The Philippine Urological Association Clinical Practice Guidelines on Lower Urinary Tract Symptoms in Men

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Standard: A guideline statement is a standard if: 1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and 2) there is virtual unanimity about which intervention is preferred.

Recommendation: A guideline statement is a recommendation if: 1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and 2) an appreciable but not unanimous majority agrees on which intervention is preferred.

Option: A guideline statement is an option if: 1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or 2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

1. In men with LUTS, does performing URINALYSIS affect treatment outcome?

Standard:
Examination of the urine (by dipstick or by urine microscopy) must be used in the assessment of men with LUTS.

A midstream urine sample is the usual method of collection for urinalysis. It must be stressed however to collect urine sample as sterile as possible. A catheterized sample may also be used. An office dipstick test maybe useful if available as a screening test, however, abnormal findings in a dipstick examination needs confirmation from a midstream urine or it may indicate examination of the urinary sediment and culture.

Evidence:
Guidelines considered:
NICE: Level 4
EAU: Level 3
AUA: Level 3

Recommendations from NICE were mainly based on expert opinion. One low quality study was found in an indirect population. The study reported the accuracy of erythrocytes sediment detection from urinalysis, which is only one component of a urine dipstick test.

Recommendations from EAU were based from Guidelines for the diagnosis of benign prostatic hyperplasia: a comparative, international overview by Roehrborn published 2001, and from Abrams et al on the Evaluation and treatment of lower urinary tract symptoms in older men, and the European guidelines.

Recommendations from AUA were also based from the publication of Abrams et al. a publication of the 2005 International Consultation of Urologic Diseases and reiterated in 2009. The diagnostic guidelines were formulated after series

Table 1. Clinical evidence studies for urinalysis (NICE guidelines)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Bladder Cancer[85]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Urinary tract infection[85]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Urinary calculi (stones)[85]	1	Cross-sectional study	Serious limitations (a)	No serious inconsistency	Serious indirectness (b)	No serious imprecision
Diabetes	0					
Renal Disease	0					

(a) It was not reported whether investigators and patients were masked to the results of the earlier tests.
(b) This study analysed erythrocyte sediment following a positive urine dipstick result.
The study population was outpatients from a urology department (secondary care setting) rather than a primary care setting where this test would be used in practice.

Outcome	Prevalence (%)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Likelihood Ratio (+ve)	Likelihood Ratio (-ve)	Quality
Bladder tumours	0.4	66.7	68.9	99.8	0.9	2.15	0.48	Low
Urinary tract infection	2.3	58.8	69.4	98.6	4.3	1.92	0.59	Low
Urinary calculi (stones)	6.5	28.6	68.6	93.2	6.0	0.91	1.04	Low

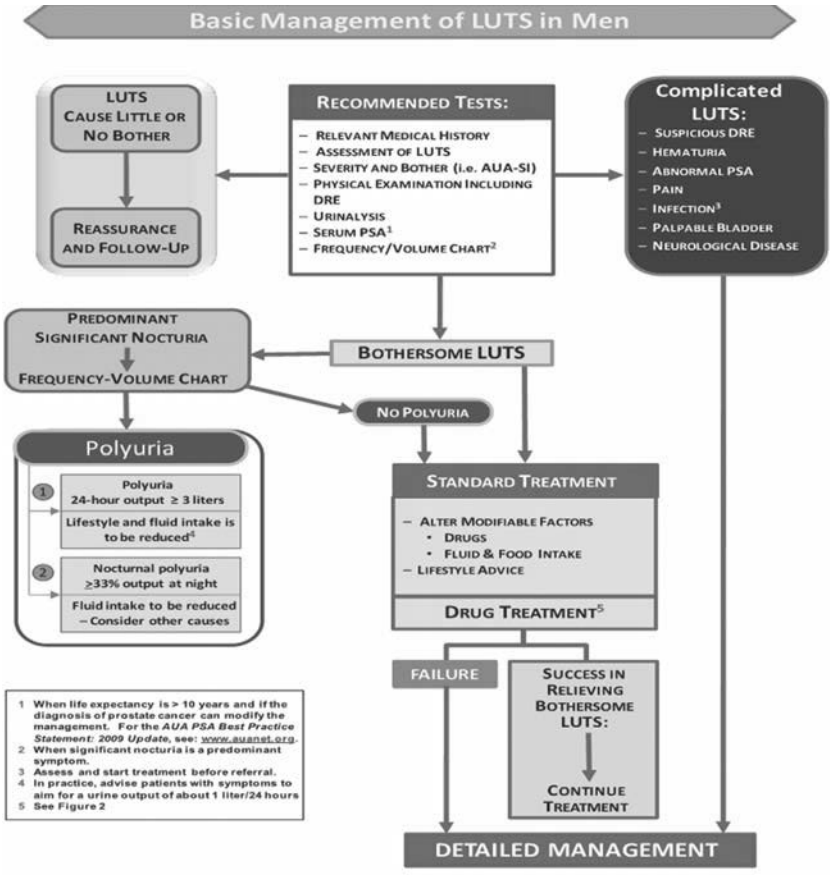

Figure 1. Flow chart for basic management of LUTS in men as adapted from Abrams (from AUA guidelines)

of committees performed a thorough review of the available literature and consolidated a global subjective opinion of recognized experts serving on focused committees.

Equity/Implementation issue(s):

Cost of urinalysis may be a limitation for the indigent patients.

The use of office urine dipstick test though more cost effective is not in routine practice in out patient clinics.

For significant urine dipstick results, additional work ups may be warranted such as formal urinalysis and culture.

2. In men with LUTS, does performing IPSS / other structured symptom questionnaire affect treatment outcome?

Standard:

The elements of the IPSS questionnaire should be incorporated in the history taking for men with LUTS at the initial assessment.

Symptom scoring using the validated Tagalog IPSS questionnaire should be done for men with LUTS who are considering treatment.

A validated Tagalog version of a symptom score questionnaire with QoL question(s) should be used for the routine assessment of male patients with LUTS and should be repeated for re-evaluation of LUTS during treatment.

Symptom score questionnaires are used to evaluate male LUTS, these have become a standard as part of the assessment of male LUTS. All three guidelines, which were considered in this guideline recommends the use of validated symptom score questionnaires.

Several questionnaires are available, the American Urological Association Symptom Index (AUA-SI), Quality of Life (QoL) question, Benign prostatic hyperplasia (BPH) Impact Index (BII), Danish Prostate Symptom Score (DAN-PSS), International Consultation on Incontinence Questionnaire (ICIQ-MLUTS), International Prostate Symptom Score (IPSS) are validated, quantitative assessment tools to evaluate symptoms and bother (QoL question). The use of symptom questionnaire is recommended to grade the severity of LUTS and to understand the degree of bother caused by those symptoms. These questionnaires may be used as an initial assessment tool and as a guide in monitoring as a response to therapy. It is may also identify the type of symptom, whether storage or voiding symptom.

In our setting, the IPSS is the most widely used assessment tool. ***The International Prostate Symptom Score (IPSS)*** is an 8 question (7 symptom questions + 1 quality of life question) written screening tool designed to be completed by the patient. It is used to screen for, rapidly diagnose, track the symptoms of, and suggest a plan for management of the symptoms of benign prostatic hyperplasia (BPH). The seven symptom questions assess (referring to the patient's previous month) a feeling of incomplete bladder emptying, weak stream, intermittency, and straining ***(voiding symptoms)***, as well as frequency, urgency and nocturia ***(storage symptoms)***. Response options range from 0-5 (not at all or almost always), with a maximum total of 35 points. Severity score is classified as Mild (0-7), Moderate (8-19), Severe symptoms (20-35).

A limitation of the IPSS is lack of assessment of urinary incontinence and post micturition symptoms. In our setting, the IPSS is the most widely used assessment tool. Currently, two validated questionnaires in Tagalog are available but both have not been widely used for treatment response monitoring.

Evidence:

Guidelines considered:

NICE: Level 4
EAU: Level 3
AUA: Level 3

The use of IPSS / other structured symptom questionnaire is recommended by AUA, NICE, and EAU. Nice recommendation was based on a panel expert opinion. Recommendation from

EAU was based on limited evidence, yet there is general expert consensus that the benefits outweigh the costs. Basis for recommendation by AUA was based from a publication of Abrams, et al. 2009 (Figure 1.).

Equity issue/Implementation issue(s):

The use of questionnaire maybe time consuming, the panel recommends incorporating the questionnaire during history taking.

Validated Tagalog version of the IPPS should be launched and enforced among institutions.

3. In men with LUTS, does performing PSA determination affect treatment outcome?

Standard:

Information and advice regarding PSA assessment should be given to men with LUTS. The patient must be given time to decide if he wishes PSA to be done.

Recommendation:

PSA determination should be done only if a diagnosis of prostate cancer will change the management or if PSA can assist in decision-making in patients at risk of disease progression of BPE.

Prostate specific antigen (PSA) is a kallikrein-like serine protease produced by ductal epithelium of the prostate gland, and is measured in nanograms of PSA per millilitre (ng/mL) of blood. It is part of the seminal fluid and it liquefies the seminal coagulum and frees any entrapped spermatozoa. It is normal for men to have a low level of PSA in their blood, PSA is not considered as being disease-specific, but organ-specific in such, that prostate cancer or benign conditions (such as in chronic prostatitis, BPH, urinary infections, retention and catheterisation) can increase a man's PSA level.

PSA may be used as an alternative way of estimating prostate size, particularly useful for prostate size that is greater or less than a threshold volume. In a study by Roehnborn in 1999, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL have been found to be at PSA levels >1.6 ng/mL at 50s; >2.0 ng/mL at 60s; and >2.3 ng/mL for men aged 70 plus, achieving a specificity of 70% while maintaining a sensitivity between 65% and 70%, (Roehrborn, Boyle et al. 1999). Bohnen, Groenveld, et al in 2007 also had similar results, it was found that a PSA threshold value of 1.5 ng/mL could best predict a prostate volume of >30 mL, with a positive predictive value (PPV) of 78%. (AUA, EAU)

The use of PSA to diagnose prostate cancer should be explained to the patient due to possibilities of false-positive and false-negative results, complications of subsequent TRUS-guided biopsy, and false-negative biopsies.

Evidence:

Guidelines considered:

NICE: Level 4
EAU: Level 1b
AUA: Level 3

NICE recommendations were based on data suggesting that PSA has prognostic value in predicting symptom progression. However on their review, data were inconsistent.

Recommendations from EAU were based from studies such as the PLESS study which showed that PSA also predicted the changes in symptoms, QoL/bother, and Qmax. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression. More importantly, in the placebo arms of large double-blind controlled studies, baseline serum PSA level consistently predicted the risk of acute urinary retention (AUR) and BPE-related surgery. The relationship between baseline serum PSA and the risk for BPH-related outcomes was also confirmed by the Olmsted County Study.

Recommendations from AUA was based from was based from a publication of Abrams, et al. 2009 (Figure 1).

Equity issue/Implementation issue(s):

It is important to explain the test to the patient for him to make an informed decision in performing the test.

4. In men with LUTS, does performing a FREQUENCY-VOLUME CHART affect treatment outcome?

Recommendation:
At initial assessment, men with bothersome storage LUTS or nocturia should be asked to complete a frequency-volume chart (at least 3 days)

Micturition frequency volume charts (FVC) or bladder diaries or time and amount voiding charts, should be used to evaluate LUTS with a prominent storage component such as frequency, nocturia, and incontinence. Frequency volume chart (FVC) is the recording of the volume and time of each void by the patient done for the duration of at least 3-5 days. The duration of observation during FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance, this in accordance to several studies and from a systematic review published in 2007.

International Continence Society (ICS) have defined different FVCs:

Micturition Time Chart - records only the times that voids occur with no volumetric data.

Frequency/Volume Chart (FVC) - records the time and volume of each micturition.

Bladder Diary - records the time and volume of each micturition and may also include other data such as incontinence episodes, pad usage, fluid intake and urgency.

Evidence:
Guidelines considered:
NICE: Level 4
EAU: Level 2b
AUA: Level 3

NICE recommendations were based on the consensus opinion of the panel.

EAU recommendations were based on systematic review of the reliability of frequency-volume charts in urological research by Yap, et al. BJU Int 2007 and from several studies on FVCs. Recommendations from AUA were based from a publication of Abrams, et al. 2009 (Figure 1.)

Equity issue/Implementation issue(s):
Implementation issues with regards to illiterate patients who maybe unable to comply with instructions on recording voids.

5. In men with LUTS, does performing a UROFLOWMETRY affect treatment outcome, specifically in predicting bladder outlet obstruction?

Standard:
Uroflowmetry should NOT be done routinely at initial assessment of men with LUTS

Option:
Uroflowmetry, with postvoid residual determination may be offered for the assessment of men with LUTS

Urinary flowrate measurement is an optional noninvasive test that measures rate of flow of voided urine using a flowmeter, a device that measures the quantity of fluid voided (measured as volume or mass) per unit time. Post void residual may also be measured in conjunction to uroflowmetry.

Uroflowmetry is useful in the assessment of voiding function for a wide range of urological conditions. The observed flow pattern should be assessed, as well as any absolute values obtained. The results must always be interpreted within the context of the clinical situation, recognising the limitations of the study.

Uroflow is performed by instructing the patient to void a representative void in a uroflowmeter. A flow rate based upon a voided volume of under 150 ml is insufficient for reliable interpretation.

Men under 40 years of age generally have maximum flow rates over 25 ml/s. Flow rates decrease with age and men over 60 years of age with no urinary obstruction usually have maximum flow rates over 15 ml/s. Peak urinary flow or the Qmax is the best single measure to predict probability of obstruction.

Evidence:
Guidelines considered:
NICE: Level 2
EAU: Level 2b
AUA: Level 3

NICE guideline recommends uroflowmetry at specialized assessment especially when considering treatment. NICE considered several cross-sectional studies comparing sensitivity and specificity of accuracy of Qmax in predicting bladder outlet obstruction. However the studies had serious limitations, inconsistencies, indirectness and imprecisions. According to the studies, the range of sensitivities are higher for increasing values of Qmax, but the range of specificities are lower for corresponding values of Qmax. The range of values (47% - 99%) for sensitivity, indicate that the urinary flow rate has variable diagnostic worth in detecting true cases of obstruction, and the range of values (31% - 87%) for specificity show that the urinary flow rate has variable diagnostic worth in detecting true cases of no obstruction.

EAU guideline recommendations where based on studies on uroflowmetry variables, curve flows and association with LUTS and BPH. Based on the Reynard JM, et al. The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction; the diagnostic accuracy of uroflowmetry for detecting BOO varies considerably, and is substantially influenced by diagnostic threshold values. A threshold value of Qmax of 10 mL/s had a specificity of 70%, a positive predictive value (PPV) of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Qmax of 15 mL/s was 38%, the PPV 67% and the sensitivity 82%. Therefore, uroflowmetry alone is not suitable for the detection and quantification of BOO.

Recommendations from AUA were based from a publication of Abrams, et al. 2009 (Figure 1).

Equity issue/Implementation issue(s):
Implementation issues with problem on availability of equipment.

6. In men with LUTS, does performing a POSTVOID RESIDUAL VOLUME (PVR) DETERMINATION affect treatment outcome, specifically in predicting bladder outlet obstruction?

Standard:
Measurement of the postvoid residual urine should be considered in the initial assessment of men with LUTS, and particularly when considering treatment.

PVR is useful as a measure for changes over time especially with treatment. It also may allow for identification of patients at risk of AUR. However, PVR is not necessarily associated with obstruction, since high PVR volumes can be both a consequence of obstruction and/or poor detrusor function (detrusor underactivity).

Methods for measurement of postvoid residual (PVR) include the use of portable ultrasound devices/bladder scans or a diagnostic quality ultrasound, both of which can be used to scan and calculate the volume of urine in the bladder, either in patients in retention or post-void residual. However portable scans are less accurate than bladder volume measurements made by a trained sonographer or radiologist. Other ways of measuring residuals is through catheterisation, though more accurate this is a more invasive procedure.

Evidence:
Guidelines considered:
NICE: Level 3
EAU: Level 3
AUA: Level 3

NICE recommendation was based on a single study on diagnostic accuracy for obstruction in PVR >50 ml. The value for sensitivity shows that post void residual volume measurement has little value in detecting true positive cases of obstruction since elevation of PVR may be due to poor detrusor function (or underactivity) as well as obstruction.

According to EAU, at volumes of 50 mL, the diagnostic accuracy of PVR measurement has

been shown to have a positive predictive value of 63% and a negative predictive value of 52% to determine bladder outflow obstruction. A larger PVR volume may indicate bladder dysfunction and may predict a poor response to treatment. It was mentioned in both the MTOPS and ALTESS studies, that high baseline PVR has an increased risk of symptom deterioration.

Recommendations from AUA were based from a publication of Abrams, et al. 2009 (Figure 1).

Equity issue/Implementation issue(s):

Implementation issues with problem on availability of equipment and cost effectiveness.

