

Summary of Findings

The main study findings are summarized below while details and authors' conclusions are provided in Appendix 4.

What is the clinical effectiveness of select minimally-invasive treatments for the management of lower urinary tract symptoms in people with benign prostatic hyperplasia?

Symptom relief, quality of recovery, and quality of life

Aquablation versus TURP

Four articles reported on the same RCT – three reported on the full population recruited in Australia, New Zealand, the United Kingdom, and the Unites States[17-19] while one reported on the sub-group of men who were treated in the United States.[20]

At the six-month follow-up, the differences in the mean decreases in IPSS, mean decreases in IPSS-QoL, mean increases in Qmax and mean decreases in PVR between 114 men treated with aquablation and 62 treated with TURP were not statistically significant.[19] Sub-group analyses provided more nuanced results. The difference in the mean decreases in IPSS was statistically significant in favour of aquablation for patients with prostate volumes 50 mL or larger, and those whose IPSS scores at baseline were less than 20.[18] In patients with a middle lobe present, aquablation led to a more favourable improvement in Qmax.[18] Further sub-group analysis suggested that elevated PVR at baseline (i.e., PVR greater than 100 cc) had no significant impact on the change in PVR.[18]

At the 12-month time frame, the differences in the primary outcome measures were still insignificant for the full population of 176 men[17] as well as for the smaller US-based population of 87 men.[20] The authors reported that 12 months following treatment, 115 men were available in the aquablation arm while 61 were in the TURP arm.[17] .

Overall, there were no differences in the outcomes between the two techniques at six and 12 months except for the subset of men with prostates that were 50 mL or larger.[17,20] In this sub-population, the difference in the change in Qmax from baseline to six months favoured aquablation over TURP.[18]

PAE versus TURP and/or OP

Two systematic reviews[13,14] and one retrospective non-randomized study[22] provided results. Combining evidence from two studies in a meta-analysis, one set of authors reported that the mean QoL and prostate volumes at a single timepoint following treatment favoured TURP in a group of 55 men over PAE in a group of 32 men.[13] On the other hand, the mean Qmax favoured PAE over TURP.[13] These results did not account for the change from baseline values.[13] Accounting for baseline values, authors of the non-randomized study[22] that was included in the systematic reviews[13] suggested that at six and 12 months, decreases in IPSS, QoL, and prostate volume, and an increase in Qmax favoured TURP relative to PAE.

In an earlier systematic review,[14] the weighted mean differences in IPSS, QoL, Qmax, PVR and prostate volume relative to baseline favoured TURP and/or OP over PAE; whereas the weighted mean differences in the change in IIEF-5 favoured PAE. A sub-group analysis of three RCTs comparing PAE in 117 men to TURP (no OP) in 119 men suggested that weighted mean differences in IPSS and Qmax were statistically significant in favour of TURP whereas differences in the change in QoL, PVR, and IIEF-5 were not statistically significant. IIEF-5 was reported for 63 men treated with PAE and 66 men treated with TURP across two studies.

Overall, based on meta-analyses, the difference in Qmax post-treatment[13] and difference in the change of IIEF-5 scores[14] favoured PAE over TURP. Conversely, the difference in post-treatment QoL and prostate volume,[13] as well as the difference in the changes in IPSS, QoL, Qmax, and prostate volume favoured TURP and prostatectomy over PAE.[14,22]

PUL vs. TURP

Two systematic reviews[15,16] and one RCT[21] provided evidence on clinical effectiveness. Twelve months following treatment, patients in the TURP group responded with a higher mean decrease in IPSS and mean increase in Qmax compared with those randomized to PUL.[16] However, changes in IIEF-5 and MSHQ-EjD scores favoured PUL over TURP.

TURP was superior to PUL based on the difference in mean decrease in IPSS at 12 and 24 months, and at all time points based on the difference in mean increase in Qmax.[21] Regarding quality of recovery, PUL was superior to TURP with 82% of patients in the PUL arm achieving QoR of at least 70 points, compared with 53% of patients in the TURP arm, one month after treatment.[21] In addition, there was a mean increase in MSHQ-EjD function in the PUL group and a mean decrease in the TURP group. The improvements in health-related QoL and BPHII were not statistically different.[21]

Overall, the change in IIEF-5 and MSHQ-EjD[16] at 12 months and QoR at 12 and 24 months[21] favoured PUL over TURP whereas, the changes in IPSS and Qmax at 12 months and 24 months favoured TURP over PUL.[16,21]

Safety

Authors of all the studies reported on safety in terms of the incidence of adverse events or complications such as anejaculation, incontinence and sexual dysfunction.

Aquablation versus TURP

Safety outcomes were reported three[19] and six months[17-19] following treatment of 176 men in Australia, New Zealand, the United Kingdom and the United States. Additional outcomes were reported at twelve months for the United States-based population.[20] After three months, men who were treated with aquablation had a lower mean incidence of persistent grade 1 adverse events (7% versus 25%) and better ejaculatory function (based on MSHQ-EjD and IIEF-5 scores) compared to those who had TURP.[19] Following TURP, ejaculatory dysfunction is very common and may be due to heat-induced damage to the ejaculatory duct. In aquablation the risk of ejaculatory function is lower, possibly because of intentional avoidance of tissue destruction at the verumontanum as well as use of a heat-free mechanism to remove tissue.[17] Relative to baseline values, the ISI score increased by a factor of 0.6 in the TURP group compared with 1.2 times in the aquablation group.[19] The significance of the difference was not reported. Incidence of anejaculation was significantly lower in the aquablation group (2% versus 41%) for those men with prostates larger than 50 mL in volume.[19]

At six months, the trend in safety outcomes persisted[19] and appeared to be independent of baseline IPSS and age.[18] In patients with prostate volumes larger than or equal to 50 mL, and in whom the baseline IPSS was less than 20, the difference in the incidence of persistent grade 1 and grade 2 adverse events and the incidence of anejaculation favoured aquablation.[18] Incidentally, the differences in incidence of incontinence and sexual dysfunction were not significant six months after treatment.[17]

In the US-based sub-group, at 12 months following treatment, there was a higher mean incidence of persistent grade I and grade 2 adverse events (20% versus 40%) and incidence of anejaculation (9% versus 45%) in men treated with TURP.[20] All other safety outcomes were not statistically different between the two groups. None of the men in this sub-group experienced incontinence or erectile dysfunction.

PAE versus TURP

Combining evidence from two studies, authors of one systematic review suggested that when treated with TURP, 142 men had a 1.54 higher chance of experiencing a complication compared to 270 who were treated with PAE.[13] The difference was marginally significant. Synthesizing evidence across five studies, authors of the second systematic review and meta-analysis reported that at 12 months, the incidence of complications for 260 men who were treated with TURP or open prostatectomy was 63.8% compared to 31.1% of 396 patients treated with PAE.[14]

PUL vs. TURP

Reporting on the incidence of erectile dysfunction, retrograde or loss of ejaculation from the same RCT, two systematic reviews found PUL was safer than TURP at the 12-month time frame.[15,16]

On average, a group of 37 patients who were treated with PUL retained continence function relative to baseline as assessed by the average ISI score.[21] On the other hand, 32 patients in the TURP arm experienced poorer continence function at 2 weeks and 3 months following treatment.[21] The incidences of erectile dysfunction (6% versus 2%) and ejaculatory disfunction (34% versus0%) were higher in the TURP group.

Limitations

There are multiple limitations of note in the published body of evidence on clinical effectiveness and safety of minimally invasive surgical techniques for patients with BPH. First, the evidence on each minimally invasive intervention was sparse. For example, the evidence comparing aquablation to TURP came from a single RCT of 176 patients and the evidence comparing PUL to TURP came from two RCTs with 80 or fewer patients. Second, patient selection bias was evident, given the extensive exclusion criteria outlined in some of the studies. Patients in the aquablation trial were enrolled in a 2:1 ratio into the intervention and comparator groups, respectively.[17-20] The meta-analyses accounted for imbalances in intervention groups by weighting the outcome measurements. The nonrandomized study enrolled more than twice the number of patients in the comparator arm as in the intervention arm. It is unclear what the impact of this imbalance in study group sizes may have had on the findings. Third, outcomes were reported over relatively short time-frames ranging from three months to 2 years. The short time-frames may account for the lack of information on relapse or disease progression rates. The fourth limitation is that the studies reported on diverse outcomes measured with a variety of scales over a range of follow-up time periods. Each study reported on a subset of relevant outcomes ranging from extent of symptom relief, through to quality of recovery and incidence of complications or adverse events. Without reporting on the complete cadre of outcomes, a comprehensive picture of the impact of any of the minimally invasive techniques cannot be formed.

The fifth limitation is related to authorship, study sponsorship, and potential conflict of interest of the RCTs and other primary studies that were included in the systematic reviews. The manufacturer of the Aquabeam (aquablation) system financially-sponsored the clinical trial from which data was extracted, employed multiple authors as consultants and was involved in data management and the preparation of the manuscripts.[17-20] The manufacturer of the Urolift (PUL) system sponsored 10 out of 12 authors of the primary study that compared PUL to TURP.[21] Of note, the aquablation and PUL systems were made by single manufacturers without competitors.

Lastly, there were some gaps in the evidence. None of the studies reported on lifestyle changes, watchful waiting, or drug therapy as comparators. Recovery time was not specified as an outcome although length of hospitalization was included. Furthermore, none of the studies collected data in Canada. These limitations suggest that considerable caution must be taken in making inferences about the clinical effectiveness and safety of minimally invasive surgical treatment for BPH, specifically in relation to the Canadian context.

Conclusions and Implications for Decision or Policy Making

Four systematic reviews,[13-16] five RCTs,[17-21] and one retrospective non-randomized comparative study were included in this review.[22]

The systematic reviews were well-conducted and comprehensive, reporting on numerous outcome measures evaluating aquablation, prostatic artery embolization, prostatic urethral lift, and transurethral resection of the prostate. Treatment effect was assessed with

numerous outcomes ranging from symptom relief, quality of recovery, quality of life, and safety.

Overall, there were no statistically significant changes in symptom relief between aquablation and TURP at six[19] and 12 months,[17,20] except for men with prostates that were 50 mL or larger. In this sub-population, the difference in the change in maximum urinary flow from baseline to six months favoured aquablation over TURP.[18] Based on results from meta-analyses of five or fewer studies, the results comparing PAE to TURP were mixed with some outcomes suggesting that PAE proffered an advantage while others suggested that TURP was better.[13,14] Similarly changes in ejaculatory function at 12 months and quality of recovery at 12 and 24 months favoured PUL over TURP whereas, improvement in symptom relief at 12 months and 24 months favoured TURP over PUL.

Overall, safety outcomes favoured minimally invasive surgical techniques over TURP. Evidence from one RCT suggested that for up to six months, men who were treated with aquablation had a lower mean incidence of complications compared to those who had TURP. Evidence from two systematic reviews favoured both prostatic artery PAE and PUL over TURP up to 12 months after treatment.

Caution must be taken in interpreting the evidence presented in this report due to potential conflicts of interest due to sponsorship by the manufacturers of two of the minimally invasive surgical technologies, substantial overlap in study populations, and apparent patient selection bias. In addition to the uncertainty in the findings that is introduced by these biases, none of the data was collected in Canada, thereby precluding generalizability of the evidence to the Canadian context. While contemplating the lack of robust findings in the literature and the various limitations, decision-makers and policy makers may need to consider the impact of lack of training among surgeons in the use of the devices and the paucity of competition among manufacturers. Furthermore, the various minimally invasive techniques are based on vastly different technologies, making blinded comparisons challenging if not impossible. Additional research involving surgeons with comparable training, using approved technologies on unselected patients who are consecutively enrolled in a blinded fashion may help to produce evidence that will be useful in informing public health policies that are relevant to the Canadian population.