7. In men with LUTS, does performing a MULTICHANNEL CYSTOMETRY affect treatment outcome?

Recommendation:

The performance of a multichannel cystometry / pressure flow study may be offered in men with LUTS if they are considering surgical treatment, in the following case scenarios:

- those who cannot void with a volume > 150ml
- those with a PVR > 300 ml
- those < 50 years of age
- those > 80 years of age

The general objective of urodynamics is to explore the functional mechanisms of LUTS and to identify potential risk factors for adverse outcome. Multichannel cystometry allows the best assessment for bladder outlet obstruction via simultaneous measurement of bladder pressure and flow rate. It also provides information regarding the function and behavior of the lower urinary tract during both the storage and voiding phases of the bladder cycle. Compliance, sensations, and capacity of the bladder are also evaluated in a multichannel cystometry.

Multichannel cystometry is an invasive procedure, so risks-benefit of the procedure should be explained to the patient. It should be offered in situations where the diagnosis of BPO is uncertain and there is the significant possibility that pathophysiology includes additional problems, such as detrusor overactivity during the storage phase or detrusor underactivity during the voiding phase. It should be emphasized that patients with neurological disease including those with previous pelvic surgery should be assessed using the multichannel cystometry. Other factions with LUTS that should be offered with this examination are men >80 years and men <50 years and those with bothersome predominantly voiding LUTS with a Qmax of >10ml/sec.

Evidence:
Guidelines considered:
NICE: Level 4
EAU: Level 3
AUA: none

NICE recommendation was based on a panel expert opinion. Unpublished Cochrane review on UDS for LUTS showed no significant improvement in treatment outcomes among patient who underwent the test but with a higher rate of change in management plans from surgical to medical. Recommendations from the EAU were from nonrandomized studies and based on the work panel expert opinion.

Equity issue/Implementation issue(s):

Limited access to quipment and lack on expertise on performing and interpreting results.

8. In men with LUTS, does performing CYSTOSCOPY affect treatment outcome?

Standard:
Do NOT offer cystoscopy routinely to men with uncomplicated LUTS. Offer only when clinically indicated.

Recommendation:
Urethrocystoscopy should be performed in men with LUTS to exclude suspected bladder or urethral pathology and/or prior to minimally invasive / surgical therapy. This should be done within the same operative instance as the planned surgical treatment if

office cystoscopy cannot be performed, and not as a separate procedure.

The lower urinary tract is easily accessible to endoscopic assessment. Patients presenting with LUTS with concomitant history of gross hematuria or previous diagnosis of bladder cancer, risk factors for urethral strictures such as urethral trauma, instrumentation, previous infection and surgery should undergo urethrocystosocopy for evaluation.

Flexible and rigid cystoscopies are available for use. Flexible cystoscopies require topical urethral local anesthesia. Rigid cystoscopy, requiring local or regional anesthesia, is still indicated when the view is likely to be poor or biopsies are required.

Evidence:
Guidelines considered:
NICE: Level 4
EAU: Level 3
AUA: none

NICE recommendation was based on a panel expert opinion. EAU recommendations were based on nonrandomized studies correlating urethrocystoscopic findings with urodynamic studies. Correlation between the degree of bladder trabeculation and the pre-operative Qmax were studied. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS. The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and urethral occlusion) and urodynamic indices, detrusor overactivity and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation

Equity issue/Implementation issue(s):
There are significant costs and discomfort associated with cystoscopy, so only in the presence of indications is it warranted and is recommended to peform it in a setting where there is a planned surgical treatment.

9. In men with LUTS how do performing imaging (transabdominal ultrasound, intravenous urogram or plain abdominal x-ray) affect patient outcomes versus not performing the diagnostic test?

Standard:
Performance of imaging studies should NOT be done routinely as part of the assessment of men with LUTS.

Standard:
Offer imaging studies only when clinically indicated.

Recommendation:
The appropriate imaging studies may be offered in the following indications :

a. Imaging of the upper tracts for:
   i. History of chronic retention
   ii. Hematuria
   iii. Recurrent infection
   iv. Sterile pyuria
   v. Profound symtoms
   vi. Pain

b. Imaging of the prostate :
   i. When considering medical treatment of LUTS and imaging of the prostate will assist the selection of the appropriate drug
   ii. When considering surgical treatment of the prostate

Imaging studies are not a routine part for evaluation of men with LUTS. Imaging of the prostate maybe included during ultrasonography for determination of residual urine. Prostate size, protrusion of the prostate into the bladder, bladder and prostate configuration maybe visualized in ultrasonography for measurement of residual urine; however these are not done as routine. Only in selected patients is imaging of prostate and urinary tracts indicated. Prostate imaging may be indicated for determining treatment options such in choosing medications, for hormonal therapy, surgical options (trans urethral incision/resection of the prostate/open surgical options) based on anatomical characteristics of the prostate. Methods for prostate imaging include transrectal,

transabdominal, CT and MRI. TRUS is superior to suprapubic (transabdominal) volume measurement as all three distances can be measured much more accurately by the transrectal approach. MRI may accurately estimate prostatic zonal volume however according to one study MRI could overestimate prostate volume compared to TRUS prostate volume.

Imaging of the upper urinary tracts maybe done with ultrasonography, CT scan, intravenous urography, but is not offered as a routine diagnostic evaluation for men with LUTS, especially with some risk for radiation exposure for the first two. Indications for imaging include patients with history of chronic urinary retention, hematuria, recurrent urinary tract infection (UTI), microscopic findings of pyuria in sterile urine, patients with profound voiding symptoms and pain. Imaging may be indicated for those with renal insufficiency and with history urolithiasis.

Guidelines considered:
NICE: Level 4
EAU: Level 3
AUA: 3

NICE recommendation was based on a panel expert opinion. EAU recommendations were based on nonrandomized studies on diagnostic evaluation of patients with LUTS. Recommendations from AUA were based from a publication of Abrams, et al. 2009 (Figure 1).

Equity issue/Implementation issue(s):

There are significant costs with use of different imaging so cost effectiveness as a diagnostic tool should be practiced and only when indications are present.

10. In men with LUTS how does measuring renal function affect patient outcomes versus not performing the diagnostic test?

Standard:
Routine creatinine determination should NOT be performed.

Recommendation:
Measurement of renal function may be done at the initial assessment of LUTS only if renal impairment is suspected.

Renal function may be assessed using serum creatinine levels or by computing for the estimated glomerular filtration rate (eGFR). Other biochemical byproduct that can be used to measure renal filtration and function is serum urea. Serum urea concentration is less reliable, being affected by hydration, dietary protein intake and tubular reabsorption of urea. Creatinine is more reliable however alterations in serum creatinine will not be seen until at least 50% of the renal function has been lost. Measurement of renal function should be based on history and clinical examination or in the presence of hydronephrosis or when considering surgical treatment for male LUTS.

Guidelines considered:
NICE: Level 4
EAU: Level 3
AUA: none

NICE recommendations were based on the lack of clinical studies to recommend routine creatinine determination to patient with LUTS.

EAU recommendations were based on studies on patients with LUTS, patients with non-neurogenic voiding dysfunction and renal insufficiency or an increase in creatinine. One of the studies by Gerber et al evaluated 246 men presenting with LUTS and found that approximately one in 10 (11%) had renal insufficiency. It was also shown that neither the symptom score nor the QoL assessment was associated with the serum creatinine concentration. They identified the most probable causes of renal dysfunction in these patients were diabetes mellitus and hypertension. In another study by Comiter et al on patients with voiding dysfunction of a non-neurogenic etiology, elevated creatinine levels did not appear to be a risk factor. Also in the MTOPS study, < 1% of men with LUTS presented with renal insufficiency.

Equity issue/Implementation issue(s):

There are costs associated with this test which does not add any important information except in the case of clinically suspected renal impairment

11. How does baseline PSA predict symptom progression?

Standard:
PSA should NOT be used as a sole predictor of symptom progression.

Note : This is in the light of inconsistent data on PSA's prognostic value in published literature, and the absence of PSA's diagnostic utility among Filipinos.

PSA has been identified as a useful marker for risk of progression of LUTS possibly leading to surgical therapy. PSA may be used to advice risk of progression however should not be the sole determinant for an active intervention.

Data suggesting that PSA has prognostic value in predicting symptom progression were inconsistent.

Guidelines considered:
NICE: Studies were Inconsistent
EAU: Level 1b
AUA: none

NICE guidelines cited several studies with regard to the use of PSA and disease progression, these studies however were inconsistent.

Table 2. PSA summary of findings.

Study	Study design	Population	Intervention & comparison	Analysis	Outcome
Crawford 2006, [57] *analysing data from* **McConnell** 2003[189,191]	Longitudinal follow up of the placebo arm of an RCT with 4 years follow up	Men with BPH and moderate to severe symptom (AUASS) mean 17 (range of 8-20). The average age was 62 years. (N=737)	None (placebo arm)	Patients in the placebo arm of the trial were divided into high (≥1.6ng/ml) vs. low (<1.6ng/ml) PSA at the median baseline level. Overall BPH progression was defined as the first occurrence of an increase of at least 4 points in the AUASS, AUR, urinary incontinence or renal insufficiency or recurrent urinary tract infection.	Baseline PSA level was associated with symptom progression. At 4 years, the cumulative probability and incidence rate of overall BPH progression was significantly higher in the baseline high PSA group (p<0.001). Incidence rate of ≥ 4 points increase in AUASS was significantly higher in the high PSA group (4.5 vs. 2.8 events/100 person year). The incidence rate of acute urinary retention and invasive therapy was also significantly higher in the group with higher baseline PSA.
Carter 2005[46]	Longitudinal cohort study.	Healthy men less than 70 years (N=704).	None	Regression analysis (mixed effect Poisson model) for change in PSA percentile group and symptom score (IPSS score) with time.	No correlation (analysis not shown).
O'Leary 2003[229]	Analysis from 3 RCTs with a 2 year follow up.	Men with BPH (N=4335), moderate to severe symptoms.	Dutasteride vs. placebo	Logistic regression model to identify predictors for men most likely to be bothered at the end of the study.	PSA at baseline was not one of the factors which predicted bother (as measured by item 3 of BII - Benign Prostatic Hyperplasia Impact Index).
Roehrborn 1999[256]	RCT with follow up of 4 years.	Men with clinical BPH, moderate to severe symptoms (N=3040)	Finasteride vs. placebo	Mean change in quasi-AUA symptom score over time. Analysis of variance within PSA tertiles and between treatment group.	Baseline PSA predicts deterioration of symptoms in untreated patients. Baseline PSA predicts improvement of symptoms for those patients treated with finasteride relative to placebo Baseline PSA does not predict improvement of symptoms in the finasteride treatment group alone.
Roehrborn 2006[255]	RCT	Men at risk of progression events from LUTS/BPH (N=1522)	Alfuzosin vs. placebo	Analysis of baseline PSA as predictor of IPSS using logistic regression expressed as hazard ratios.	PSA levels were not found to be a significant predictor of IPSS worsening in the intervention or placebo arm

According to the EAU, PSA maybe a significant predictor of symptom progression. It, mentioned the PLESS study, which showed that PSA also predicted the changes in symptoms, QoL/bother, and Qmax. In large double-blind controlled studies, baseline serum PSA level consistently predicted the risk of acute urinary retention (AUR) and BPE-related surgery. The relationship between baseline serum PSA and the risk for BPH-related outcomes was also confirmed by the Olmsted County Study. It was found that the risk for treatment for LUTS and BPH in men with a baseline PSA of 1.4 ng/mL or greater was significantly higher.

In a study by Laniado, et al. on Serum prostate-specific antigen to predict the presence of bladder outlet obstruction in men with urinary symptoms of 302 men with moderate LUTS, it was found that PSA is significantly associated with BPO with significant likelihood ratios altering the probability of BPO. If the PSA is > 4 ng/mL, mild or definite BPO is likely (89%), whereas if the PSA is < 2ng/mL, BPO is unlikely (33%).

Equity issue/Implementation issue(s):

There is a trade-off between the cost of performing PSA and the useful information that this test could provide.

Guidelines on Treatment

1. **In men who report LUTS, what is the effect of pelvic floor muscle training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?**

Recommendation:

PFMT may be offered to men with stress urinary incontinence. It is NOT recommended as treatment of LUTS suggestive of BPE.

Pelvic floor muscle training (PFMT) involves recruiting pelvic floor muscles for muscle strengthening and skill training. Contraction of pelvic floor muscles causes inward lift of the muscles, which results in increase in urethral closure pressure, stabilisation and resistance to downward movement. PFMT maybe offered to patients but many protocols exist and initiation of this exercises and duration of exercises has not been established.

Guidelines considered:

NICE: Studies were Inconsistent
EAU: none
AUA: none

Protocols on use of PFMT have been studied; there are many variations on PFMT protocols however many unanswered questions regarding when PFMT are still unanswered. For men with who underwent radical prostatectomy, eight studies were cited by NICE.

Two RCTs investigated PFMT prior to surgery in men undergoing TURP, and in one study conducted in men with post-micturition dribbling who had no history of stress or urgency incontinence. These studies have variations in the number and duration of training sessions provided, recommended type and intensity of exercise to practice at home, when these were initiated (pre or post surgery) and the type of intervention received by the control group. The studies also had serious limitations, inconsistencies, indirectness and imprecision.

Equity issue/Implementation issue(s):

There are costs associated to NHS in terms of time spent on pelvic floor exercise instruction by the healthcare professional. However these could be offset by minimising the costs of products for incontinence management if the conservative strategy is successful.

2. **In men who report LUTS, what is the effect of bladder training versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?**

Recommendation:

Bladder training may be offered to men with storage LUTS suggestive of overactive bladder syndrome.

Bladder retraining is an educational and behavioural approach which maybe offered as part of conservative therapy which encourages men to hold on when they have sensory urgency. This is done in attempt to regain bladder control, to increase their bladder capacity and restore a normal bladder pattern by actively involving the individual in attempting to increase the interval between the desire to void and the actual and the time between voids. It is thought to be useful in managing the symptoms of urinary urgency and frequency. This approach may involve mandatory

Table 3. Clinical study characteristics for pelvic floor muscle training vs control (NICE)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Men with post-prostatectomy incontinence						
Incontinence at 0 - 3 months follow up 38,91,96,180,185,203,233,304	8	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Incontinence at 3 - 6 months follow up38,91,96,180,203,233,304	7	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Incontinence at 6 - 12 months follow up38,91,180,233,304	5	RCT (a)	Serious limitations (b)	Serious inconsistency(c)	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost(g) per 24 hour pad test at 0 - 3 months follow up 91,185,203	3	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost (g) per 24 hour (pad test) at 3 - 6 months follow up91,203	2	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness(d)	Serious imprecision (e)
Mean urine lost (g) per 24 hour (pad test) at 6 - 12 months follow up91	1	RCT (a)	Very serious limitations (b)	No serious inconsistency	No serious indirectness (d)	Serious imprecision (e)
Men with post-TURP incontinence						
Incontinence at 0 - 3 months follow up240,294	2	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Serious imprecision (e)
Incontinence at > 3 months follow up	0	RCT				
Men with post-micturition dribbling (PMD)						
Decrease in mean urine loss adjusted for initial pad weight gain (g) in men with PMD at 0 – 3 months237	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness (f)	Very serious imprecision (e)
Adverse events	0	RCT				

(a) *Data from studies are supplemented by data from the Cochrane systematic reviews Hunter 2007*[123].

(b) *4 studies*[96,233,237,240] *do not report randomisation method and 8 studies*[91,96,180,185,233,237,240,294] *do not report allocation concealment. Masking of outcome assessment was not performed or unclear in all but 5 of the studies*[38,180,203,237,304]. *Drop out rate was high or unexplained in 5 studies*[38,96,180,185,294]. *Standard deviations reported for mean urine loss in 4 studies*[91,185,203,237] *were very high indicating possible skewed data. One study* [237] *did not report standard deviations for adjusted mean improvement in pad weight gain.*

(c) *Significant statistical heterogeneity is noted and is not explained by subgroup analysis, for example: timing of exercises (pre- or post-operative) or treatment duration (months). Other factors such as number of exercises performed or their intensity may also contribute to differences. The control arms also received different amount and type of additional written or verbal instructions. Different definitions for incontinence were used.*

(d) *Patients in studies* [38,91,96,180,185,203,233,304] *under went prostatectomy for localised prostate cancer and therefore likely to experience more severe incontinence as a result of surgery compared to men with overactive bladder or those following a TURP. However this is unlikely to significantly reduce the applicability of the results.*

(e) *Confidence intervals cross MID despite adequate cumulative sample size for some outcomes. 1 study*[237] *has 15 only patients or less in each arm.*

(f) *The study was conducted in men with PMD without a history of incontinence or surgeries. The data were only considered for making recommendation specifically for this group of patients.*

Table 4. Clinical study characteristics for Pelvic floor muscle training vs control (NICE)

Outcome	PFMT*	Control *	Relative risk	Absolute effect	Quality
Men with Incontinence after prostatectomy					
Incontinence at 0 - 3 months follow up (a)	154/392 (39.3%)	249/389 (64.0%)	0.67 [0.42 to 1.05]	211 fewer per 1000 [371 fewer to 32 more]	Very Low
Incontinence at 3 - 6 months follow up (a)	71/365 (19.5%)	144/365 (39.5%)	0.50 [0.26 to 0.97]	198 fewer per 1000 [12 to 292 fewer]	Very Low
Incontinence at 6 - 12 months follow up (a)	38/330 (11.5%)	82/329 (24.9%)	0.42 [0.22 to 0.80]	144 fewer per 1000 [50 to 194 fewer]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 0 - 3 months follow up	197	195	Not applicable	Mean difference (MD): -10.24 [-19.13 to -1.35]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 3 - 6 months follow up	170	171	Not applicable	MD: -18.79 [-23.99 to -13.58]	Very Low
Mean urine lost (g) per 24 hour (pad test) at 6 - 12 months follow up	150	150	Not applicable	MD: -14.40 [-18.27 to -10.53]	Very Low
Men with Incontinence after TURP					
Incontinence after TURP at 0 - 3 months follow up	4/56 (7.1%)	6/50 (12%)	0.58 [0.97 to 1.96]	50 fewer per 1000 [4 fewer to 115 more]	Low
Men with post micturition dribbling PMD					
Decrease in mean urine loss adjusted for initial pad weight gain (g) in men with PMD at 0 – 3 months	13	15	Not applicable	Not estimable p<0.001 reported in study	Very Low
Adverse events	0	0			

(a) Data were analysed using random effects due to unexplained heterogeneity.
** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

schedules in which the individual may not use the toilet between set times for voiding, or a self-scheduled regimen where the patient gradually increases their intervoiding times, and may use the toilet between times if urgency becomes unbearable.