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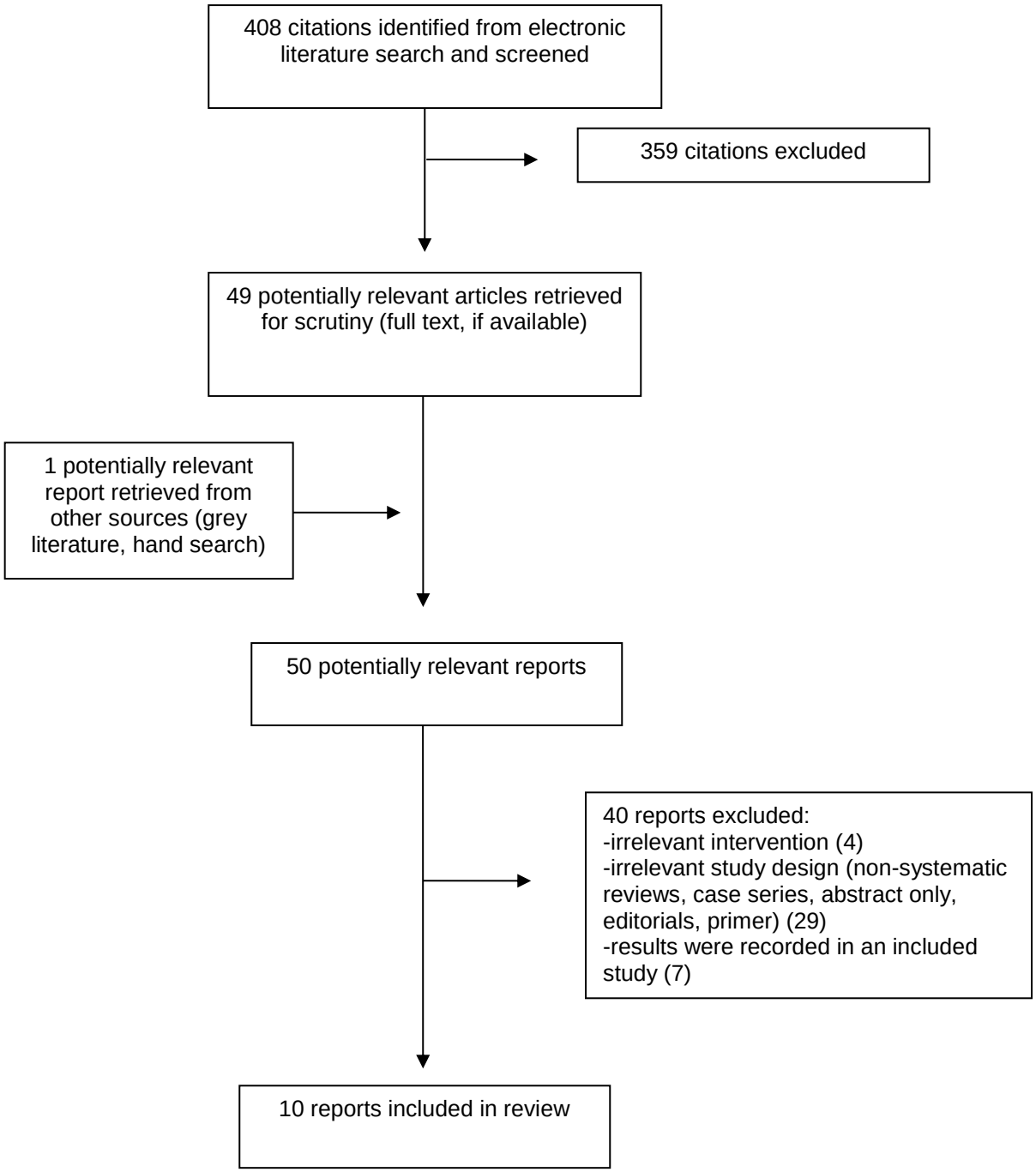
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
PAE vs. TURP				
Jiang and Qian, 2019[13,a] **China** The authors declared they had no conflicts of interest	A systematic review and meta-analysis of the clinical efficacy and safety of PAE versus TURP in treating BPH Included: 2 RCTs, 1 prospective comparative study, 1 retrospective comparative study; published between 2014 and 2018 Excluded: case reports, reviews, editorial comments, meeting abstracts and articles without applicable data; studies with insufficient data, and studies that were not comparative	506 patients with BPH	Intervention (n = 178): PAE Comparator (n = 328): TURP	Change in IPSS, QoL, Qmax, prostate volume Follow-up: > 12 months Operation times were reported but not included in this review
Zumstein et al., 2018[14,a] **Germany and Switzerland** The authors declared they had no conflicts of interest	A systematic review and meta-analysis of the clinical efficacy and safety of PAE versus TURP in treating BPH Included: 3 RCTs, 1 prospective propensity score matched-pair analysis, 1 retrospective, registry-based observational and propensity score matched-pair analysis; published between 2014 and 2018 Excluded: Non-comparative studies	708 patients with LUTS secondary to BPH	Intervention (n = 416): PAE Comparator (n = 292): TURP (n = 212) or open prostatectomy (n = 80)	Change in IPSS, IPSS-QoL, IIEF-5, Qmax, PVR, prostate volume; incidence of complications and adverse events Follow-up: 12 months[b] Change in prostate-specific antigen, operation time, and length of hospital stay were reported but not included in this review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
PUL vs. TURP				
Verze et al., 2019[15,c] **Germany and Italy** The authors declared they had no conflicts of interest	A systematic review of MISTs in treating LUTS in BPH Included: 15 RCTs including 1 RCT comparing PUL to TURP; Published between 1998 and 2018 Excluded: narrative reviews, case reports, case series, and preliminary results	79 men with LUTS secondary to BPH	Intervention (n = 44): PUL Comparator (n = 35): TURP	Change in IIEF and MSHQ-EjD scores; incidence of erectile dysfunction Follow-up: 12 months
Nunes et al., 2018[16,c] **Brasil** The authors declared they had no conflicts of interest	A systematic review of MISTs in treating LUTS in BPH Included: 15 studies including 1 RCT comparing PUL to TURP; publication date limits were not specified Excluded: narrative reviews, case reports, case series, and preliminary results	80 men with LUTS secondary to BPH	Intervention (n = 45): PUL Comparator (n = 35): TURP	Change in IPSS and Qmax; incidence of retrograde ejaculation or loss of ejaculation Follow-up: 12 months

BPH = benign prostatic hyperplasia or hypertrophy; IIEF = international index of erectile function; IPSS = international prostate symptoms score; ISI = Incontinence severity index; LUTS = lower urinary tract symptoms; MIST = minimally invasive surgical techniques; MSHQ-EjD = men's sexual health questionnaire for ejaculatory dysfunction; PAE = prostatic artery embolization or embolotherapy; PUL = prostatic urethral lift; PVR = post-void residual urine volume; Qmax = maximum urinary flow; QoL = quality of life; QoR = quality of recovery; RCT = randomized controlled trial; SHIM = sexual health inventory for men; TURP = transurethral resection of the prostate

[a] Included in three overlapping studies

[b] If unavailable at 12 months, the authors included outcomes at a time closest to 12 months

[c] Reported results from the same RCT

Table 3: Characteristics of the Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Aquablation vs. TURP				
Gilling et al., 2019[17,a] **Australia, New Zealand, United Kingdom, United States** The study and two authors were sponsored by the manufacturer of the aquablation system	The WATER study – a prospective double-blinded multicenter international RCT	184 men aged 45 to 80 years with prostate sizes 30-80 cc, moderate-to-severe LUTS as indicated by IPSS ≥ 12, and Qmax < 15 mL/s; enrolled between October 2015 and December 2016, included Mean age: 65.9 years Exclusion: a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence, PVR >300 mL or urinary retention, use of self-catheterization, prior prostate surgery, on anticoagulants or bladder anticholinergics, or with severe cardiovascular disease	Intervention: Aquablation (n = 115) Comparator: TURP with electrocautery (n = 61) Lost to follow-up: 8	Change in IPSS, IPSS-QoL, Qmax, and PVR; incidence of Clavien-Dindo persistent grade 1 or higher adverse events Follow-up: 6 months, 12 months Change in prostate-specific antigen at 12 months and outcomes that were measured at 1 and 3 months but not included in this review
Plante et al., 2019[18,a] **Australia, New Zealand, United Kingdom, United States**	The WATER study – a prospective double-blinded multicenter international RCT Subgroup analyses: baseline IPSS (< 20 vs.	184 men aged 45 to 80 years with prostate sizes 30-80 cc, moderate-to-severe LUTS as indicated by IPSS ≥ 12, and Qmax < 15 mL/s; enrolled between	Intervention: Aquablation (n = 116) Comparator: TURP with electrocautery (n = 65)	Change in IPSS, IPSS-QoL, Qmax, and PVR; incidence of Clavien-Dindo persistent grade 1 or higher adverse events Follow-up: 6 months

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
The study and all authors were sponsored by the manufacturer of the aquablation system	≥ 20), prostate size (< 50 vs ≥ 50 mL) and age (< 65 vs ≥ 65 years) Exploratory sub-group analyses: Qmax, presence of middle lobe and degree of middle lobe obstruction and bladder neck obstruction and PVR	October 2015 and December 2016, included Mean age: 65.9 years Exclusion: a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence,PVR >300 mL or urinary retention, use of self-catheterization, prior prostate surgery, on anticoagulants or bladder anticholinergics, or with severe cardiovascular disease	Withdrawals: 3 prior to treatment Lost to follow-up: Not reported	Results reported at 1 and 3 months were not included in this review
Gilling et al., 2018[19,a] **Australia, New Zealand, United Kingdom, United States** The study and five authors were sponsored by the manufacturer of the aquablation system	The WATER study – a prospective double-blinded multicenter international RCT	184 men aged 45 to 80 years with prostate sizes 30-80 cc, moderate-to-severe LUTS as indicated by IPSS ≥ 12, and Qmax < 15 mL/s; enrolled between October 2015 and December 2016, included Mean age: 65.9 years Exclusion: a history of prostate or bladder cancer, neurogenic	Intervention: Aquablation (n = 114) Comparator: TURP with electrocautery (n = 62) Withdrawals: 3 prior to treatment Lost to follow-up: 5 with undisclosed reasons	Change in IPSS, IPSS-QoL, Qmax, and PVR; incidence of Clavien-Dindo persistent grade 1 or grade 2 adverse events; worsening sexual function, serious device or procedure related adverse event Follow-up: 3 months, 6 months Secondary outcomes such as resection time, length of hospital stay, total operative time, and the reoperation or

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture, damaged external urinary sphincter, stress urinary incontinence, PVR >300 mL or urinary retention, use of self-catheterization, prior prostate surgery, on anticoagulants or bladder anticholinergics, or with severe cardiovascular disease		repeat intervention rate were reported but not included in this review
Kasivisvanathan and Hussain, 2018[20] **United States** The study was sponsored by the manufacturer of the aquablation system	The WATER study – a prospective double-blinded multicenter international RCT Sub-group analysis of data that was collected in the United States.	142 men aged 45 to 80 years with prostate sizes 30-80 cc, moderate-to-severe LUTS as indicated by IPSS10 ≥ 12, and Qmax < 15 mL/s; enrolled between October 2015 and December 2016, included Mean age: 65.9 years Exclusion: a history of prostate or bladder cancer, neurogenic bladder, bladder calculus or clinically significant bladder diverticulum, active infection, treatment for chronic prostatitis, diagnosis of urethral stricture, meatal stenosis or bladder neck contracture,	Intervention: Aquablation (n = 59) Comparator: TURP with electrocautery (n = 28) Withdrawals: 3 prior to treatment Lost to follow-up: 5 with undisclosed reasons Excluded without reason: 47	Change in IPSS, IPSS-QoL, Qmax, and PVR; incidence of Clavien-Dindo persistent grade 1 or higher adverse events Follow-up: 12 months

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		damaged external urinary sphincter, stress urinary incontinence, PVR > 300 mL or urinary retention, use of self-catheterization, prior prostate surgery, on anticoagulants or bladder anticholinergics, or with severe cardiovascular disease		
PAE vs. TURP				
Qiu et al., 2017[22,b] **China** The authors declared they had no conflicts of interest The study was sponsored by: Medical Guidance Program of Qingdao City (2015-WJZD002) and Qingdao Outstanding Health Professional Development Fund.	A retrospective comparison of the efficacy and safety of PAE versus TURP for treating BPH	17 men with severe LUTS secondary to BPH in whom medical treatment had failed and surgery was contraindicated and treated with PAE between February 2012 and March 2015; and a randomly selected sample of 40 men with no serious cardiovascular or cerebrovascular disease who underwent TURP in the same time frame Mean age: 75.53 ± 4.74 years, range: 68 to 87 years	Intervention: PAE (n = 17) Comparator: TURP (n = 40) Lost to follow-up: NR	Change in IPSS, QoL Qmax, and prostate volume Follow-up: 7 days, 6 months, 12 months Operation time, intraoperative complications, and non-comparative complication rates were reported in the study but not included in this review
PUL vs. TURP				
Gratzke et al., 2017[21] **Denmark, Germany, United Kingdom** Ten of twelve authors received funding from the manufacturer of the PUL system	The BPH6 trial – a prospective non-blinded, multicenter European RCT	80 men with LUTS attributed to BPH; aged ≥ 50 years, eligible for TURP, with IPSS > 12, Qmax ≤ 15 mL/s, prostate volume ≤ 60 cc, and ISI ≤ 4 (i.e., continent); enrolled between February 2012 and October 2013 Mean age: NR	Intervention: PUL (Urolift) (n = 37) Comparator: TURP according to site standards (n = 32) Lost to follow-up: 11 for undergoing another treatment (n = 8), removing the PUL implant removed (n = 1), discontinuing	Change in IPSS, BPHII, Qmax, and PVR; incidence of adverse events Patient perspectives, IPSS-QoL, and sleep outcomes were reported in the study but not included in this review

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			following epididymitis (n = 1), and protocol deviation (n = 1)	Follow-up: 24 months; outcomes were also measured at 2 weeks, 1 month, 3 months, 6 months, and 24 months but were not reported in the study

BPH = benign prostatic hyperplasia or hypertrophy; IPSS = international prostate symptoms score; ISI = Incontinence severity index; LUTS = lower urinary tract symptoms; PAE = prostatic artery embolization or embolotherapy; PUL = prostatic urethral lift; PVR = post-void residual urine volume; Qmax = maximum urinary flow; QoL = quality of life; RCT = randomized controlled trial; TURP = transurethral resection of the prostate; WATER = Waterjet Ablation Therapy for Endoscopic Resection of Prostate Tissue