Guidelines considered:
NICE: Level 4
EAU: 1b
AUA: none

NICE recommendation was based on a panel expert opinion. Recommendations from EAU were based on studies on conservative management as self management for LUTS.

EAU recommendation was based on a study by Brown et al on men randomized on 3 self management sessions in addition to standard care

Equity issue/Implementation issue(s):

There are costs associated with the time spent by healthcare professionals on supervising bladder training, and healthcare professionals may need to spend more time explaining the lifestyle modifications. However these could be offset by minimising the costs of products for incontinence management if the conservative strategy is successful.

Table 5. Self management as part of watchful waiting.

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) (7)	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

*IPSS = International Prostate Symptom Score; n= number of patients;Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine; *significant compared with standard care (p <0.05); †significant compared with baseline (p <0.05)*

3. In men who report LUTS, what is the effect of post void milking versus any other conservative therapy or no treatment on patient related and biometric outcomes and adverse events?

Standard:
Post void urethral milking, which involves pushing up and forward to expel the pooled urine, should be offered to patients to prevent and treat postmicturition dribble (PMD).

Post void urethral milking eliminates post micturition dribble, which may be caused by the urethra being emptied incompletely by the muscles surrounding it. Post void urethral milking involves drawing the tips of the fingers behind the scrotum and pushing up and forward to expel the pooled urine.

Guidelines considered:
NICE: Level 2
EAU: 1b
AUA: none

NICE recommendation was based from one small RCT with three arms comparing post-void milking, PFMT and no intervention in men with post-micturition dribbling was found.

EAU recommendation was based on a study by Brown et al, on men randomized on 3 self management sessions in addition to standard care.

Equity issue/Implementation issue(s):
None

Table 6. Post void urethral milking vs no intervention - Clinical study characteristics (NICE)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Decrease in mean urine loss adjusted for initial pad weight gain (g) at 0 – 3 months[237]	1	RCT (a)	Serious limitations (b)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)

a) *The study is supplemented by data from the Cochrane systematic reviews Hunter 2007[123].*
b) *The study[237] does not report randomisation method or allocation concealment. Standard deviations reported for the unadjusted mean urine loss in were very high indicating possible skewed data. In addition mean improvement in pad weight gain adjusted for initial pad weight again gain were not reported with standard deviations so an absolute effect between interventions could not be calculated.*
c) *The study has 15 only patients or less in each arm.*

Outcome	Post void milking	No intervention	Relative risk	Absolute effect	Quality
Decrease in mean urine loss adjusted for initial pad weight gain (g) at 0 – 3 months	15	15	Not applicable	Not estimable p<0.01 reported in study, favouring post void milking	Very Low

Table 7. Self management as part of watchful waiting reduces symptoms and progression (EAU)

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) (7)	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

*IPSS = International Prostate Symptom Score; n= number of patients;Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine; *significant compared with standard care (p <0.05); †significant compared with baseline (p <0.05)*

4. In men who report LUTS, what is the effect of timing of fluid intake versus no change in timing of fluid intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

Recommendation:
Offer men with storage LUTS advice on fluid intake with reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (eg. At night or going out in public).

Fluid intake advice should be based on patient's body weight. Confusion over how much people should drink should be based on their fluid requirements. Patients should be adviced against excessively reducing fluid intake, as a coping strategy, resulting in worsened symptoms and increased risk of infection. Reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public).

Guidelines considered:
NICE: Level 4
EAU: Level 1b
AUA: none

There were no clinical studies identified by NICE for this recommendation. NICE recommendation was based on a panel expert opinion.

EAU recommendation was based on a study by Brown et al on men randomized on 3 self management sessions in addition to standard care (Table 7.)

Equity issue/Implementation issue(s):
Proper guidance to patients who might excessively decrease intake to avoid effects inadequate hydration.

5. In men who report LUTS, what is the effect of reducing alcohol/caffeine/artificial sweeteners/carbonated drink intake versus no reduction in their intake or any other conservative therapy on patient related and biometric outcomes and adverse events?

Recommendation:
Offer men with storage LUTS advice on reduction of alcohol or caffeine or other substances that may have a diuretic and irritant effect to control frequency, urgency and nocturia.

Reduction in the intake of fluids containing alcohol, caffeine and artificial sweeteners together with avoidance of carbonated drinks, which may have irritant or diuretic effect may decrease incidence of increasing fluid output and enhanced frequency, urgency and nocturia.

Guidelines considered:
NICE: Level 4
EAU: Level 1b
AUA: none

There were no clinical studies identified by NICE for this recommendation. NICE recommendation was based on a panel expert opinion.

EAU recommendation was based on a study by Brown et al on men randomized on 3 self management sessions in addition to standard care (Table 7)

6. In men who report LUTS, what is the effect of intermittent catheters compared to indwelling catheters on patient related and biometric outcomes and adverse events?

Standard:
Offer intermittent bladder catheterization BEFORE indwelling urethral or suprapubic catheterization to men with voiding LUTS that cannot be corrected by less invasive measures.

Recommendation:
Consider offering long-term indwelling urethral catheterization to men with LUTS :

a. For whom medical management has failed and surgery is not appropriate and who are unable to manage intermittent self-catheterization
b. With skin wounds, pressure ulcers or irritation that are being contaminated by urine

Intermittent catheterisation may be performed by the patient or a caregiver by passage of a single-use catheter to empty the bladder. This is associated with lower risks than continuous indwelling catheterisation but is dependent on the ability of the patient or caregiver to perform the procedure.

Long-term indwelling catheters maybe urethral and suprapubic type. The urethral catheters have the advantage of easier initial insertion but suprapubic catheters may provide benefits in the long term such as reduced impact on sexual function, reduced infection and easier replacement.

Consider offering self- or caregiver-administered intermittent urethral catheterisation before offering indwelling catheterisation for men with chronic urinary retention. One should also consider offering intermittent or indwelling catheterisation before offering surgery in men with chronic urinary retention instead of surgery in men with chronic retention who you suspect have markedly impaired bladder function.

Aside from proper technique in catheter insertions, it should be adequately lubricated, and addition of local/topical anesthetics may be used.

Guidelines considered:
NICE: Level 4
EAU: none
AUA: none

There are no clinical studies questions on effect of intermittent catheters compared to indwelling catheters, only experiences on indwelling catheter installation, wearing and handling and background data.

Equity issue/Implementation issue(s):
The duration of catheterisation and the ability of patients to self-catheterise and availability of support from carers are important considerations. Proper advice on technique and care is important to avoid adverse effects of these techniques.

7. For those not on treatment for LUTS, what is the most clinically effective and cost effective recall intervals for detecting progression?

Recommendation:
Allow the patient to follow up after 6 months, and then annually, provided there is no deterioration of symptoms or development of absolute indication for surgical treatment

Following an initial assessment not entailing any treatment for LUTS, many men will still need to be seen again to check on patient's progress, and possible consideration of treatment. There is no evidence on appropriate intervals for follow up, but rather by clinical "common sense" and experience, sometimes in combination. EAU recommends, that patients on watchful waiting or those without treatment to be reviewed every 6 months and then annually, provided no deterioration of symptoms or development of absolute indications for medical or surgical treatment.

Guidelines considered:
NICE: Level 4
EAU: Level 4
AUA: none

There is no evidence on appropriate intervals for follow up, recommendations were based on a panel expert opinion.

Equity issue/Implementation issue(s):
If symptoms are unlikely to worsen and the man does not want to proceed to active intervention, active surveillance can save resources without decreasing the man's quality of life.

8. In men with LUTS who take alpha blockers, on combination therapy and on anticholinergics, what are the most clinically effective and cost effective recall intervals for review for detecting progression of symptoms?

Recommendation:
For those on these medications, allow the patient to follow after 4 weeks after drug initiation to determine

treatment response. If the patient gains relief in the absence of troublesome adverse events, drug treatment may be continued and subsequent follow up may be at 6 month intervals, provided there is no deterioration of symptoms or development of absolute indication for surgical treatment.

Patients receiving a_1-blockers, muscarinic receptor antagonists, phosphodiesterase 5 inhibitors or the combination of a1-blockers + 5-reductase inhibitors or muscarinic receptor antagonists should be reviewed 4-6 weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in?the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following tests are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume.

In those taking desmopressin, serum sodium should be measured at day 3, day 7 and after 1 month, and if serum sodium concentration has remained normal, every 3 months subsequently. A frequency volume chart aside from serum-sodium concentration should be done. The follow-up sequence should be restarted after dose escalation.

Guidelines considered:
NICE: Level 4
EAU: Level 3-4
AUA: Level 4

NICE recommendations were formulated using expert opinion and pharmacological trials showing the time course of symptom change. No clinical or economic evidence was retrieved.

EAU recommendations was based on empirical data or theoretical considerations, but not on evidence-based studies.

Equity issue/Implementation issue(s):
None

9. In men with LUTS who take 5-Alpha reductase inhibitors what is the most clinically effective and cost effective recall intervals for review for detecting progression of symptoms?

Recommendation:
For those on 5-ARIs, allow the patient to follow up after 3 and then 6 months to determine response and adverse events, and then every 6-12 months

In patients prescribed with 5-ARI, serial PSA should be followed up regularly if life expectancy is > 10 years and if a diagnosis of prostate cancer could alter management.

Guidelines considered:
NICE: Level 4
EAU: Level 3-4
AUA: Level 4

NICE recommendations were formulated using expert opinion and pharmacological trials showing the time course of symptom change. No clinical or economic evidence was retrieved.

EAU recommendations were based on empirical data or theoretical considerations, but not on evidence-based studies.

AUA recommendations were from previous analyses of randomized, placebo-controlled trials which had shown a reduction in prostate volume by about 15-25%, achieved at 6 months and sustained over time. However there are no specific studies recommending specific follow up for 5-ARIs, recommendations were based on expert opinion.

Equity issue/Implementation issue(s):
5-alpha reductase inhibitors should be effective in 3-6 months, the effectiveness of this intervention must be assessed at this time to avoid unnecessary treatment if it proves ineffective. It would not be cost-effective to schedule an earlier assessment.

10. What is the effectiveness of alpha blockers in patients with LUTS?

Standard:
Offer an alpha blocker to men with moderate to severe LUTS. Alpha blockers are considered the first line drug treatment. They are cost-effective compared to placebo among patients with moderate to severe LUTS.

Both a 1_a- and a 1_b receptors have been identified within the prostate. The a 1_a -receptors are the predominant adrenoreceptors expressed by stromal smooth muscle cells. Current alpha blockers work by relaxing the stromal muscle cells by focused binding to the a1receptors and with reduced activity at a_2 receptors. Thereby, reducing resistance and improving symptoms and flow rate.

Second generation agents included terazosin, doxazosin and alfuzosin and third generation agents, e.g. tamsulosin, are thought to be more selective antagonists for prostatic $a1_a$receptors.

Improvements take a few weeks to develop to its maximum effect, however significant efficacy over placebo has been demonstrated within hours to days. Different a1-blockers have similar efficacy, expressed as a percentage improvement in International Prostate Symptom Score (IPSS), in patients with mild, moderate, or severe LUTS.

Guidelines considered:
NICE: Level 1b
EAU: Level 1a
AUA: Level 1b

NICE guidelines reviewed studies involving the effect and side effects of alpha blockers in comparison with placebo.

Table 8. Alpha blockers vs placebo -Clinical summary of findings (NICE)

Outcome	Alpha blocker*	Placebo*	Relative risk	Absolute effect	Quality
Symptom score (a), (b)	5109	4226	Not applicable	Mean difference (MD) -2.55 [-3.17, -1.92]	Moderate
Qmax(ml/s)(a),(c)	3472	2982	Not applicable	MD 1.23 [0.90, 1.55]	Moderate
Quality of life (IPSS question) (a),(d)	2407	1672	Not applicable	MD -0.41 [-0.57, -0.25]	Low
Dizziness (a)	643/7949 (8.1%)	266/5855 (4.5%)	Relative risk (RR) 1.91 [1.54, 2.36]	41 more per 1000 [25 to 61 more]	Low
Fatigue (asthenia)	353/6600 (5.4%)	159/5333 (3.0%)	RR 1.89 [1.57, 2.27]	27 more per 1000 [17 to 38 more]	High
Headache	285/4636 (6.2%)	195/3316 (5.9%)	RR 1.11 [0.93, 1.32]	6 more per 1000 [4 fewer to 19 more]	Moderate
Postural Hypotension	126/5116 (2.5%)	32/4140 (0.8%)	RR 3.09 [2.12, 4.50]	17 more per 1000 [9 to 28 more]	Moderate
Rhinitis	101/1660 (6.1%)	68/1465 (4.6%)	RR 1.45 [1.08, 1.95]	21 more per 1000 [4 to 44 more]	Moderate
Erectile dysfunction/ impotence	72/2382 (3.0%)	46/2055 (2.2%)	RR 1.44 [1.00, 2.07]	10 more per 1000 [0 to 24 more]	Low
Abnormal ejaculation (a)	123/5655 (2.2%)	32/4549 (0.7%)	RR 2.98 [1.20, 7.40]	14 more per 1000 [1 to 45 more]	Low
Withdrawal due to adverse events	476/6622 (7.2%)	287/4709 (6.1%)	RR 1.37 [1.19, 1.58]	23 more per 1000 [12 to 35 more]	Moderate

** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

Notes about analysis of results:

(a) These outcomes were analysed using random effects analysis. . All analyses were conducted using the fixed effect model except where indicated

(b) For symptoms scores, Chapple 2005:Tamsulosin combined 0.4mg arms and excluded 0.8mg arm; Roehrborn 2001: Alfuzosin 10mg arm included and 15mg arm excluded; Vankerrebroeck 2000: Alfuzosin 10mg and 7.5mg arm combined; Wilt 2002: tamsulosin included 0.4mg arm and excluded 0.8mg arm.

(c) For Qmax: Wilt 2002 as above, Gillenwater1995: Doxazosin 2, 4,8mg arms combined and 12mg excluded; Roehrborn 2001 and Vankerrebroeck 2000 as above.

(d) Quality of life: as above.

(e) Cochrane systematic review for Wilt on tamsulosin used 0.4mg and not 0.8mg data. For adverse events, asthenia and withdrawal due to adverse events the reviewers went back to the original studies to retrieve the data for 0.4mg as the results were combined in the Cochrane review. Chapple 1996 did not report this outcome separately.

NICE guidelines summarized evidence statements from these studies.:

Alpha blockers are more effective than placebo in improving symptom scores.
Alpha blockers are more effective than placebo in improving Qmax (ml/s).
Alpha blockers are more effective than placebo in improving quality of life (IPSS question).
More men treated with alpha blockers than placebo experienced dizziness, fatigue (asthenia), postural hypotension, rhinitis, erectile dysfunction and abnormal ejaculation.
There is no statistically significant difference between alpha blockers and placebo in men experiencing headaches.
More men treated with alpha blockers than placebo withdrew due to adverse events.

EAU guidelines based their recommendations on randomized, placebo controlled trials with alpha blockers.