[a] Overlapping authors

[b] Included in a systematic review[13] but reported outcomes differently

Appendix 3: Critical Appraisal of Included Publications

Table 4: Quality Assessment of the Systematic Reviews using AMSTAR 2[22]

Strengths	Limitations
Jiang et and Qian,2019[13]	
• The statement of objectives included the population, intervention, comparator, and outcomes of interest • The authors searched three databases, and outlined key words and a search strategy • The authors performed study selection, data extraction and quality assessment in duplicate • The study eligibility criteria included the population, intervention, study types, outcomes, and minimum length of follow-up • The authors critically assessed the quality of individual studies • The authors declared that they had no conflicts of interest	• An explicit statement that the review methods were established prior to the conduct of the review was not provided • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not describe the study settings, the population of interest and parameters of the intervention in detail • The authors did not critically assess the body of evidence of the outcomes • The sources of funding of the primary studies were not disclosed
Zumstein et al., 2018[14]	
• The statement of objectives included the population, and intervention of interest • The authors searched three databases, and outlined key words and a search strategy • The authors performed study selection, data extraction and quality assessment in duplicate • The study eligibility criteria included the intervention of interest • The authors critically assessed the quality of individual studies • The authors declared that they had no conflicts of interest	• The authors did not provide an explanation for their inclusion of specific study designs • Studies were included irrespective of comparators, outcomes and length of follow-up • The authors did not provide a list of excluded studies nor explicit exclusion criteria • The authors did not describe the population of interest, study settings, and parameters of the intervention in detail • The authors did not critically assess the body of evidence of the outcomes
Verze et al., 2019[15]	
• The statement of objectives included the population, intervention, and outcomes of interest • The authors searched three databases, an extensive list of key words and a search strategy • The authors performed study selection in duplicate • The study eligibility criteria included the population, study design, preferred data collection method, and outcomes • The authors critically assessed the quality of individual studies. Only studies with high level of evidence were included. • The authors declared that they had no conflicts of interest	• An explicit statement that the review methods were established prior to the conduct of the review was not provided • Details regarding the number of individuals who extracted data and conducted quality assessment were missing. • The authors did not provide an explanation for including only RCTs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors excluded studies that did not report on erectile or ejaculatory function • The authors did not place limits on the minimally invasive surgical techniques under evaluation • The authors did not describe the study settings, population of interest or parameters of the intervention in detail • The authors did not critically assess the body of evidence of the outcomes of interest • The sources of funding of the primary studies were not disclosed

Strengths	Limitations
Nunes et al., 2018[16]	
• The authors provided evidence that the review methods were established *a priori* • The statement of objectives included the population, interventions and outcomes of interest • The authors searched three databases, and outlined key words and a search strategy • The study eligibility criteria included the population, intervention, study design, outcomes, and minimum length of follow-up • The exclusion criteria referred to patient populations, interventions, comparators, outcomes, and study types • The authors critically assessed the quality of individual studies and the overall evidence for each outcome • The authors declared that they had no conflicts of interest	• The study selection, data extraction and quality assessment procedures were not described in detail • The authors did not provide an explanation for their inclusion of specific study designs • The authors did not provide a list of excluded studies nor justification for the exclusion criteria • The authors did not describe the population of interest, study settings and parameters of the interventions in detail • The sources of funding of the primary studies were not disclosed

Table 5: Quality Assessment of the Primary Studies using the Downs and Black checklist[11]

Criteria	Gilling et al., 2019[17]	Plante et al., 2019[18]	Gilling et al., 2018[19]	Kasivisvanathan and Hussain, 2018[20]	Qiu et al., 2017[22]	Gratzke et al., 2017[21]
Reporting						
1. Is the hypothesis/aim/objective of the study clearly described?	No	Yes	Yes	Yes	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	No	Yes	Yes	Yes	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
4. Are the interventions of interest clearly described?	No	No	Yes	No	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No	Yes	No	Yes	No	No
6. Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes

Criteria	Gilling et al., 2019[17]	Plante et al., 2019[18]	Gilling et al., 2018[19]	Kasivisvanathan and Hussain, 2018[20]	Qiu et al., 2017[22]	Gratzke et al., 2017[21]
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	No	No	No	No	Yes
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes	Yes	Yes	No	Yes
9. Have the characteristics of patients lost to follow-up been described?	No	No	No	No	Not applicable	No
10. Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	Yes	Yes	Yes	Yes	Yes
External validity						
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	No	No	No	No	No	No
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes	Yes	Yes	No	No	No
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
Internal validity - bias						
14. Was an attempt made to blind study subjects to the intervention they have received?	Yes	Yes	Yes	Yes	Not applicable	No

Criteria	Gilling et al., 2019[17]	Plante et al., 2019[18]	Gilling et al., 2018[19]	Kasivisvanathan and Hussain, 2018[20]	Qiu et al., 2017[22]	Gratzke et al., 2017[21]
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	Yes	Yes	Yes	No	No
16. If any of the results of the study were based on "data dredging", was this made clear?	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Not applicable	Not applicable	Not applicable	Not applicable	No	No
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
19. Was compliance with the intervention(s) reliable?	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Unable to determine
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes	Yes	Yes
Internal validity – confounding (selection bias)						
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	Yes	Yes	No	Yes
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes	Yes	Yes	Yes	Yes	Yes

Criteria	Gilling et al., 2019[17]	Plante et al., 2019[18]	Gilling et al., 2018[19]	Kasivisvanathan and Hussain, 2018[20]	Qiu et al., 2017[22]	Gratzke et al., 2017[21]
23. Were study subjects randomised to intervention groups?	Yes	Yes	Yes	Yes	No	Yes
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Unable to determine	Unable to determine	Unable to determine	Unable to determine	Not applicable	No
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Unable to determine	Yes	Unable to determine	Unable to determine	Unable to determine	Unable to determine
26. Were losses of patients to follow-up taken into account?	Yes	Yes	Yes	Yes	No applicable	No
Power						
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Unable to determine	Partially	No	Unable to determine	Not applicable	Partially