Table 9. Randomised, placebo-controlled trials with a1 blockers in men with LUTS (EAU)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) [14]	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 [a] -42 [a,b]	+1.3 [a] +1.4 [a]	-9 -39 [a,b]	1b
Buzelin et al. (1997) [15]	12	Placebo Alfuzson 2 x 5 mg	196 194	-18 -31 [a,b]	+1.1 +2.4 [a,b]	0 -17 [a,b]	1b
van Kerrebroeck et al. (2000) [16]	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 [a,b] -39.9 [a,b]	+1.4 +3.2 [a,b] +2.3 [a,b]	- - -	1b
MacDonald and Wilt (2005) [17]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 [b] (Boyarski) [†] -1.8 [b] (IPSS) [†]	+1.2 [b]	-	1a
Kirby et al. (2001) [18]	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 [a] -45 [a,b] -45 [a,b]	+1.1 [a] +2.6 [a,b] +2.8 [a,b]	- - -	1b
McConnell et al. (2003) [8]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 [b]	+1.4 +2.5 [a,b]	- -	1b
Chapple et al. (1996) [19]	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 [a,b]	+0.6 +1.6 [a,b]	-13.4 -22.4 [a]	1b
Lepor (1998) [20]	13	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin MR 1 x 0.8 mg	253 254 247	-28.1 -41.9 [a,b] -48.2 [a,b]	+0.5 +1.8 [a,b] +1.8 [a,b]	- - -	1b
Chapple et al. (2005) [21]	12	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8 mg	350 700 354 707	-32 -43.2 [b] -41.7 [b] -42.4 [b]	- - - -	- - - -	1b
Wilt et al. (2002) [22]	4-26	Placebo Tamsulosin 1 x 0.4-0.8 mg	4122	-12 [b] (-1.1 Boyarski [†]) -11 [b] (-2.1 IPSS [†])	+1.1 [b]	-	1a

Brawer et al. (1993) [23]	24	Placebo Terazosin 1 x 1-10 mg	72 69	-11 -42 [a,b]	+1.2 +2.6 [a,b]	- -	1b
Roehrborn et al. (1996) [24]	52	Placebo Terazosin 1 x 1-10 mg	973 976	-18.4 -37.8 [a,b]	+0.8 [a] +2.2 [a,b]	- -	1b
Wilt et al. (2000) [25]	4-52	Placebo Terazosin	5151	-37 [b] (-2.9 Boyarski †) -38 [b] (IPSS †)	+1.7 [b]	-	1a

Q_{max} = maximum urinary flow rate (free uroflowmetry); PVR = post-void residual urine; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; † = absolute value.

These controlled studies have shown that a1-blockers typically reduce IPSS, after a placebo run-in period, by approximately 30-40% and increase the maximum flow rate (Q_{max}) by approximately 20-25%. Alpha1-blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect a1-blocker efficacy in studies with follow-up periods of less than one year, but a1-blockers do seem to be more efficacious in patients with smaller prostates (<40 mL) than in those with larger glands in longer-term studies.

Alpha$_1$blocker efficacy is similar across age groups. a_1-Blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies; some patients must therefore be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during a_1-blocker treatment appears to be maintained over at least four years.

AUA guidelines individually reviewed alfuzosin, doxazosin, tamsulosin and terazosin.

Alfuzosin. The incidence of AUR was similar between the alfuzosin and placebo groups at two-years follow-up (p=0.82). One study noted high rates of urinary retention during 3-month follow-up (64% with alfuzosin and 97% with doxazosin, p-value not reported). In the active comparator trials, I-PSS improved more with doxazosin (mean dose, 6.1 mg daily; mean change, -9.2) than with alfuzosin 2.5 mg twice to three times daily (mean change, 7.5; between- group p<0.05). QoL score also improved in all the studies (p<0.05). However, data were insufficient to perform a meta-analysis; only two studies presented comparable doses and follow-up period. In terms of improvement, total I-PSS and QoL score improved significantly (p<0.05) compared with placebo in all five RCTs. Data were insufficient to perform a meta-analysis. Q_{max} also improved significantly with alfuzosin 10 mg daily compared with placebo in three trials with follow-up between three and 12 months, as well as in the meta-analysis.

Doxazosin. Doxazosin elicits a dose-dependent response as well as a dose dependent side-effect profile. A dose-ranging study comparing 4 mg and 8 mg daily doses over three months (n=82) noted improved AUA-SI in both treatment groups with a significant difference between groups (p=0.03). In a study with standard formulation doxazosin and placebo, the total I-PSS improved in all three groups (p<.0.001) at 13-weeks of follow-up. In terms of AUR, Doxazosin delayed, but did not prevent AUR (p=0.23)

Tamsulosin. It has a greater specificity for the a1a-adrenoreceptor in relation to the a1badrenoreceptor with an advantage in reduced need for titration and less hypotensive side effects. Total I-PSS decreased compared with placebo in the three studies reporting this outcome (P<0.05), all with 12-week follow- up. QoL score improved more with tamsulosin OCAS 0.4 mg and modified-release 0.4 mg daily than with placebo.

Terazosin. Terazosin is an a1-selective antagonist with a relatively long half-life with a dose dependent response and side effect profile. Typically initiated at a dose of 1 mg once daily. Depending on response to therapy and tolerability, the dosage may be increased to 10 mg/day. In a RCT, the VA CO-OP trial, it compared terazosin 10 mg daily, finasteride 5 mg daily, combination therapy of both drugs, and placebo. The study

showed that after one-year of treatment, the mean number of episodes of nocturia was 1.8 with terazosin, 2.1 with finasteride, 2.1 with placebo, and 2.0 with combination therapy compared with baseline values of 2.5, 2.5, 2.4, and 2.4, respectively.

Equity issue/Implementation issue(s):

Alpha blockers are cost-effective compared to placebo/no treatment in patients with moderate and severe symptoms.

11. What is the effectiveness of 5- ARI's in patients with LUTS?

Standard:

Offer a 5-ARI to men with moderate to severe LUTS who have prostates estimated to be larger than 30 grams or a PSA level greater than 1.4 ng/ml, and who are considered to be at high risk of disease progression. 5-ARIs are suitable only for long-term treatment, with a minimum treatment at 6 months.

5-ARI use in BPH is based on the premise on the development and growth of the prostate is dependent on the presence of androgens and dihydrotestosterone (DHT). DHT is converted primarily from its precursor testosterone by the enzyme 5a-reductase in the prostatic stroma cells. The Testosterone/DHT-androgen receptor complex within the nucleus of the cells of the prostate initiates transcription and translation, thus promoting cellular growth and ultimately contributing to the condition of BPH. An imbalance between growth and apoptosis or cellular death, favor growth and subsequent cellular mass or volume increase.

5-ARIs reduce levels of DHT which induce apoptosis of prostate epithelial cells leading to prostate size reduction of about 18-28% and circulating PSA levels of about 50% after 6-12 months of treatment.

There are two 5a-reductase inhibitors were available for clinical use: dutasteride and finasteride; with continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5a-reductase inhibitors.

Guidelines considered:

NICE: Level 1b
EAU: Level 1b
AUA: Level 1b

NICE guidelines summarized the studies they have reviewed and their clinical findings.

There was no statistically significant difference between 5-ARI and placebo in symptom score improvement at 3 months, 6 months and 4 or more years of follow up.

5-Alpha reductase inhibitors are more effective than placebo in improving symptom at 1 to 3 years follow up.

There was no statistically significant difference between 5-ARI and placebo Qmax improvement at 3 months follow up.

5-Alpha reductase inhibitors are more effective than placebo in improving Qmax at 6 months or longer follow up periods.

5-Alpha reductase inhibitors are more effective than placebo in reducing prostate volume.

5-Alpha reductase inhibitors are more effective than placebo in reducing PSA level.

Significantly more men treated with 5-ARI compared to placebo experienced decreased libido, ejaculation disorders, gynaecomastia and impotence.

There was no statistically significant difference between 5-ARI and placebo in number of men experiencing dizziness or who withdrew from studies due to adverse events.

Significantly fewer men treated with 5-ARI compared to placebo experienced fatigue or urinary retention.

Table 10. 5-ARI vs placebo -clinical summary of findings (NICE)

Outcome	5-ARI	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 3 months(a)	1821	644	Not applicable	-1.38 [-3.10, 0.33]	Very Low
Symptom score at 6 months(a)	1821	644	Not applicable	1.63 [-3.72, 0.46]	Very Low
Symptom score at 1 year	3774	2545	Not applicable	-0.84 [-1.13, -0.56]	Moderate
Symptom score at 2 years(a)	3630	3562	Not applicable	-1.78 [-2.34, -1.23]	Moderate
Symptom score at 3 years	1047	961	Not applicable	-1.80 [-2.32, -1.28]	High
Symptom score at ≥ 4 years(a)	1733	1590	Not applicable	-1.45 [-2.91, 0.02]	Moderate
Qmax(ml/s) at 3 months	310	303	Not applicable	0.05 [-0.77, 0.87]	High
Qmax(ml/s) at 6 months	87	81	Not applicable	0.50 [0.08, 0.92]	Moderate
Qmax(ml/s) at 1 year (a)	2186	2136	Not applicable	1.15 [0.77, 1.52]	Low
Qmax(ml/s) at 2 years	3571	3490	Not applicable	1.55 [1.32, 1.77]	High
Qmax(ml/s) at 3 years	691	608	Not applicable	1.80 [1.25, 2.35]	Moderate
Qmax(ml/s) at 4 years plus	588	496	Not applicable	1.80 [1.21, 2.39]	Moderate
Prostate volume (ml)at 1 year	509	521	Not applicable	-9.18 [-11.01,-7.35]	High
Prostate volume (ml)at 2 year (a)	2364	2355	Not applicable	-22.60 [-37.56, -7.63]	Moderate
PSA (ng/ml) at 2 years	2167	2158	Not applicable	-3.60 [-3.72, -3.48]	High
Decreased libido	448/9815 (4.6%)	191/7433 (2.6%)	1.87 [1.58, 2.21]	23 more per 1000 [15 to 31 more]	High
Dizziness	26/607 (4.3%)	24/605 (4.0%)	1.07 [0.63, 1.81]	3 more per 1000 [15 fewer to 32 more]	Low
Ejaculation disorder	231/9721 (2.4%)	50/7345 (0.7%)	3.39 [2.48, 4.63]	17 more per 1000 [10 to 25 more]	High
Fatigue	11/1577 (0.7%)	24/1591 (1.5%)	0.46 [0.23, 0.94]	8 fewer per 1000 [1 to 12 fewer]	Moderate
Gynaecomastia	58/3670 (1.6%)	18/3671 (0.5%)	3.21 [1.90, 5.44]	11 more per 1000 [4 to 22 more]	High
Impotence	719/10126 (7.1%)	291/7749 (3.8%)	1.96 [1.71, 2.25]	36 more per 1000 [27 to 48 more]	High
Urinary retention	107/6886 (1.6%)	164/4534 (3.6%)	0.48 [0.37, 0.61]	19 fewer per 1000 [14 to 23 fewer]	Moderate
Withdrawal due to adverse events	795/10498 (7.6%)	692/8082 (8.6%)	1.00 [0.91, 1.11]	1 more per 1000 [8 fewer to 9 more]	High

(a) These outcomes were analysed using random effects analyses.

EAU guidelines mentions, clinical effects relative to placebo are seen after minimum treatment duration of at least 6 to 12 months. After 2 to 4 years of treatment, 5a-reductase inhibitors reduce LUTS (IPSS) by approximately 15-30%, decrease prostate volume by approximately 18-28% and increase Q_{max} of free uroflowmetry by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement.

A long-term trial with dutasteride in symptomatic men with a prostate volume greater than 30 mL (average prostate volume in the CombAT trial was approximately 55 mL) showed that the 5a-reductase inhibitor reduced LUTS in these patients at least as much or even more effectively than tamsulosin. The greater the baseline prostate volume (serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride. 5a-reductase inhibitors, but not a1blockers, reduce the long-term (> 1 year) risk of acute urinary retention or need for surgery.

Table 11. Randomised trials witn 5a-reductase inhibitors in men with LUTS and benign prostatic enlargement due to BPH

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [4]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b]	
Kirby et al. (2003) [5]	52	Placebo	253	-33.1	+1.4	-	1b
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
Andersen et al. (1995) [6]	104	Placebo	346	+1.5	-0.3	+11.5 [a]	1b
		Finasteride 1 x 5 mg	348	-14.9 [a,b]	+1.5 [a,b]	-19.2 [a,b]	
Nickel et al. (1996) [7]	104	Placebo	226	-4.2	+0.3	+8.4 [a]	1b
		Finasteride 1 x 5 mg	246	-13.3 [a,b]	+1.4 [a,b]	-21	
McConnell et al. (1998) [8]	208	Placebo	1503	-8.7	+0.2	+14 [a]	1b
		Finasteride 1 x 5 mg	1513	-22 [a,b]	+1.9 [a,b]	-18 [a,b]	
Marberger et al. (1998) [9]	104	Placebo	1452	-9.8 †	0.8	+9	1b
		Finasteride 1 x 5 mg	1450	-21.4 [†b]	+1.4 [b]	-15 [b]	
McConnell et al. (2003) [10]	234	Placebo	737	-23.8	+1.4 [a]	+24 [a]	1b
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b]	
Roehrborn et al. (2002) [11]	104	Placebo	2158	-13.5 [a]	+0.6	+1.5 [a]	1b
		Dutasteride 1 x 0.5 mg	2167	-26.5 [a,b]	+2.2 [a,b]	-25.7 [a,b]	
Roehrborn et al. (2008) [12]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4 [a]	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5 [a]	+1.9	-28 [b]	
Roehrborn et al. (2010) [13]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2 [a]	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3 [a]	+2.0	-28 [b]	

Q_{max} = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; † Boyarski Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo/ active control.

AUA guidelines individually reviewed Dutastaride and Finasteride

Finasteride. A thorough review of a large body of evidence consisting of randomized, placebo-controlled studies of one year, two years, and four years duration has found finasteride to be an appropriate BPH treatment option, however these studies were published before 2003. Two recent studies include one placebo-controlled trial, the Proscar Long-Term Efficacy and Safety Study (PLESS), another second open label extension study was identified, which reported six-year follow-up data from a one-year placebo-controlled RCT comparing finasteride 1 mg or 5 mg daily to placebo. Results of the studies showed improvements of IPSS of upto three to four points and this results were maintained for six to 10 years of follow up. Its effect is more accentuated in patients with larger prostates over time. In the

PLESS of age cohorts of men 65 years of age or more, and men less than 65 years, finasteride significantly improved a modified AUA-SI, and reduced prostate volume and the risk for AUR and/or BPH-related surgery at four-year follow-up in both age cohorts.

Dutasteride. Dutasteride is the 2nd ARIs approved for use. Dutasteride differs from finasteride in that it inhibits both isoenzymes of the 5-alpha reductase, it has a longer half-life (five weeks versus six to eight hours), and thus leads to a more profound reduction in both serum and intraprostatic DHT levels. Studies on dutasteride included patients with prostate size >30 g and/or PSA level of >1.5 ng/ml as opposed to patients studied in finasteride which included patients with prostate size >40 g. Studies included for its review included a phase-three randomized, a study aiming to test the effect of a placebo-controlled withdrawal of an alpha-blocker from a combination therapy arm (SMART 1), and a four-year study comparing dutasteride vs. tamsulosin vs. combination (CombAT) for which only the two year interim data are published. However the last two compared Dutasteride in combination therapy. In the phase-three randomized study, AUA-SI improved significantly in the treatment groups ($p<0.001$), with significantly greater improvement with dutasteride compared with placebo. In terms of urodynamic studies Qmax increased by +0.6 ml/sec under placebo and +2.2 ml/sec under dutasteride (between-group $p<0.001$). For prostate reduction the phase-three randomized study showed reduction of total prostate and transition zone volumes by a mean of -25.7% and -20.4%, respectively, in the dutasteride arm ($P <0.001$). The relative risk of AUR with dutasteride vs. placebo was 0.43 (95% CI, 0.29 to 0.62) and the relative risk for BPH-related surgery was also significantly decreased [relative risk 0.52 (95% CI, 0.37 to 0.74)].

Another use for 5-ARIs that has been reviewed is its use for pre-TURP patients. Overall, there is insufficient evidence to recommend using 5-ARIs in the setting of a pre-TURP to reduce intraoperative bleeding or reduce the need for blood transfusions.

Equity issue/Implementation issue(s):
Patients qualified for the use of 5-Alpha reductase inhibitors must be advised that 5ARIs are given at long term basis.

12. What is the effectiveness of combination Alpha blockers and 5-ARI in patients with LUTS?

Recommendation:
Consider offering a combination of an alpha blocker and a 5-ARI to men with bothersome moderate to severe LUTS and prostates estimated to be larger than 30 gms or a PSA >1.4ng/ml

Drug combination aims to combine the effects of both drug classes for synergistic efficacy in symptom improvement and prevention of disease progression. The alpha-blocker exhibits clinical effects within hours or days, whereas the 5a-reductase inhibitor needs several months to develop significant clinical efficacy. Among the drug combinations, finasteride together with alfuzosin, doxazosin, or terazosin, and dutasteride together with tamsulosin, have been tested in clinical trials. No differences in pharmacokinetic or pharmacodynamic properties of the combined use of both drugs have been reported compared to single drug.

Guidelines considered:
NICE: Level 1b
EAU: Level 1b
AUA: Level 1b

According to the NICE guidelines, combination treatment of alpha blocker plus 5-ARI is more effective than placebo in improving symptom score at 1and 4 years follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in improving Q_{max} (ml/s) at 1 year follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in reducing prostate volume at 1 year and 4 years follow up.

Combination treatment of alpha blocker plus 5-ARI is more effective than placebo in reducing PSA level at1 year follow up.

Significantly more men treated with a combination of alpha blockers plus 5-ARI compared to placebo experienced adverse effects such as syncope, dizziness, fatigue (asthenia), erectile dysfunction (impotence), ejaculatory abnormality, postural hypotension, orthostatic hypotension or decreased libido.

There is no statistically significant difference between men treated with a combination of alpha blockers plus 5-ARI compared to placebo in number of men experiencing adverse effects such as headache, vertigo, rhinitis, somnolence, or withdrawal from study due to adverse reactions.

The table below summarizes the studies included in the review.

Table 12. Alpha blockers plus 5-ARI vs placebo- clinical study characteristics.

Outcome	*Number of studies*	*Design*	*Limitations*	*Inconsistency*	*Indirectness*	*Imprecision*
Symptom score t 6-months	0	RCT				
Symptom score at 1 year [147,163]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Symptom score at 2 years	0	RCT				
Symptom score at 4 years [191]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0	RCT	-			
Qmax(ml/s) at 1 year[147,163]	2	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	Serious imprecision (c)
PSA(ng/ml)at 1 year[147]	1	RCT	Serious limitations (a)	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume (ml) at 1 year [163]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Prostate volume (ml) at 4 year [191]	1	RCT	No serious limitations	No serious inconsistency (b)	No serious indirectness	No serious imprecision (f)
Syncope[147,163]	2	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Postural hypotension[147,163,191]	3	RCT	No serious limitations	Serious inconsistency (d)	No serious indirectness	No serious imprecision
Orthostatic hypotension [163]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[147,163,191]	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Vertigo[147]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[163]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Fatigue(Asthenia)[147,163,191]	3	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision
Somnolence[147,191]	2	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Rhinitis[163]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Decreased libido[147,163,191]	3	RCT	No serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Ejaculatory abnormality/ retrograde ejaculation[147,163,191]	3	RCT	Serious limitations (e)	No serious inconsistency	No serious indirectness	No serious imprecision
Impotence or erectile dysfunction[147,191]	2	RCT	Serious limitations (e)	No serious inconsistency	No serious indirectness	No serious imprecision
Withdrawals due to adverse events[147,163]	2	RCT	No serious limitations	Serious inconsistency (d)	No serious indirectness	Serious imprecision (c)

(a) RCT(s) with which did not report randomisation allocation and concealment methods [147] contributed to more than 50% of the weight of the pooled outcome.

(b) Treatment effects at different time points were different, therefore duration of treatment and follow-up are may affect the direction and treatment effect size. This observation is consistent with the pharmacology of these drugs. Therefore, the quality was not downgraded.

(c) Outcomes were downgraded when the confidence intervals crossed the MID. It was not downgraded if the size of the benefit/harm was small or not statistically significant, and the confidence intervals did not reach cross MID.

(d) There were substantial heterogeneity and random analysis was conducted.

(e) There were variations in the terms used to describe and report the sexual side effects such as retrograde ejaculation, reduced semen volume ejaculatory abnormalities; erectile dysfunction and impotence.

(f) The MID of prostate volume or PSA level is not known.

Outcome	Alpha-blockers + 5-ARI	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 1 year	543	518	Not applicable	MD -3.37 [-4.01 to -2.72]	Moderate
Symptom score at 4 years	786	737	Not applicable	MD -2.5 [-3 to -2]	Moderate
Qmax(ml/s) at 1 year	542	517	Not applicable	MD 2.13 [1.51 to 2.76]	Moderate
PSA(ng/ml) at 1 year	265	253	Not applicable	MD-1.60 [-1.85, -1.35]	Moderate
Prostate volume (ml) at 1 year	275	258	Not applicable	MD -7.5 [-11.5 to -3.5]	Moderate
Prostate volume (ml) at 1 year	778	736	Not applicable	MD -8.58 [-10.08 to -7.08]	High
Syncope	11/595 (1.8%)	1/574 (0.2%)	RR 7.35 [1.35 to 40.0]	13 more per 1000 [1 to 78 more]	Moderate
Postural hypotension(a)	39/1381 (2.8%)	9/1311 (0.7%)	RR 3.35 [1.11 to 10.15]	16 more per 1000 [1 to 63 more]	Moderate
Orthostatic hypotension	121/309 (39.2%)	92/310 (29.7%)	RR 1.32 [1.06 to 1.65]	95 more per 1000 [18 to 193 more]	Moderate
Dizziness	110/1381 (8%)	44/1311 (3.4%)	RR 2.41 [1.73 to 3.36]	48 more per 1000 [25 to 80 more]	High
Vertigo	8/286 (2.8%)	3/269 (1.1%)	RR 2.51 [0.67 to 9.36]	17 more per 1000 [4 fewer to 93 more]	Low
Headache	16/309 (5.2%)	10/305 (3.3%)	RR 1.58 [0.73 to 3.42]	19 more per 1000 [9 fewer to 80 more]	Moderate
Fatigue(Asthenia)	73/1381 (5.3%)	34/1311 (2.6%)	RR 2.08 [1.41 to 3.08]	28 more per 1000 [11 to 54 more]	High
Somnolence	10/1072 (0.9%)	6/1006 (0.6%)	RR 1.52 [0.58 to 3.99]	3 more per 1000 [3 fewer to 18 more]	Moderate
Rhinitis	24/309 (7.8%)	14/305 (4.6%)	RR 1.69 [0.89 to 3.21]	32 more per 1000 [5 fewer to 102 more]	Moderate
Decreased libido	24/1381 (1.7%)	10/1311 (0.8%)	RR 2.31 [1.12 to 4.8]	10 more per 1000 [1 to 30 more]	Moderate
Ejaculatory abnormality or retrograde ejaculation	31/1381 (2.2%)	9/1311 (0.7%)	RR 3.33 [1.6 to 6.93]	16 more per 1000 [4 to 42 more]	Moderate
Impotence or erectile dysfunction	35/1072 (3.3%)	12/1006 (1.2%)	RR 2.74 [1.44 to 5.21]	21 more per 1000 [5 to 51 more]	Moderate
Withdrawals due to adverse events(a)	59/574 (10.3%)	35/574 (6.1%)	RR 2.22 [0.56 to 8.8]	74 more per 1000 [27 fewer to 476 more]	Low

(a) Random effects analysis was conducted

According to the EAU, there are several studies that have investigated the efficacy of combination therapy against the efficacy of an alpha1-blocker, 5a-reductase inhibitor, or placebo alone. 4-year data analysis from MTOPS as well as the 2- and 4-year results from the CombAT (Combination of Avodart® and Tamsulosin) trials, have been reported. The CombAT trial included older men with larger prostates and higher serum PSA concentrations and therefore appears to represent men at greater risk of disease progression. Long-term data have demonstrated that combination treatment is superior to either monotherapy with regard to symptom reduction and Q_{max} improvement starting from month 9 and superior to alpha-blocker in reducing the risk of acute urinary retention and the need for surgery after month 8.

In both the MTOPS and CombAT trials, combination therapy was shown to be superior to monotherapy in preventing overall clinical progression. Clinical progression is defined by an IPSS increase of at least 4 points, acute urinary retention, urinary tract infection, incontinence, or an increase in serum creatinine > 50% compared to baseline values. For combination therapy in the MTOPS trial versus the CombAT trial, the following reductions were observed: overall risk of disease progression was 66% versus 44%; symptomatic progression, 64% vs. 41%; acute urinary retention, 81% vs. 68%; urinary incontinence, 65% vs. 26%; BPH-related surgery, 67% vs. 71%.

Table 13. Randomised trials using a1 blockers, 5-a reductase inhibitor, and the combination of both drugs (EAU)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Symptom change (% IPSS)	Change in Q_{max} (mL/s)	Change in prostate volume (%)	LE
Lepor et al. (1996) [1]	52	Placebo	305	-16.5 [a]	+1.4	+1.3	1b
		Terazosin 1 x 10 mg	305	-37.7 [a,b,d]	+2.7 [b,d]	+1.3	
		Finasteride 1 x 5 mg	310	-19.8 [a]	+1.6	-16.9 [b,c]	
		Terazosin 1 x 10 mg + finasteride 1 x 5 mg	309	-39 [a, b ,d]	+3.2 [b,d]	-18.8 [b,c]	
Debruyne et al. (1998) [2]	26	Alfuzosin 2 x 5 mg	358	-41.2 [d]	+1.8	-0.5	1b
		Finasteride 1 x 5 mg	344	-33.5	+1.8	-10.5 [c]	
		Alfuzosin 2 x 5 mg + finasteride 1 x 5 mg	349	-39.1 [d]	+2.3	-11.9 [c]	
Kirby et al. (2003) [3]	52	Placebo	253	-33.1	+1.4	-	1b
		Doxazosin 1 x 1-8 mg	250	-49.1 [b,d]	+3.6 [b,d]	-	
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	265	-49.7 [b,d]	+3.8 [d]	-	
McConnell et al. (2003) [4]	234	Placebo	737	-23.8 [a]	+1.4 [a]	+24 [a]	1b
		Doxazosin 1 x 1-8 mg	756	-35.3 [a,b,d]	+2.5 [a,b]	+24 [a]	
		Finasteride 1 x 5 mg	768	-28.4 [a,b]	+2.2 [a,b]	-19 [a,b,c]	
		Doxazosin 1 x 1-8 mg + finasteride 1 x 5 mg	786	-41.7 [a,b,c,d]	+3.7 [a,b,c,d]	-19 [a,b,c]	
Roehrborn et al. (2008) [5]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5	+1.9	-28 [c]	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-39.2 [c,d]	+2.4 [c,d]	-26.9 [c]	
Roehrborn et al. (2010) [6]	208	Tamsulosin 1 x 0.4 mg	1611	-23.2	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3	+2.0	-28 [c]	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-38 [c,d]	+2.4 [c]	-27.3 [c]	

Q_{max} = maximum urinary flow rate (free uroflowmetry); IPSS = International Prostate Symptom Score; a = significant compared to baseline (indexed wherever evaluated); b = significant compared to placebo; c = significant compared to α_1-blocker monotherapy; d = significant compared to 5α-reductase inhibitor monotherapy.

AUA guidelines also based their recommendations on the MTOPS and CombAt trials.

Equity issue/Implementation issue(s):
Patients on combination therapy should be advised of long term medication.

13. What is the effectiveness of anticholinergics in patients with LUTS?

Recommendation:
Offer an anticholinergic to men to manage the symptoms of OAB, but should not have an elevated post void residual. However, they should be prescribed with caution and regular reevaluation of symptoms score and PVR is advised.

Bladder contraction is mediated via the parasympathetic cholinergic nerves. Five muscarinic receptor subtypes (M1-M5) have been described in humans, of which the M2 and?M3subtypes are predominantly expressed in the detrusor. Although approximately 80% of these muscarinic receptors are M2 and 20% M3 subtypes, only M3 seems to be involved in bladder contractions in healthy humans. Blockade of this interaction results in a reduction in smooth muscle tone and theoretically an amelioration of diseases associated with excess contraction of these muscles.

Guidelines considered:
NICE: Level 1b
EAU: Level 1b
AUA: Level 1b

NICE summarized clinical findings based on the different studies included in their review. Table below show the summary of studies and clinical findings on these studies.

Anticholinergics are more effective than placebo in reducing the number of urinary urgency incontinence episodes per 24 hours at 3 months follow up.

There is no statistically significant difference between anticholinergics and placebo in improvement of symptom score, quality of life scores, Q_{max} (ml/s), urinary urgency per 24 hours, frequency per 24 hours, and frequency at night.

There is no statistically significant difference between anticholinergics and placebo in number of men experiencing, constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache, nasal congestion or withdrew from study due to adverse events.

Significantly more patients treated with anticholinergics experiencing dry mouth compared to placebo.

Table 14. Anticholinergic vs Placebo - Clinical study characteristics.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptom score at 3 months[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Qmax at 3 months[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c), (d)
Urgency incontinence episodes/24h[136]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c),(e)
Urgency/24h[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/24h[136]	1	RCT	Serious limitations(a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Frequency/night[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Ejaculation Failure[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Urinary Retention[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Fatigue[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Somnolence[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dizziness[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Rhinitis[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Diarrhoea[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Constipation[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dyspepsia[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Headache[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Dry Mouth[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)
Withdrawals due to adverse events[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness (b)	Serious imprecision (c)

(a) *There was incomplete or unclear reporting for many outcomes. This study [134,136] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance ($p<0.05$ or $p<0.01$) of combination vs. placebo was indicated in the paper for some of the outcomes. Actual values and standard deviations were not reported. It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was reported.*

(b) *Patients recruited in this study have higher IPSS scores than most trials (mean IPSS ~20) and significant storage symptoms. Anticholinergics were licensed for storage symptoms. Recommendation was made for patients with OAB – no indirectness of evidence.*

(c) *Confidence intervals for continuous outcomes unknown, while those for adverse events met the criteria for downgrading.*

Outcome	Anti-Ch	Placebo	Relative risk	Absolute effect	Quality
Symptom score at 3 months	197	206	Not applicable	MD -0.60 Not stats sig. (a)	Low
Quality of life (IPSS question) at 3 months	198	206	Not applicable	MD -0.20 Not stat sig (a)	Low
Qmax at 3 months	NR (b)	NR (b)	Not applicable	MD -0.07 P >0.3	Low
Urgency incontinence episodes/24h (c)	48	43	Not applicable	MD -0.52 p value 0.008 (a)	Low
Urgency/24h	209	210	Not applicable	MD -0.30 Not stats sig. (a)	Low
Frequency/24h	209	212	Not applicable	MD -0.30 Not stats sig. (a)	Low
Frequency/night	209	212	Not applicable	MD 0.04 Not stats sig. (a)	Low
Fatigue	2/217 (0.9%)	6/220 (2.7%)	RR 0.34 [0.07 to 1.66]	18 fewer per 1000 [25 fewer to 18 more]	Low
Somnolence	2/217 (0.9%)	2/220 (0.9%)	RR 1.01 [0.14 to 7.13]	0 more per 1000 [8 fewer to 56 more]	Low
Dizziness	3/217 (1.4%)	2/220 (0.9%)	RR 1.52 [0.26 to 9.01]	5 more per 1000 [7 fewer to 73 more]	Low
Rhinitis	0/217 (0%)	2/220 (0.9%)	RR 0.2 [0.01 to 4.2]	7 fewer per 1000 [9 fewer to 29 more]	Low
Diarrhoea	7/217 (3.2%)	3/220 (1.4%)	RR 2.37 [0.62 to 9.03]	19 more per 1000 [5 fewer to 109 more]	Low
Constipation	9/217 (4.1%)	5/220 (2.3%)	RR 1.82 [0.62 to 5.36]	19 more per 1000 [9 fewer to 99 more]	Low
Dyspepsia	2/217 (0.9%)	5/220 (2.3%)	RR 0.41 [0.08 to 2.07]	13 fewer per 1000 [21 fewer to 24 more]	Low
Headache	2/217 (0.9%)	7/220 (3.2%)	RR 0.29 [0.06 to 1.38]	23 fewer per 1000 [30 fewer to 12 more]	Low
Dry Mouth	16/217 (7.4%)	5/220 (2.3%)	RR 3.24 [1.21 to 8.7]	51 more per 1000 [5 more to 175 more]	Low
Ejaculation Failure	0/217 (0%)	0/220 (0%)	Not estimable	0 fewer per 1000 [0 fewer to 0 fewer]	Low
Urinary Retention	2/217 (0.9%)	3/220 (1.4%)	RR 0.68 [0.11 to 4.01]	4 fewer per 1000 [12 fewer to 41 more]	Low
Withdrawal due to adverse events	5/217 (2.3%)	7/220 (3.2%)	RR 0.72 [0.23 to 2.25]	9 fewer per 1000 [24 fewer to 40 more]	Low

(a) Not stat sig. = no statistically significant difference, i.e. P >0.05, Values reported are adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre. The study reported outcomes as graphs only and there were no p values or standard deviations for comparison to calculate confidence intervals.

(b) NR = not reported. Number of patients with Qmax measurements at follow up not reported

(c) Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries filled for 5 days before visit.

EAU based their recommendations on open-label trials one of which used tolterodine effect on daytime frequency, nocturia, urgency incontinence, and IPSS; toeterodine were all significantly reduced compared to baseline values after 12-25 weeks. In another open-label study with a1-blocker nonresponders, IPSS scores were improved during tolterodine treatment irrespective of storage or voiding symptoms. In randomised, placebo-controlled trials with tolterodine, it showed it can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. It was also demonstrated that urgency related voiding is significantly reduced by tolterodine. However, tolterodine's effects did not reach statistical significance in most of the trials. In studies however considering the prostate volume/PSA, tolterodine significantly reduced daytime frequency, 24h voiding frequency and IPSS storage symptoms in those men with PSA concentrations below 1.3 ng/mL, which was not the case in men with PSA concentrations of 1.3 ng/mL or more indicating that men with smaller prostates might profit more from antimuscarinic drugs.

In men with bladder outlet obstruction, antimuscarinic drugs are not recommended due to the theoretical decrease of bladder strength, that might be associated with post-void residual urine

or urinary retention. A 12-week placebo-controlled safety study dealing with men who had mild to moderate bladder outlet obstruction demonstrated that tolterodine significantly increased the amount of post-void residual urine (49 vs. 16 mL) but was not associated with increased events of acute urinary retention (3% in both study arms). Urodynamic effects of tolterodine included significant larger bladder volumes to first detrusor contraction, higher maximum cystometric bladder capacity, and decreased bladder contractility index, qmax however remained the same.