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of the Systematic Reviews

Main Study Findings	Authors' Conclusion
PAE vs. TURP	
Jiang and Qian, 2019[13]	
Clinical effectiveness **TURP (n = 55) vs. PAE (n = 32); 2 studies** • Post-operative IPSS WMD: 1.56 (CI: −0.67 to 3.78), I^2 = 88%; *P* = 0.17; trending in favour of PAE • Post-operative QoL WMD: −0.53 (CI: −0.88 to −0.18), I^2 = 67%; *P* < 0.05; in favour of TURP • Post-operative Qmax WMD (mL/s): 4.66 (CI: 2.54 to 6.79), I^2 = 96%, *P* < 0.05; in favour of PAE • Post-operative prostate volume WMD: -8.26 (CI: −12.64 to −3.88), I^2 = 76%, *P* < 0.05; in favour of TURP **Safety** **TURP (n = 142) vs. PAE (n = 270); 2 studies** • Incidence of complications OR: 1.54 (CI: 1.00 to 2.38), I^2 = 95%; *P* = 0.05; in favour of PAE	*"…PAE is an efficient and safe procedure that achieves better improvement in urodynamics and QoL. Our meta-analysis indicates that TURP is superior to PAE in clinical efficiency improvement. More multi-center high quality RCTs with large sample size are needed to verify the clinical efficiency of TURP and PAE for the treatment of BPH."* (p 7)
Zumstein et al., 2018[14]	
Clinical effectiveness **PAE (n = 314) vs. TURP and OP (n = 220); 5 studies** • Change in IPSS WMD: 3.80 (CI: 2.77 to 4.83), I^2 = 80%; *P* <0.00001; in favour of TURP and OP **PAE (n = 323) vs. TURP and OP (n = 225); 5 studies** • Change in QoL WMD: 0.73 (CI: 0.56 to 0.91), I^2 = 95%; *P* < 0.00001; in favour of TURP and OP **PAE (n = 275) vs. TURP and OP (n = 209); 5 studies** • Change in Qmax (mL/s) WMD: 3.62 (CI: 2.90 to 4.34), I^2 = 94%, *P* < 0.00001; in favour of TURP and OP **PAE (n = 314) vs. TURP and OP (n = 220); 5 studies** • Change in PVR (mL/s) WMD: 11.86 (CI: 1.89 to 21.83), I^2 = 58%, *P* = 0.02; in favour of TURP and OP **PAE (n = 282) vs. TURP (n = 119); 4 studies (no OP)** • Change in Prostate volume (mL/s) WMD: 11.51 (CI: 6.11 to 16.91), I^2 = 18%, *P* < 0.00001; in favour of TURP **PAE (n = 237) vs. TURP and OP (n = 161); 5 studies** • Change in IIEF-5 WMD: -2.56 (CI: -3.92 to -1.20), I^2 = 84%, *P* = 0.0002; in favour of PAE *Sub-group analysis (RCTs only)* **PAE (n = 117) vs. TURP (n = 119); 3 studies** • Change in IPSS WMD: 2.09 (CI: 0.61 to 3.56), I^2 = 80%; *P* = 0.005; in favour of TURP **PAE (n = 117) vs. TURP (n = 119); 3 studies** • Change in QoL WMD: 0.13 (CI: −0.10 to 0.37), I^2 = 82%; *P* =0.26; indicating no statistically significant difference	*"This systematic review shows that PAE might be a valuable alternative for the treatment of BPH-LUTS in a selected group of patients in whom the indication for surgery is primarily based on their symptoms... Further RCTs with longer follow-up periods are mandatory to evaluate the mid- and long-term efficacy and safety of PAE and to assess its ideal spectrum of indications, also compared to less invasive procedures... Therefore, PAE should still be applied within clinical trials at present"* (p 9)

Main Study Findings	Authors' Conclusion
PAE (n = 117) vs. TURP (n = 119); 3 studies • Post-operative Qmax WMD (mL/s): 2.23 (CI: 1.35 to 3.11), I^2 = 95%, *P* < 0.00001; in favour of TURP **PAE (n = 117) vs. TURP (n = 119); 3 studies** • Post-operative PVR (mL/s) WMD: 6.76 (CI: -15.43 to 28.94), I^2 = 78%, *P* = 0.55; indicating no statistically significant difference **PAE (n = 63) vs. TURP (n = 66); 2 studies** • Post-operative IIEF-5 WMD: 0.61 (CI: -1.74 to 2.97), I^2 = 79%, *P* = 0.61; indicating no statistically significant difference **Safety** **PAE (n = 396) vs. TURP AND OP (n = 260); 5 studies** • Incidence of complications: 31.1% vs. 63.8%; *P* < 0.001 • Incidence of Clavien-Dindo Grade ≥ 3: 2.5% vs. 6.2%; *P* = 0.2	
PUL vs. TURP	
Verze et al., 2019[15a]	
Clinical effectiveness @ 12 months **PUL (n = 32) vs. TURP (n = 27); 1 RCT** • Decrease in IIEF-5: 0.1 vs. 0.9; *P* = NR • Increase in MSHQ-EjD function: 1.3 vs. -3.7; *P* = NR • Decrease in MSHQ-EjD bother: 0.5 vs. 0; *P* = NR **Safety @ 12 months** **PUL (n = 44) vs. TURP (n = 35); 1 RCT** • Incidence of erectile dysfunction: 0% vs. 9% (3); *P* = NR • Incidence of retrograde ejaculation: 0% vs. 20%; *P* < 0.05 Results on Holmium Laser Ablation of the Prostate (HoLAP), Holmium Laser Enucleation of the Prostate (HoLEP), Laser vaporization, non-contact laser treatments, Photoselective Prostate Vaporization (PVP), Thermal treatment, Transurethral Microwave Thermotherapy (TUMT), Transurethral Vaporization of the Prostate (TUVP) were reported but were not included in this review	"*Available RCTs evaluating both erectile and ejaculatory function as study outcomes in LUTS/BPE patients undergoing prostate surgery demonstrate the lack of statistically significant variations in terms of erectile function in most cases, and an improvement after TURP in one single study. The effect on ejaculatory function varies depending on the surgical procedure adopted. Conventional TURP is associated in most cases with a significant deterioration of ejaculatory function. PUL can provide a statistically significant improvement of ejaculatory function..*" (p 8)
Nunes et al., 2018[16a]	
Clinical effectiveness @ 12 months **PUL (n = 45) vs. TURP (n = 35); 1 RCT** • Decrease in IPSS: 11.4 vs. 15.4; *P* = 0.05; trending in favour of TURP • Increase in Qmax (mL/s): 4.0 ± 4.8 vs. 13.7 ± 10.4; *P* = NR **Safety @ 12 months** • Incidence of retrograde ejaculation or loss of ejaculation: 0% vs. 40%; *P* < 0.0001; in favour of PUL	"*Long-term studies are needed to evaluate the duration of effect compared to other techniques.*" (p 878)

Main Study Findings	Authors' Conclusion
Results comparing quality of surgical recovery from PUL and TURP, results on transurethral thermotherapy with microwaves, transurethral prostatic ablation with needle, prostatic stents, and results comparing PUL to a sham procedure were reported in the study but not included in this review	