AUA identified Three RCTs; however these studies do not sufficiently demonstrate the efficacy or effectiveness of tolterodine. Two single-group cohort studies were identified. These studies resulted in a median I-PSS scores decreased from 17 to 10. Mean post-void residual did not increase although two patients did develop AUR requiring catheterization. In another cohort study tolterodine resulted to a mean 24-hour micturition frequency decreased from 9.8 to 6.3 voids and nocturia decreased from 4.1 to 2.9 episodes nightly. Significant changes in the AUA-SI (-6.1), Qmax (1.9 mL per second), and post-void residual (-22 mL) were also observed. To date, tolterodine has been the only anticholinergic agent significantly studied in men with LUTS.

Equity issue/Implementation issue(s):

Table 15. Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with overactive bladder symptoms (EAU)

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	Urgency incontinence [%]	IPSS [%]	LE
Kaplan et al. (2005) [10]	25	Tolterodine 1 x 4 mg/d (after α-blocker failure)	43	-35.7[a]	-29.3[a]	-	-35.3[a]	2b
Roehrborn et al. (2006) [18]	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4 mg/d	77	-12	-	-71[b]	-	
Kaplan et al. (2006) [13]	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-10.8[b]	-18.8	-	-	
Kaplan et al. (2006) [19]	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-85[b]	-54	
Dmochowski et al. (2007) [14]	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-8.7[b]	-18.8	-	-	
Höfner et al. (2007) [11]	12	Tolterodine 1 x 4 mg/d	741	-20[a]	-42.9 a	-100	-37.9[a]	2b
Herschorn et al. (2009) [16]	12	Placebo	124	-10.2	-	-59.3	-	1b
		Fesoterodine 1 x 4 mg/d	111	-13.2[b]	-	-84.5[b]	-	
		Fesoterodine 1 x 8 mg/d	109	-15.6[b]	-	-100[b,c]	-	

IPSS = International Prostate Symptom Score; [a] = significant compared to baseline ($p < 0.01$; indexed wherever evaluated); [b] = significant compared to placebo ($p < 0.05$); c = significant compared to fesoterodine 4 mg ($p < 0.05$)

14. What is the effectiveness with treatment combination of alpha blocker with anticholinergic in patients with LUTS

Recommendation:

Consider offering an anticholinergic as well as an alpha-blocker to men who still have storage symptoms after treatment with alpha-blocker alone.

Guidelines considered:

NICE: Level 1b
EAU: Level 1b
AUA: Level 1b

NICE summarized studies and their clinical findings on the combination of alpha blockers and anticholinergics. Based on clinical evidence, anticholinergic added to an alpha blocker is more effective than alpha blockers alone in improving symptom scores and quality of life (IPSS question). In comparison to a placebo, combination for alpha blockers plus anticholinergics are more effective in improving symptom score, quality of life (IPSS question), urgency incontinence episodes, urgency episodes and frequency and frequency of micturition at

Table 16. Alpha blockers plus anticholinergic vs alpha blockers - Clinical study characteristics (NICE)

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptoms score at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life IPSS question at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax(ml/s) at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency incontinence episodes/24h [136]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency episodes/24h[136]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/24h[136]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/night[136]	1	RCT	Serious limitations (a)(d)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Constipation[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Diarrhoea[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dizziness[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Dry mouth[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Dyspepsia[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Ejaculation failure[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (c)
Fatigue[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Somnolence[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Headache[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Nasal congestion[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)

(a) *There was incomplete or unclear reporting for many outcomes. This study [134,136] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance ($p<0.05$ or $p<0.01$) of combination vs. placebo was indicated in the paper for some of the outcomes. (Actual values and standard deviations of these outcomes were also not reported.*

(b) *It was unclear from the graph whether standard deviation, 95% confidence intervals or standard error of the mean was reported. All efficacy outcomes were rated "very serious imprecision" as it was unclear whether the combination strategy was more effective than any of the monotherapies There is very high uncertainty in the results.*

(c) *Serious to very serious imprecision as confidence interval crossed the MID(s).*

(d) *Only about 48-52 patients in each group had urgency urinary incontinence. Bladder diaries filled for 5 days before visit.*

night. In terms of improvement of Qmax, there is no statistically significant difference compared to placebo.

There is no statistically significant difference between combination treatment of alpha blockers plus anticholinergics compared to placebo in number of men experiencing adverse events such as constipation, diarrhoea, dizziness, dyspepsia, ejaculation failure, urinary retention, fatigue, somnolence, headache or nasal congestion. However, more patients treated with a combination of alpha blockers plus anticholinergics than placebo experienced dry mouth and nasal congestion.

Table 16-b.

Outcome	Alpha-blockers + Anti-Ch	Alpha-blockers	Relative risk	Absolute effect	Quality
Symptoms score at 3 months	203	197	Not applicable	-0.4 p value NR(a)	Very Low
Quality of life (IPSS question) at 3 months	205	198	Not applicable	-0.2 p value NR(a)	Very Low
Qmax(ml/s) at 3 months	NR(b)	NR(b)	Not applicable	0.29 p value NR(a)	Very Low
Urgency incontinence episodes/24h	47	46	Not applicable	-0.1 p value NR(a)	Very Low
Urgency episodes/24h	211	205	Not applicable	-0.9 p value NR(a)	Very Low
Frequency/24h	211	205	Not applicable	-0.7 p value NR(a)	Very Low
Frequency/night	209	205	Not applicable	-0.05 p value NR(a)	Very Low
Constipation	8/225 (3.6%)	2/215 (0.9%)	RR 3.82 [0.82 to 17.8]	25 more per 1000 [2 fewer to 151 more]	Low
Diarrhoea	5/225 (2.2%)	6/215 (2.8%)	RR 0.8 [0.25 to 2.57]	17 fewer per 1000 [63 fewer to 132 more]	Low
Dizziness	6/225 (2.7%)	12/215 (5.6%)	RR 0.48 [0.18 to 1.25]	29 fewer per 1000 [46 fewer to 14 more]	Low
Dry mouth	47/225 (20.9%)	15/215 (7%)	RR 2.99 [1.73 to 5.19]	139 more per 1000 [51 to 293 more]	Moderate
Dyspepsia	3/225 (1.3%)	1/215 (0.5%)	RR 2.87 [0.3 to 27.35]	9 more per 1000 [3 fewer to 132 more]	Very Low
Ejaculation failure	7/225 (3.1%)	4/215 (1.9%)	RR 1.67 [0.5 to 5.63]	13 more per 1000 [10 fewer to 88 more]	Low
Urinary retention	2/225 (0.9%)	0/215 (0%)	RR 4.78 [0.23 to 98.97]	0 more per 1000 [0 fewer to 0 more]	Very Low
Fatigue	2/225 (0.9%)	3/215 (1.4%)	RR 0.64 [0.11 to 3.78]	5 fewer per 1000 [12 fewer to 39 more]	Low
Somnolence	4/225 (1.8%)	5/215 (2.3%)	RR 0.76 [0.21 to 2.81]	6 fewer per 1000 [18 fewer to 42 more]	Low
Headache	14/225 (6.2%)	9/215 (4.2%)	RR 1.49 [0.66 to 3.36]	21 more per 1000 [14 fewer to 99 more]	Low
Nasal congestion	10/225 (4.4%)	3/215 (1.4%)	RR 3.19 [0.89 to 11.42]	31 more per 1000 [2 fewer to 146 more]	Low

(a) The study reported outcomes as graphs only and there were no p values or standard deviations for comparison. Therefore confidence intervals could not be obtained. These values were adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre.

(b) Numbers of patients with Qmax measurements at follow up were not reported.

Table 16-c. Anticholinergics added on to alpha blockers vs. alpha blockers - Clinical study characteristics.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptom score at 3 months)[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Quality of life (IPSS question) at 3 months[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Qmax(ml/s) at 3 months[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Dry mouth- 3 months follow up[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	No serious imprecision
Infections and infestations- 3 months follow up[179]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Renal and urinary adverse events- 3 months follow up[179]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Constipations- 3 months follow up[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Nervous system disorders- 3 months follow up[179]	1	RCT	Serious limitations (a),(b)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Acute urinary retention- 3 months follow up[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Withdrawals due to adverse events[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Obstruction - Qmax<5ml/s at end point(12 weeks)[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)
Retention - PVR >300ml at end-point(12 weeks)[179]	1	RCT	Serious limitations (a)	No serious inconsistency	Serious indirectness(b)	Serious imprecision (c)

(a) Only one study where randomisation allocation and concealment methods were not reported was found [179]. Patient characteristics at screening visit (before receiving alpha-blocker) were not described.

(b) Only about half of all patients who were screened and received alpha-blockers were eligible to be randomised and the breakdown of reasons for ineligibility for randomisation was not reported.

(c) The confidence interval crossed minimum important difference.

(d) Adverse events not well defined.

Table 16-d. Anticholinergics added on to alpha blockers vs. alpha blockers - Clinical summary of findings.

Outcome	Anti-Ch add on	Alpha blockers	Relative risk	Absolute effect	Quality
Symptom score at 3 months	209	209	Not applicable	MD -1.7 [-2.92 to -0.48]	Very Low
Quality of life (IPSS-question) at 3 months	209	209	Not applicable	MD -0.5 [-0.78 to -0.22]	Very Low
Qmax(ml/s) at 3 months	209	209	Not applicable	MD -0.30 [-1.78 to1.18]	Very Low
Dry mouth- 3 months follow up	32/209 (15.3%)	10/209 (4.8%)	RR 3.2 [1.62 to 6.34]	106 more per 1000 [30 to 256 more]	Low
Infections and infestations- 3 months follow up	18/209 (8.6%)	22/209 (10.5%)	RR 0.82 [0.45 to 1.48]	19 fewer per 1000 [58 fewer to 50 more]	Very Low
Renal and urinary adverse events- 3 months follow up	10/209 (4.8%)	10/209 (4.8%)	RR 1 [0.43 to 2.35]	0 fewer per 1000 [27 fewer to 65 more]	Very Low
Constipations- 3 months follow up	1/209 (0.5%)	4/209 (1.9%)	RR 0.25 [0.03 to 2.22]	14 fewer per 1000 [18 fewer to 23 more]	Very Low
Nervous system disorders- 3 months follow up	8/209 (3.8%)	9/209 (4.3%)	RR 0.89 [0.35 to 2.26]	5 fewer per 1000 [28 fewer to 54 more]	Very Low
Acute urinary retention- 3 months follow up	0/209 (0%)	0/209 (0%)	Not estimable	Not estimable	Very Low
Withdrawals due to adverse events	21/209 (10%)	20/209 (9.6%)	RR 1.05 [0.59 to 1.88]	5 more per 1000 [39 fewer to 84 more]	Very Low
Obstruction - Qmax<5ml/s at end point(12 weeks)	14/209 (6.7%)	13/209 (6.2%)	RR 1.08 [0.52 to 2.24]	5 more per 1000 [30 fewer to 77 more]	Very Low
Retention - PVR >300ml at end-point(12 weeks)	8/209 (3.8%)	12/209 (5.7%)	RR 0.67 [0.28 to 1.6]	19 fewer per 1000 [41 fewer to 34 more]	Very Low

Table 16-e. Alpha blockers plus anticholinergics vs. placebo - Clinical study characteristics.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Symptoms score at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Quality of life (IPSS question) at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Qmax(ml/s) at 3 months [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency incontinence episodes/24h [136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Urgency episodes/24h[136]	1	RCT	Serious limitations (a)(c)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Frequency/24h[136]	1	RCT	Serious limitations (a)(c)	No serious inconsistency	No serious indirectness	Serious imprecision (b)
Frequency/night[136]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision (b)
Constipation	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Diarrhoea	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Dizziness	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Dry mouth	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Dyspepsia	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Ejaculation failure	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Urinary retention	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Fatigue	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Somnolence	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Headache	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)
Nasal congestion	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Very serious imprecision(b)

(a) This study [134,136] had 4 arms (combination, alpha-blocker, anticholinergic and placebo), but only the statistical significance of results for combination vs. placebo was reported for the effectiveness results. The standard deviations of these outcomes were also not reported and therefore not able to tell whether the combination strategy was more effective than monotherapy.

(b) Although reported as statistically significant efficacy outcomes downgraded as it was unknown whether the confidence intervals crossed the MIDs and mean difference of treatment effects were smaller than MIDs.

(c) The confidence intervals crossed the MID.

Table 16-f. Alpha blockers plus anticholinergics vs. placebo - Clinical summary of findings.

Outcome	Alpha-blockers + Anti-Ch	placebo	Relative risk	Absolute effect	Quality
Symptoms score at 3 months	203	213	Not applicable	MD-1.8 P value =0.003 (a)	Very Low
Quality of life (IPSS question) at 3 months	205	213	Not applicable	MD-0.4 p value = 0.003 (a)	Very Low
Qmax(ml/s) at 3 months	NR(b)	NR(b)	Not applicable	MD 0.60 p value = Not sig (a)	Very Low
Urgency incontinence episodes/24h	47	43	Not applicable	MD-0.57 p value = 0.005 (a)	Very Low
Urgency episodes/24h	211	210	Not applicable	MD -0.8 p value =0.03 (a)	Very Low
Frequency/24h	211	212	Not applicable	MD -1.1 p value < 0.001(a)	Low
Frequency/night	209	212	Not applicable	MD -0.2 p value =0.02 (a)	Very Low
Constipation	8/225 (3.6%)	5/220 (2.3%)	RR 1.56 [0.52 to 4.71]	13 more per 1000 [11 fewer to 85 more]	Low
Diarrhoea	5/225 (2.2%)	3/220 (1.4%)	RR 1.63 [0.39 to 6.74]	9 more per 1000 [9 fewer to 80 more]	Low
Dizziness	6/225 (2.7%)	2/220 (0.9%)	RR 2.93 [0.6 to 14.38]	17 more per 1000 [4 fewer to 120 more]	Low
Dry mouth	47/225 (20.9%)	5/220 (2.3%)	RR 9.19 [3.73 to 22.68]	188 more per 1000 [63 more to 499 more]	Moderate
Dyspepsia	3/225 (1.3%)	5/220 (2.3%)	RR 0.59 [0.14 to 2.43]	9 fewer per 1000 [20 fewer to 33 more]	Low
Ejaculation failure	7/225 (3.1%)	0/220 (0%)	RR 14.67 [0.84 to 255.28]	Not estimable	Low
Urinary retention	2/225 (0.9%)	3/220 (1.4%)	RR 0.65 [0.11 to 3.86]	5 fewer per 1000 [12 fewer to 40 more]	Low
Fatigue	2/225 (0.9%)	6/220 (2.7%)	RR 0.33 [0.07 to 1.6]	18 fewer per 1000 [25 fewer to 16 more]	Low
Somnolence	4/225 (1.8%)	2/220 (0.9%)	RR 1.96 [0.36 to 10.57]	9 more per 1000 [6 fewer to 86 more]	Low
Headache	14/225 (6.2%)	7/220 (3.2%)	RR 1.96 [0.80 to 4.75]	31 more [6 fewer to 119 more]	Low
Nasal congestion	10/225 (4.4%)	2/220 (0.9%)	RR4.89 [1.08 to 22.06]	35 more [1 to 191 more]	Low

(a) The study reported outcomes as graphs only and there were no p values or standard deviations for comparison. Therefore confidence intervals could not be obtained. These values were adjusted for smoking status, age, baseline score, duration of storage symptoms and study centre.

(b) Numbers of patients with Qmax measurements at follow up were not reported.

According to EAU, the only the combinations of the alpha blocker doxazosin, tamsulosin, or terazosin and the muscarinic receptor antagonist oxybutynin, propiverine, solifenacin, or tolterodine have been tested in clinical trials so far. Until now, both drug classes have to be taken as separate pills as no combination pill is yet available. There are at least nine trials have been published investigating the efficacy of the combination treatment with alpha blockers and muscarinic receptor antagonists in adult male patients with LUTS.

The combination of drugs was in general more efficacious in reducing voiding frequency, nocturia, or IPSS compared to a_1-blockers or placebo alone. Furthermore, the combination treatment significantly reduced urgency urinary incontinence episodes as well as urgency and significantly increased QoL.

Table 17. Efficacy of muscarinic receptor antagonists together with a1-blockers (EAU).

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency [%]	Nocturia [%]	IPSS [%]	LE
Saito et al. (1999) [1]	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20 mg/d	75	-44.7	-44.4[a]	-	
Lee et al. (2005) [3]	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4 mg/d + propiverine 1 x 20 mg/d	131	-27.5[a]	-46.7	-50.7	
Kaplan et al. (2006) [4]	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9[b]	
		Tolterodine 1 x 4 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1[b]	-39.9[b]	-66.4[b]	
MacDiarmid et al. (2008) [5]	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynine 1 x 10 mg/d	209	-	-	-51.9[b]	
Kaplan et al. (2005) [7] ‡	25	Tolterodine 1 x 4 mg/d	43	-35.7[a]	-29.3 [a]	-35.3	2b
Yang et al. (2007) [8] ‡	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7[a]	2b
Kaplan et al. (2009) [11] ‡	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2[a]	-	-29	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1[a]	-	-31.8	

IPSS = International Prostate Symptom Score
‡ persisting LUTS during α_1-blocker treatment (add-on approach)
a = significant compared to baseline ($p \leq 0.05$, indexed wherever evaluated)
b = significant reduction compared to placebo ($p < 0.05$)

In the AUA, one trials studied combination therapy with tolterodine 4 mg daily and tamsulosin 0.4 mg which demonstrated similar efficacy in QoL. Another study suggests that the combination of tamsulosin and tolterodine significantly improved total I-PSS compared to placebo and monotherapy with either agent.

Equity issue/Implementation issue(s):
None

15. What is the effectiveness of treatment with phytotherapy in patients with LUTS?

Standard:
Phytotherapeutics should NOT be prescribed as treatment to men with LUTS.

Phytotherapies include several herbal alternative therapeutics that have not been subject to the degree of efficacy and safety research that would be required of a conventional treatment. However, some perceive these as a 'natural' alternative to pharmaceutical preparations. Studies available only compare the efficacy of phytotherapies against placebo and some conventional treatments, but side effect and safety of these therapeutics have not been established.

In vitro studies have shown that plant extracts:

have anti-inflammatory, antiandrogenic, or oestrogenic effects;

decrease sexual hormone binding globulin (SHBG);

inhibit aromatase, lipoxygenase, growth-factor stimulated proliferation of prostatic cells, α-adrenoceptors, 5a-reductase, muscarinic cholinoceptors, dihydropyridine receptors, or vanilloid receptors;

improve detrusor function;

neutralise free radicals

However, most in vitro effects have not been confirmed in vivo and the precise mechanisms of action of plant extracts remain unclear.

Guidelines considered:
NICE: Level 1b
EAU: Level 1b-1a
AUA: Level 1b-1a

NICE guidelines reviewed studies on efficacy of phythotherapeutics versus a placebo, alpha blockers and 5-ARIs. The alternative therapeutics they covered were the following

Serenoa repens is an extract of the fruit serenoa repens. It has high levels of phytosterols and fatty acids and has been used to treat benign prostatic hyperplasia.

Pygeum is an extract from the bark of Prunus africana and is used to reduce symptoms of LUTS.

Urtica diocia is an extract of the root of the common stinging nettle that has been used to treat benign prostatic hyperplasia.

Beta sitosterols are phytosterols found in a number of plants including serenoa repens and pygeum africanum. They are chemically similar to cholesterol and have been used to treat LUTS.

Cernilton® is an extract prepared from the rye grass pollen (secale cereale) and has been used to treat benign prostatic hyperplasia.

Phytotherapy versus placebo

Beta-sitosterol is more effective than placebo in improving symptoms scores.

There is no statistically significant difference between serenoa repens and placebo in improving symptom scores or quality of life (IPSS question).

Serenoa repens is more effective than placebo in improving flow rates.

Urtica dioica is more effective than placebo in improving symptom scores and flow rates

Pygeum is more effective than placebo in improving flow rate.

There is no statistically significant difference between Cernilton and placebo in improving flow rate.

Phytotherapy versus alpha blockers

There is no statistically significant difference between serenoa repens and alpha blockers in change in symptom score at 6 months and at 1 year follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in change in IPSS QoL score, at 6 months.

There is no statistically significant difference between serenoa repens and alpha blockers in improving Qmax at 6 months and at 1 year follow up.

There is no statistically significant difference between serenoa repens and alpha blockers in number of patients experiencing urinary retention.
Table 19. Phytotherapy combinations vs alpha blockers -clinical study characteristics

Table 18. Phytotherapy combinations vs placebo -clinical study characteristics.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Serenoa repens and urtica diocia: symptom score[171,326]	2	RCT (a)	No serious limitations	Serious inconsistency	No serious indirectness	Serious imprecision (d)
Serenoa repens and urtica diocia: Qmax[171,326]	2	RCT (a)	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Serenoa repens and urtica diocia: quality of life (IPSS question)	0					
Urinary retention	0					
Urinary incontinence	0					
Pygeum and urtica: symptom score[199]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Pygeum and urtica: Qmax[199]	1	RCT	No serious limitations	No serious inconsistency (c)	No serious indirectness	Serious imprecision (d)
Pygeum and urtica: quality of life (IPSS question)[199]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Urinary retention	0					
Urinary incontinence	0					
Cernitin, Serenoa repens phytosterol and Vitamin E: symptom score[242]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Cernitin, Serenoa repens, phytosterol and Vitamin E: Qmax[242]	1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	Serious imprecision (d)
Urinary retention	0					
Urinary incontinence	0					

(a) Study quality and outcome effect sizes taken from Cochrane Systematic Reviews by Wilt et al., 2002[326]
(b) Statistically significant heterogeneity present
(c) Imprecision due to effect size crossing minimally important difference

Table 18-b. Phytotherapy combination vs. placebo - Clinical summary of findings.

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Serenoa repens and urtica diocia: symptom score	147	146	Not applicable	MD: 1.76 [-4.02, -0.49]	Low
Serenoa repens and urtica diocia: Qmax	147	146	Not applicable	MD: -1.76 [-4.02, 0.49]	Moderate
Pygeum and urtica: symptom score	27	22	Not applicable	MD: -1.00 [-5.30, 3.30]	Moderate
Pygeum and urtica: Qmax	27	22	Not applicable	MD: 1.10 [-1.70, 3.90]	Moderate
Pygeum and urtica: quality of life (IPSS question)	27	22	Not applicable	MD: -0.40 [-1.20, 0.40]	Moderate
Cernitin, serenoa repens, phytosterol and Vitamin E: change in symptom score	70	57	Not applicable	MD: -2.93 [-5.06, -0.80]	Moderate
Cernitin, serenoa repens, phytosterol and Vitamin E: Qmax	70	57	Not applicable	MD: -1.30 [-3.69, 1.09]	Moderate

Table 19. Phytotherapy combination vs. placebo - Clinical summary of findings.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Change in symptom score at 6 months[119]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Symptom score at 12 months[68]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Change in quality of life (IPSS question) at 6 months follow up[119]	1	RCT	Very Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Change in Qmax at 6 month[119]	1	RCT	Very serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Q max at 12 months[68]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary retention[68]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence	0					

(a) The study by Hizli 2007[119] was open label and its outcomes have been downgraded with very serious limitations. Neither study reports randomisation method, allocation concealment but follow up data was clearly reported and patients were masked to treatment allocation in one study[68] Neither study was placebo controlled.

(b) Statistical heterogeneity observed

(c) Imprecision resulting from wide confidence intervals crossing minimally important difference or small sample size.

Table 19-b.

Outcome	Serenoa repens*	Alpha blocker*	Relative risk	Absolute effect	Quality
Change in symptom score at 6 months	20	20	Not applicable	MD 1.50 [-0.37 to 3.37]	Very low
Symptom score at 12 months	269	273	Not applicable	MD -0.20 [-1.17 to 0.77]	Low
Change in quality of life (IPSS question) score at 6 months	20	20	Not applicable	MD 0.50 [-0.03 to 1.03]	Very low
Change in Qmax at 6 months	20	20	Not applicable	MD -0.50 [-1.99 to 0.99]	Very low
Q max at 12 months	267	265	Not applicable	MD -0.30 [-1.16 to 0.56]	Low
Adverse events: urinary retention	3/349 (0.9%)	3/354 (0.8%)	Relative Risk (RR): 1.01 [0.21 to 4.99]	0 more per 1000 [6 fewer to 32 more]	Low

** Column indicates pooled sample sizes. For binary outcomes, event rates are shown with percentages.*

Phythotherapy versus 5 alpha reductase inhibitors

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in improving symptom score, quality of life (IPSS score) at 6 months follow up.

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in improving Qmax at longest follow up.

There is no statistically significant difference between serenoa repens and 5-alpha reductase inhibitors in number of patients experiencing urinary retention.

There is no statistically significant difference between serenoa repens/uritica diocia combination and 5-alpha reductase inhibitors in improving symptom score at 6 and 12 months follow up.

There is no statistically significant difference between serenoa repens/uritica diocia combination and 5-alpha reductase inhibitors in improving Qmax at 3 months and longest follow up.

Table 19-c. Phytotherapy combinations vs 5 alpha reductase -clinical study characteristics.

Outcome	Number of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision
Serenoa repens: Symptom score at 6 months[43]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: QoL(IPSS question) at 6 months[43]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: Qmax at longest follow-up[43]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens: Urinary Retention[43]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Urinary incontinence	0					
Serenoa repens and uritica diocia: Symptom score at 6 months[282]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Symptom score at 12 months[282]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Qmax at 3 months[282]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	No serious imprecision
Serenoa repens and uritica diocia: Qmax at longest follow-up[282]	1	RCT	Serious limitations (a)	No serious inconsistency	No serious indirectness	Serious imprecision (c)
Quality of life (IPSS question)	0					
Urinary retention	0					
Urinary incontinence	0					

(a) Both studies reported adequate randomisation method but one study[43] did not report allocation concealment and one study[282] did not report follow up data for all patients. In both studies patients were masked to treatment but masking of outcome assessment was not clear. Neither study was placebo controlled.

(b) Statistical heterogeneity observed

(c) Imprecision resulting from wide confidence intervals crossing minimally important difference or small sample size.

Table 19-d. Phytotherapy combinations vs 5 alpha reductase inhibitors (SARI) - Clinical summary of findings.

Outcome	Serenoa repens*	5ARI*	Relative risk	Absolute effect	Quality
Serenoa repens: Symptom score at 6 months	476	484	Not applicable	MD: 0.40 [-0.29 to 1.09]	Moderate
Serenoa repens: QoL (IPSS question) at 6 months	464	484	Not applicable	MD: 0.10 [-0.06 to 0.26]	Moderate
Serenoa repens: Qmax at longest follow-up	467	484	Not applicable	MD: 0.70 [-1.60 to 0.20]	Moderate
Serenoa repens: Urinary Retention	7/553 (1.3%)	3/545 (0.6%)	RR: 2.3 [0.60 to 8.85]	8 more per 1000 [2 more to 47 more]	Low
Serenoa repens and uritica diocia: Symptom score at 6 months	233	230	Not applicable	MD: 0.20 [-0.85 to 1.25]	Moderate
Serenoa repens and uritica diocia: Symptom score at 12 months	230	223	Not applicable	MD: 0.30 [-0.71 to 1.31]	Moderate
Serenoa repens and uritica diocia: Qmax at 3 months	240	242	Not applicable	MD: -0.40 [-1.53 to 0.73]	Moderate
Serenoa repens and uritica diocia: Qmax at longest follow-up	233	232	Not applicable	MD: -0.80 [-2.00 to -0.40]	Low

EAU guidelines individually reviewed available drugs.

Cucurbita pepo: Only one trial has evaluated the efficacy of pumpkin seeds extracts (Prosta Fink™ forte) in patients with BPH-LUTS. After a follow-up of 12 months, IPSS and daytime voiding frequency were significantly reduced in the pumpkin seed group. However, uroflowmetry parameters (Qmax), post-void residual urine, prostate volume, PSA concentration, nocturia, or quality of life (QoL) Score were not statistically different between the groups.

Hypoxis rooperi: These phytopharmacological extracts contain a mixture of phytosterols bonded with glycosides of which ß-sitosterol is the most important compound (Harzol™, Azuprostat™). Four randomised, placebo-controlled trials with durations between 4 and 26 weeks were published and summarised in a Cochrane report. Daily doses of plant extracts ranged from 60 to 195 mg. Two trials evaluated symptoms and all four trials investigated Qmax and post-void residual urine. A meta-analysis calculated weighted mean differences of -4.9 IPSS points, +3.9 mL/s in terms of Qmax and -28.6 mL in terms of post-void residual urine in favour of β-sitosterol. Prostate size remained unchanged in all trials.

Pygeum africanum: A Cochrane report dealing with the clinical results of Pygeum africanum extracts (mono- or combination preparations) summarised the results of 18 randomised, placebo-controlled trials.[10] Most trials used the *Pygeum africanum* extract TadenanTM. The meta-analysis comprised 1,562 men, but individual trials were small in size and lasted only between 30 and 122 days. Most trials were performed in the 1970s and 1980s and did not use validated questionnaires such as the IPSS. Men treated with *Pygeum africanum* were twice as likely to report symptom improvement (relative risk [RR] 2.07) compared to men treated with placebo. The mean weighted difference of Q_{max} was +2.5 mL/s and of post-void residual volume -13.2 mL in favour of *Pygeum africanum*. No further trials have been published since the Cochrane report in 2002.

Secale cereale: A Cochrane report dealt with the clinical results of the main Secale cereale product Cernilton™. Men treated with Cernilton™ reported that they were twice as likely to benefit from therapy compared to placebo (RR 2.4). However, there were no significant differences between Cernilton™ and placebo with regard to Q_{max}, post-void residual urine, or prostate volume.

Sabal serrulata/Serenoa repens: A recently updated Cochrane report summarised the clinical results of 30 randomised trials comprising 5,222 men. *Serenoa repens* (mainly Permixon™ or Prostaserene™) was compared as mono or combination preparations either with placebo, other plant extracts (*Pygeum africanum, Utica dioica*), the 5-reductase inhibitor finasteride, or the -blocker tamuslosin. Mean follow-up of these trials varied between 4 and 60 weeks. The Cochrane report concluded that Serenoa repens was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction. Similar levels of IPSS or Qmax improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence. For nocturia, *Serenoa repens* was significantly better than placebo (mean weighted difference -0.78).

Urtica diocia: Two trials investigated the efficacy of stinging nettle mono preparations compared to placebo. One trial investigated men with BPH-LUTS over a period of 52 weeks; only IPSS decreased significantly in the phytotherapy group (Bazoton™ uno), whereas Q_{max} and post-void residual urine were not statistically different between the groups at the end of the trial. The second trial investigated patients with BPH-LUTS over a period of 26 weeks; IPSS, Q_{max}, and post-void residual urine significantly improved compared to placebo.

Combination preparations: Trials have been carried out, especially with the extract combination of Sabal serrulata and Utica dioica (PRO 160/120, ProstatguttTM forte). A 24-weeks placebo-controlled trial demonstrated a significant improvement in IPSS in the phytotherapy arm (-2 IPSS points difference); Q_{max} reduction was similar

in both groups. A 24-week open label extension trial of the same patients, in which all patients were treated with PRO 160/120, showed similar improvements of IPSS at week 48 in both groups (-7 IPSS points). A second trial, in which PRO 160/120 was randomised against finasteride, showed similar results for IPSS and Qmax in both groups.

Table 20. Trials with plant extracts in patients with BPH-LUS (EAU).

Trials	Duration (weeks)	Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q_{max} [mL/s]	PVR [mL]	LE
Bach (2000) (6)	52	placebo Cucurbita pepo (Prosta Fink™ forte)	243 233	-5.5 -6.7[a]	n.s. n.s.	n.s. n.s	1b
Berges et al. (1995) (8)	24	placebo *Hypoxis rooperi* (Harzol™)	100 100	-2.3 -7.4[a]	+1.1 +5.2[a]	-16.8 -35.4[a]	1b
Klippel et al. (1997) (9)	26	placebo *Hypoxis rooperi* (Azuprostat™)	89 88	-2.8 -8.2[a]	+4.3 +8.8[a]	-4.1 -37.5[a]	1b
Wilt et al. (2000) (7)	4-26	placebo Hypoxis rooperi	475	-4.9[b]	+3.9[b]	-28.6[b]	1a
Wilt et al. (2002) (10)	4-18	placebo *Pygeum africanum* (β-sitosterol)	1562	RR 2.07[b]	+2.5[b]	-13.2[b]	1a
Wilt et al. (2000) (11)	12-24	placebo *Secale cereale* (Cernilton™)	444	RR 2.4[b]	-1.6	-14.4	1a
Wilt et al. (2002) (18)	4-48	placebo Serenoa repens/ Sabal cerrulata	3139	-1.41[b]	+1.86[b]	-23[b]	1a
Bent et al. (2006) (19)	52	placebo Serenoa repens	113 112	-0.7 -0.7	-0.01 +0.42	-19 -14	1b
Carraro et al. (1996) (20)	26	finasteride *Serenoa repens* (Permixon™)	545 553	-6.2 -5.8	+3.2[a] +2.7	- -	1b
Debruyne et al. (2002) (21)	52	tamsulosin *Serenoa repens* (Permixon™)	354 350	-4.4 -4.4	+1.9 +1.8	- -	1b
Schneider & Rübben (2004) (14)	52	placebo *Urtica dioica* (Bazoton uno™)	122 124	-4.7 -5.7[a]	+2.9 +3.0	-4 -5	1b
Safarinejad (2005) (15)	26	placebo Urtica dioica	316 305	-1.5 -8.0[a]	+3.4 +8.2[a]	0 -37	1b
Lopatkin et al. (2005) (16)	24	placebo *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	126 127	-4 -6[b]	+1.9 +1.8	- -	1b
Sökeland & Albrecht (1997) (17)	48	finasteride *Sabal cerrulata* + *Urtica dioica* (Prostatgutt™ forte)	244 245	-5.6 -4.8	+2.8 +2.0	-17.1 -10.2	1b

IPSS = International Prostate Symptom Score; Q_{max} = maximal urinary flow rate (free uroflowmetry); PVR = post-void residual urine; n.s. = not significant; RR = relative risk

† absolute values; a = significant reduction compared to placebo/comparison treatment arm (p<0.05); b = in favour of plant extract.