BPH = benign prostatic hyperplasia or hypertrophy; CI = 95% confidence interval; IIEF = international index of erectile function; IPSS = international prostate symptoms score; LUTS = lower urinary tract symptoms; MSHQ-EjD = men's sexual health questionnaire for ejaculatory dysfunction; NR = not reported; OP = open prostatectomy; PAE = prostatic artery embolization or embolotherapy; PUL = prostatic urethral lift; PVR = post-void residual urine volume; Qmax = maximum urinary flow; QoL = quality of life; RCT = randomized controlled trial; TURP = transurethral resection of the prostate; WMD = weighted mean difference

[a] Authors reported different sets of outcomes from the same study

Table 7: Summary of Findings of the Primary Studies

Main Study Findings	Authors' Conclusion
Aquablation vs. TURP	
Gilling et al., 2019[17]	
Aquablation (n = 115) vs. TURP (n = 61) **Clinical effectiveness @ 12 months** Decrease in IPSS: 15.1(7.0) vs. 15.1(8.3); *P* = 0.9898 Decrease in IPSS-QoL: 3.2(1.7) vs. 3.5(1.6); *P* = 0.3179 Increase in Qmax (cc/s): 10.3(11) vs. 10.6(11); *P* = 0.8632 Decrease in PVR (cc): 52(79) vs. 63(97); *P* = 0.4625 *Sub-group analysis (baseline PVR > 100 cc)* Decrease in PVR (cc): 107 vs. 114 **Safety @ 6 months or prior** Incidence of incontinence: 8 vs. 6; *P* = NR Incidence of sexual dysfunction: 0 vs. 1; *P* = 0.3591 Change in prostate-specific antigen at 12 months and outcomes that were measured at 1 and 3 months were reported but not included in this review	*"[This] study provides high-quality evidence demonstrating that Aquablation for LUTS due to BPH provides sustained (12-month) symptom-reduction efficacy with a low rate of late adverse events in men with prostates between 30 and 80 cc."* (p 73)
Plante et al., 2019[18]	
Aquablation (n = 116) vs. TURP (n = 65) **Clinical effectiveness @ 6 months** *Sub-group analysis* (prostate < 50 mL) Decrease in IPSS: *P* = 0.5500 *Sub-group analysis* (prostate ≥ 50 mL) Decrease in IPSS: *P* = 0.0197[a] *Sub-group analysis (baseline IPSS < 20)* Decrease in IPSS voiding and storage scores: *P* = 0.049 in favour of aquablation *Sub-group analysis (baseline IPSS ≥ 20)* Decrease in IPSS voiding and storage scores: *P* = 0.7100	*"…the prespecified subgroup analysis from a blinded randomized clinical trial showed that, in men with larger (>50 g) prostates, resection using aquablation provided higher symptom score reduction and a reduced rate of postoperative complications compared with TURP."* (p 660)

Main Study Findings	Authors' Conclusion
Sub-group analysis (age < 65 years) Decrease in IPSS voiding and storage scores: *P* = 0.225 *Sub-group analysis (age ≥ 65 years)* Decrease in IPSS voiding and storage scores: *P* = 0.3754 *Sub-group analysis (middle lobe)* Improvement in Qmax: *P* = 0.048 in favour of aquablation *Sub-group analysis (elevated PVR > 100 cc)* Improvement in PVR: *P* = NS Change in Qmax: *P* = NS **Safety @ 6 months** *Sub-group analysis* (prostate < 50 mL) Incidence of persistent grade 1 and grade 2 events: 33% vs. 37%; *P* = 0.448 Incidence of anejaculation: 21% vs 30%; *P* < 0.295 *Sub-group analysis* (prostate ≥ 50 mL) Incidence of persistent grade 1 and grade 2 events: 20% vs. 46%; *P* = 0.008 in favour of aquablation Incidence of anejaculation: 2% vs 41%; *P* < 0.001 *Sub-group analysis (baseline IPSS < 20)* Incidence of persistent grade 1 and grade 2 events: 17% vs. 39%; *P* = 0.049 in favour of aquablation Incidence of anejaculation: 7% vs 44%; *P* < 0.005 *Sub-group analysis (baseline IPSS ≥ 20)* Incidence of persistent grade 1 and grade 2 events: 30% vs. 43%; *P* = 0.112 Incidence of anejaculation: 12% vs 31%; *P* < 0.47 *Sub-group analysis (age < 65 years)* Incidence of persistent grade 1 and grade 2 events: 20% vs. 41%; *P* = 0.058 Incidence of anejaculation: 8% vs 33%; *P* < 0.016 *Sub-group analysis (age ≥ 65 years)* Incidence of persistent grade 1 and grade 2 events: 30% vs. 42%; *P* = 0.116 Incidence of anejaculation: 12% vs 38%; *P* < 0.022 Results on change in prostate-specific antigen and exploratory sub-group analyses are not presented here	
Gilling et al., 2018[19]	
Aquablation (n = 114) vs. TURP (n = 62); lost to follow-up 8 **Clinical effectiveness @ 6 months** Decrease in IPSS: 16.9 vs. 15.1; *P* = 0.1347 Decrease in IPSS-QoL score: 3.5 vs. 3.3; *P* = 0.4582 Increase in Qmax (mL/sec): 10.9 vs. 8.9; *P* = 0.10[b] Decrease in PVR (mL): 55 vs. 64; *P* = NS[b] *Sub-group analysis* (prostate > 50 mL)	*"These results suggest that Aquablation of the prostate may be an effective and safe approach to the surgical management of LUTS secondary to BPH…. Longer follow-up would help assess the clinical value of Aquablation."* (p 1260)

Main Study Findings	Authors' Conclusion
Decrease in IPSS: *P* = 0.0197[a]; in favour of aquablation **Safety @ 3 months** Increase in incontinence symptom score: 1.2 vs. 0.6 Change in MSHQ-EjD function: stable vs. worse; *P* = 0.0254 in favour of aquablation[c] Change in IIEF-5 score: stable vs. worse[c] Incidence of combined persistent grade 1 and grade 2: 26% vs. 42%; *P* = 0.0149 Persistent grade 1 events: 7% vs 25%; *P* = 0.0004 Grade 2 and higher events: 20% vs. 23%; *P* = 0.3038 Dysuria frequency: *P* = NS Dysuria severity: *P* = 0.1277 *Sub-group analysis* (prostate > 50 mL) Combined grade 1 and grade 2 events: 20% vs. 46%; *P* = 0.0111 Persistent grade 1 events: 2% vs 26%; *P* = 0.0003 Grade 2 and higher events: 19% vs. 29%; *P* = 0.3146 Anejaculation: 2% vs. 41%; *P* = 0.0001 **Safety @ 6 months** Primary safety endpoint, persistent grade 1 events, and grade 2 events remained consistent[d] Incidence of anejaculation: 10% vs. 36%; *P* = 0.0003 Incidence of anejaculation (without posttreatment cautery): 7% vs. 16%; *P* = 0.2616) Resection time, length of hospital stay, total operative time, reoperation or repeat intervention rate, pelvic pain, time off work, change in prostate-specific antigen were reported but not included in this review	
Kasivisvanathan and Hussain, 2018[20]	
Aquablation (n = 59) vs. TURP (n = 28) **Clinical effectiveness @ 12 months** Decrease in IPSS: 14.5 vs. 13.8; *P* = 0.7117 Decrease in IPSS-QoL: 3.1 vs. 3.4; *P* = 0.5760 Increase in Qmax (mL/s): 11 vs. 10; *P* = NS Decrease in PVR (mL): 54 vs. 39; *P* = NR **Safety @ 12 months** Incidence of combined persistent grade 1 and grade 2 and higher events: 20% vs. 47%; *P* = 0.0132 Incidence of Incidence of ejaculatory dysfunction: 6.7% vs. 30%; *P* = NS Incidence of incontinence: None Incidence of erectile dysfunction: None Incidence of grade 2 and higher events: 13% vs. 30%; *P* = NS Incidence of anejaculation: 9% vs. 45%; *P* = 0.0006	"*Aquablation is a reasonable alternative [to TURP] with good 1 year outcomes for men with prostates of between 30 cc-80 CC."* (p 9322)

Main Study Findings	Authors' Conclusion
Incidence of retreatment and change in prostate-specific antigen were reported but not included in this review	
PAE vs. TURP	
Qiu et al., 2017[22]	
PAE (n = 17) vs. TURP (n = 40) **Clinical effectiveness @ 12 months** Decrease in IPSS: 10.8 vs. 14.3; *P* = 0.021 Decrease in QoL: 2.0 vs. 2.4; *P* = 0.034 Increase in Qmax (mL/s): 12.3 vs. 14.9; *P* = 0.031 Decrease in prostate volume (mL): 22.6 vs. 35.8; *P* < 0.001 All changes favoured TURP **Clinical effectiveness @ 6 months** Decrease in IPSS: 11.8 vs. 16.2; *P* < 0.001 Decrease in QoL: 1.6 vs. 2.2; *P* = 0.032 Increase in Qmax (mL/s): 6.9 vs. 14.4; *P* < 0.001 Decrease in prostate volume (mL): 19.4 vs. 37.9; *P* < 0.001 All changes favoured TURP Safety outcomes for PAE that were reported after 7 days of treatment were not included in this review	*"The present clinical data showed that both super- selective PAE and TURP resulted in significant clinical improvements in the treatment of LUTS due to BPH. TURP showed superior clinical improvements at all follow-up time points compared with PAE."* (p 414)
PUL vs. TURP	
Gratze et al., 2017[21]	
PUL (n = 37) vs. TURP (n = 32) **Clinical effectiveness @ 24 months** Decrease in IPSS: 9.2 (9.2) vs. 15.3 (7.5); *P* = 0.004 in favour of TURP Decrease in BPHII: 4.1 (3.7) vs. 5.4 (3.3); *P* = -0.131 Increase in Qmax: 5.0 (5.5) vs. 15.8 (16.5); *P* = 0.002 in favour of TURP Decrease in PVR: 10.6 (56.7) vs. 42.5 (91.7); *P* = 0.091 Decrease in SHIM/IIEF-5: 0.2 (4.3) vs. 1.8 (4.9); *P* = 0.201 Increase in MSHQ-EjD function: 0.3 (3.4) vs. -4.0 (4.6); *P* < 0.01 in favour of PUL Decrease in MSHQ-EjD bother: 0.1 (2.2) vs. 0.3 (1.9); *P* = 0.771 Proportion of patients with QoR ≥ 70: 82% vs. 53%; *P* = 0.008 in favour of PUL **Safety @ 24 months** Incidence of erectile dysfunction: 2% vs. 6% Incidence of ejaculatory dysfunction: 0% vs. 34% Decrease in ISI score: Displayed in graphical format. Patients in the PUL arm were found to have stable average ISI scores, whereas patients in the TURP arm experienced a significant decrease in continence at 2 weeks and 3 months	"*…both the PUL and TURP procedures offered significant improvement in symptoms, Qmax and HRQoL. Erectile function was preserved in both arms, whereas ejaculatory function was superior for PUL compared with TURP. TURP has been found to significantly compromise continence function at 2 weeks and 3 months, whereas average continence scores among patients in the PUL arm were stable.*" (p 774)

Main Study Findings	Authors' Conclusion
Patient perspectives, sleep outcomes and incidence of retreatment were reported in the study but not included in this review	

BPH = benign prostatic hyperplasia or hypertrophy; CI = 95% confidence interval; HR = health-related; IIEF = international index of erectile function; IPSS = international prostate symptoms score; ISI = Incontinence severity index; LUTS = lower urinary tract symptoms; MSHQ-EjD = men's sexual health questionnaire for ejaculatory dysfunction; NR = not reported; PAE = prostatic artery embolization or embolotherapy; PUL = prostatic urethral lift; PVR = post-void residual urine volume; Qmax = maximum urinary flow; QoL = quality of life; RCT = randomized controlled trial; SHIM = sexual health inventory for men; TURP = transurethral resection of the prostate

[a] Reported in multiple studies

[b] Confidence intervals were reported for each group but not between groups

[c] Values were reported in graphical format and not in text

[d] Values were not reported in the article

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation			
	Jiang and Qian, 2019[13]	Zumstein et al., 2018[14]	Nunes et al., 2018[16]	Verze et al., 2019[15]
Abt et al. (2018)		X		
Carnevale et al. (2016)	X	X		
Gao et al. (2014)	X	X		
Sønksen et al. (2015)			X[a]	X[a]
Qiu et al. (2017)	X[b]			
Ray et al. (2018)	X	X		
Russo et al. (2015)		X		

[a] The RCT by Sønksen et al. (2015) reported on the same population of men as on of the RCTs[21] included in this review

[b] Jiang and Qian (2019) included data from Qiu et al. (2017)

Appendix 6: Additional References of Potential Interest

CADTH Reports

Prostatic Artery Embolization for Benign Prostatic Hyperplasia. *CADTH Health Technology Update.* 2018: https://cadth.ca/sites/default/files/pdf/Health_Technology_Update_Issue_20.pdf. Accessed 2019 Aug 23