Similar to EAU, AUA individually studied the alternative medications individually.

Saw Palmetto. A prior Cochrane meta-analysis (dated January 2002) found 21 randomized trials of saw palmetto and concluded that the evidence supported a modest beneficial effect of saw palmetto on both symptoms and flow rates and found few adverse effects associated with its use. A recent update of this systematic review (dated April 2009), incorporating more recent trials, concluded that, "*Serenoa repens* was not more effective than placebo for treatment of urinary symptoms consistent with BPH

Urtica dioica. Prior studies of Urtica dioica suggested that it may have moderate efficacy for treatment of BPH with few adverse effects. In terms of Peak Urinary Flow, the Qmax was substantially improved in the Urtica-treated group compared to the placebo group (+8.2 vs. +3.4 mL per second, $p< 0.05$).In terms of Postvoid Residual, it declined to a greater extent in the active treatment group compared to the placebo group (37 vs. 3 mL, $p<0.001$). Studying in terms of *prostate volume* measured by TRUS, decreased by 3.8 mL among the participants randomized to Urtica while the decrease was only 0.2 mL among those randomized to placebo; this difference in change scores was not statistically significant.

16. What is the effectiveness of treatment with TURP in patients with LUTS?

Standard:
If offering surgery for managing voiding LUTS presumed secondary to BPE, offer transurethral resection of the prostate. TURP is an appropriate and effective primary option for surgical therapy in men with severe LUTS and/or who are significantly bothered by these symptoms.

TURP is still regarded as the gold standard for the treatment of LUTS secondary to BPO in prostates between 30 and 80 mL. However, upper size limit of the prostate suitable for TURP has still no strong evidence. Hyperplastic prostatic tissue of the transition zone is removed endoscopically using diathermy current for prostate resection via a loop electrode using special resectoscopes. The procedure enables ablation of prostatic tissue in small slices that are then removed from the bladder at the end of surgery. It requires continuous flow with non-ionic fluid irrigant (usually glycine 1.5%) via the endoscope, which is passed down the urethra.

Guidelines considered:
NICE: Level 1a-1b
EAU: Level 1b
AUA: Level 1b

The NICE guidelines searched for RCT evidence comparing the effectiveness of different surgical interventions for lower urinary tract symptoms and made a matrix of treatment comparisons and evidence available. However, studies included were on patients having a first surgery and without prior catheterisation, and therefore not totally generalisable.

TURP is more effective than watchful waiting in improving Qmax at 3 years follow up.

Significantly more men were re-catheterised perioperatively for the TURP group compared to watchful waiting. 3.2% of men following TURP were re-catheterised.

Significantly fewer men had reoperation or received surgery for the TURP group compared to the watchful waiting group during the follow up period.

There is no significant difference between TURP and watchful waiting in the number of all cause mortality or number of men who experienced blood transfusions, urinary tract infections and urinary incontinence.

There is no statistically significant difference between Bipolar TURP and TURP in improving symptom score and improving IPSS QoL score at any follow up interval. In terms of improving the Q_{max}, there is no statistically significant difference between Bipolar TURP and TURP at 3 months or 1 year follow up.

TUNA	No									
LASER	**Yes p 225**	No								
TUMT	No	No	**Yes p 223**							
TURP	**Yes p 242**	**Yes p 249**	**Yes p 211 & p216**	**Yes p238**						
TUIP	No	No	No	No	**Yes p253**					
OP	No	No	**Yes p220**	No	No	No				
BT	No	No	No	No	No	No	No			
HOLEP	No	No	No	No	**Yes p200**	**Yes p 207**	**Yes p209**	No		
HIFU	No	No	No	No	No	No	No	No	No	
NT	No	No	No	**Yes p235**	**Yes p265**	No	No	**Yes p257**	No	No
	TUVP	TUNA	LASER	TUMT	TURP	TUIP	OP	BT	HOLEP	HIFU

TUNA – transurethral needle ablation; TUMT – transurethral microwave thermotherapy; TURP – transurethral resection of the prostate; TUIP – transurethral incision of the prostate; OP – open prostatectomy; BT – botulinum toxin in prostate; HOLEP – holmium laser enucleation of the prostate; HIFU – high intensity focused ultrasound; NT – no treatment (includes sham studies)

In addition we searched for evidence comparing bipolar TURP, bipolar TUVP, TUVRP, stents and TEAP with TURP. Below is a table showing where evidence was identified. A box filled with '**Yes**' represents where evidence was found and is reviewed in this chapter. A box filled with '**No**' represents where no evidence was found. In this case, no section on this comparison is included in the chapter.

Figure 2. Matrix of treatment comparisons and evidence (NICE).

Table 21. TURP vs watchful waiting - Clinical summary of findings (NICE).

Outcome	*TURP*	*WW*	*Relative risk*	*Absolute effect*	*Quality*
Qmax at longest available follow up(3 years)	280	276	Not applicable	MD 5.1 [3.71 to 6.49]	Moderate
All cause mortality	13/280 (4.6%)	10/276 (3.6%)	RR 1.28 [0.57 to 2.87]	10 more per 1,000 [15 fewer to 67 more]	Low
Blood transfusion	3/280 (1.1%)	0/276 (0%)	RR 6.9 [0.36 to 132.97]	0 more per 1000 [0 fewer to 0 more]	Low
TUR syndrome					No data
Re-catheterisation	9/280 (3.2%)	0/276 (0%)	RR 18.73 [1.1 to 320.24]	0 more per 1000 [0 more to 0 more]	Low
Urinary tract infection	2/280 (0.7%)	0/276 (0%)	RR 4.93 [0.24 to 102.2]	0 more per 1000 [0 fewer to 0 more]	Low
Urinary incontinence - at 3 years follow up	4/280 (1.4%)	4/276 (1.4%)	RR 0.99 [0.25 to 3.9]	0 fewer per 1000 [10 fewer to 41 more]	Low
Reoperation/received surgery in watchful waiting group (3 years)	26/280 (9.3%)	65/276 (23.6%)	RR 0.39 [0.26 to 0.6]	144 fewer per 1000 [94 to 175 fewer]	Moderate

There is no statistically significant difference between bipolar TURP and TURP in number of men experiencing TUR syndrome though the result is borderline in favor of bipolar TURP.

There is no statistically significant difference between bipolar TURP and TURP in number of men requiring transfusion, experiencing urinary retention, UTI, incontinence or strictures, reoperation rate or mortality rate.

Table 22. Bipolar TURP vs TURP -Clinical summary of findings (NICE).

Outcome	Bipolar TURP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	24	24	not applicable	MD -1.30 [-4.26 to 1.66]	Low
Symptom score at 6 months	49	48	not applicable	MD 0.45 [-0.20 to 1.11]	Low
Symptom score at 1 year	227	228	not applicable	MD 0.06 [-0.38 to 0.50]	Moderate
Symptom score at 2 year	33	34	not applicable	MD -0.30 [-2.14, 1.54]	Low
Symptom score at 3 year	33	33	not applicable	MD 0.60 [-1.90, 3.10]	Low
Symptom score at 4 year	32	31	not applicable	MD 0.50 [-1.26, 2.26]	Low
Quality of life (IPSS question) at 3 months	24	24	not applicable	MD -0.30 [-0.92 to 0.32]	Low
Quality of life (IPSS question) at 6 months	24	23	not applicable	MD 0.00 [-0.60 to 0.60]	Low
Quality of life (IPSS question) at 1 year	203	202	not applicable	MD -0.03 [-0.23 to 0.17]	Moderate
Quality of life (IPSS question) at 3 years	33	33	not applicable	MD -0.10 [-0.71 to 0.51]	Low
Quality of life (IPSS question) at 4 years	32	31	not applicable	MD -0.10 [-0.96 to 0.76]	Low
Qmax at 3 months	58	57	not applicable	MD 0.38 [-6.05 to 4.25]	Low
Qmax at 4 years	32	31	not applicable	MD -1.40 [-4.93 to 2.13]	Low
Blood transfusion	8/426 (1.9%)	12/399 (3.0%)	RR: 0.62 [0.25 to 1.50]	11 fewer from 22 fewer to 15 more	Low
Urinary retention	12/373 (3.2%)	14/383 (3.7%)	RR: 0.90 [0.44 to 1.86]	4 fewer from 21 fewer to 32 more	Low
UTI	12/156 (7.7%)	13/158 (8.2%)	RR: 0.91 [0.44 to 1.92]	7 fewer from 46 fewer to 75 more	Low
Urinary incontinence	1/172 (0.6%)	3/175 (1.7%)	RR: 0.45 [0.07 to 3.02]	9 fewer from 16 fewer to 34 more	Low
Reoperations	2/297 (0.7%)	12/301 (4.0%)	RR: 0.32 [0.09 to 1.07]	27 fewer from 36 fewer to 3 more	Low
TUR syndrome	0/428 (0%)	7/438 (1.6%)	RR: 0.23 [0.05 to 1.07]	12 fewer from 15 fewer to 1 more	Low
Strictures	20/340 (5.9%)	14/345 (4.1%)	RR: 1.42 [0.74 to 2.71]	17 more from 11 fewer to 70 more	Low
All cause mortality	0/120 (0%)	0/120 (0%)	not estimable	not estimable	Very Low
Catheterisation time (days)	397	401	not applicable	MD -0.82 [-1.20 to -0.45]	Very Low
Length of Stay (days)	200	201	not applicable	MD -0.91 [-1.87 to -0.04]	Very Low

HoLEP vs TURP

Six clinical studies were identified which compared HoLEP with TURP except for one study that compared holmium laser resection with TURP.

Table 23. HOLEP vs TURP - Clinical summary of findings (NICE)

Outcome	HoLEP*	TURP*	Relative risk	Absolute effect	Quality
Mean symptom score at 3 months	104	103	Not applicable	Mean Difference (MD): -0.18 [-1.09, 0.74]	Moderate
Mean symptom score at 6 months (a)	283	275	Not applicable	MD: -0.52 [-1.35, 0.31]	Low
Mean symptom score at 12 months (a)	269	260	Not applicable	MD: -0.71 [-1.62, 0.20	Low
Mean symptom score at 24 months (a)	147	142	Not applicable	MD: -0.80 [-2.73, 1.13]	Low
Mean symptom score at 36 months	75	69	Not applicable	MD: -0.60 [-1.61, 0.41]	Moderate
Mean symptom score at 48 months	43	30	Not applicable	-1.40 [-3.91, 1.11]	Low
Mean quality of life (IPSS question) at 3 months	89	88	Not applicable	MD: -0.19 [-0.68, 0.30]	Low
Mean quality of life (IPSS question) at 6 months (a)	139	136	Not applicable	MD: 0.06 [-0.49, 0.61]	Very low
Mean quality of life (IPSS question) at 12 months (a)	130	124	Not applicable	MD: -0.01 [-0.96, 0.95]	Very low
Mean quality of life (IPSS question) at 24 months	67	67	Not applicable	MD: -0.01 [-0.40, 0.38]	Moderate
Mean quality of life (IPSS question) at 48 months	43	30	Not applicable	MD: -0.30 [-0.90, 0.30]	Low
Mean Qmax, ml/s at 3 months	104	103	Not applicable	MD: 2.73 [0.30, 5.15]	Low
Mean Qmax, ml/s at longest follow up	257	238	Not applicable	MD: 1.40 [0.89, 1.91]	Moderate
All cause mortality	1/241 (0.4%)	2/239 (0.8%)	Relative Risk (RR): 0.59 [0.08, 4.39]	3 fewer per 1000 [7 fewer to 27 more]	Low
Infection	3/91 (3.3%)	7/89 (7.9%)	RR: 0.45 [0.13, 1.57]	43 fewer per 1000 [69 fewer to 45 more]	Low
Re-operation	13/240 (5.4%)	17/227 (7.5%)	RR: 0.73 [0.37, 1.45]	20 fewer per 1000 [47 fewer to 34 more]	Low
TUR syndrome	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000 [21 fewer to 134 more]	Low
Acute retention	16/308 (5.2%)	22/302 (7.3%)	RR: 0.72 [0.39, 1.32]	20 fewer per 1000 [45 fewer to 23 more]	Low
Blood transfusion	1/308 (0.3%)	10/302 (3.3%)	RR: 0.27 [0.08, 0.89]	24 fewer per 1000 [4 to 30 fewer]	Moderate
Stricture	13/271 (4.8%)	18/257 (7.0%)	RR: 0. 69 [0.34, 1.37]	22 fewer per 1000 [46 fewer to 26 more]	Low
Retrograde ejaculation	36/41 (87.8%)	40/50 (80.0%)	RR: 1.14 [0.95, 1.36]	112 fewer per 1000 [40 fewer to 288 more]	Low
Urinary incontinence	35/267 (13.1%)	26/258 (10.1%)	RR: 1.26 [0.83, 1.91]	26 fewer per 1000 [17 fewer to 92 more]	Low

a) Random effects analysis used

There is no statistically significant difference between HoLEP and TURP in improving symptom scores, quality of life at 3, 6, 12, 24, 36 and 48 months post-operatively. However, HoLEP is more effective than TURP in improving urinary flow rate at 3 months and longest follow up.

Comparing morbidities among the two, fewer men treated with HoLEP compared to TURP experienced blood transfusions, in other aspects such as men experiencing strictures, urinary retention, TUR, reoperations, incontinence, infection, retrograde ejaculation or mortality, there is no statistically significant difference between HoLEP and TURP.

Table 24. Thulium laser resection vs TURP - Clinical summary of findings (NICE).

Outcome	Thulium	TURP	Relative risk	Absolute effect	Quality
Mean symptom score at 6 months	52	48	Not applicable	MD: 0.20 [-0.83, 1.23]	Moderate
Mean symptom score at 12 months	52	48	Not applicable	MD: -0.40 [-1.50, 0.70]	Moderate
Qmax at long-term follow-up	52	48	Not applicable	MD: -0.40 [-2.84, 2.04]	Low
Quality of life (IPSS question) at 6 months	52	48	Not applicable	MD: 0.20 [-0.21, 0.61]	Low
Quality of life (IPSS question) at 12 months	52	48	Not applicable	MD: 0.10 [-0.23, 0.43]	Moderate
Infection	2/52 (3.8%)	4/48 (8.3%)	RR: 0.46 [0.09, 2.41]	45 fewer per 1000]76 fewer to 117 more]	Low
TUR syndrome	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000 [21 fewer to 134 more]	Low
Urinary retention	0/52 (0%)	0/48 (0%)	Not estimable	Not estimable	Low
Blood transfusion	0/52 (0%)	2/48 (4.2%)	RR: 0.18 [0.01, 3.76]	34 fewer per 1000 [42 fewer to116 more]	Low
Stricture	1/52 (1.9%)	3/48 (6.3%)	RR: 0.31 [0.03, 2.86]	43 fewer per 1000 [61 fewer to117 more]	Low
Urinary incontinence (stress)	0/52 (0%)	1/48 (2.1%)	RR: 0.31 [0.01, 7.39]	14 fewer per 1000]21 fewer to 134 more]	Low
Retrograde ejaculation	18/33 (54.5%)	20/31 (64.5%)	RR: 0.85 [0.56, 1.27]	97 fewer per 1000 [284 fewer to 174 more]	Low

There is no statistically significant difference between thulium laser resection and TURP in improving symptom scores and improving quality of life scores (IPSS question) at 6 and 12 months post-operatively. At long term follow up there is no statistically significant difference between thulium laser resection and TURP in improving maximum urinary flow.

There is no statistically significant difference between thulium laser and TURP in the number of complications for infection, TUR, urinary retention, transfusion, incontinence or retrograde ejaculation.

Laser Coagulation Techniques vs TURP

A total of 13 studies for laser coagulation vs. TURP were identified. Laser coagulation studies included visual laser ablation of the prostate (VLAP), interstitial laser coagulation (ILC), endoscopic laser ablation of the prostate and laser coagulation using bladder neck incision. There was one study specifically conducted in patients with acute urinary retention (AUR).

Laser coagulation techniques are less effective than TURP in improving symptom scores and in improving quality of life (IPSS question) at 12 months and 2 years post-operatively. There is no statistically significant difference between laser coagulation techniques and TURP in improving symptom scores at 3 and 6 months and also in improving quality of life (IPSS question) at 6 months post-operatively. No studies report quality of life at 18 months, 3 years, 4 years and 5 years.

Laser coagulation techniques are less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up post-operatively.

There is no statistically significant difference between laser coagulation techniques and TURP in all cause mortality or number of patients who experienced TUR syndrome and urinary retention. More patients treated with laser coagulation techniques compared to TURP experienced urinary tract infection and reoperations.

Table 25. Laser coagulation vs TURP - Clinical summary of findings (NICE)

Outcome	Laser Coagulation	TURP	Relative risk	Absolute effect	Quality
Symptom score - 3 months (a)	88	75	Not applicable	MD 1.74 [-3.33 to 6.80]	Very Low
Symptom score - 6 months (a)	213	197	Not applicable	MD 2.26 [-0.45 to 4.97]	Very Low
Symptom score - 12 months	30	14	Not applicable	MD 8.90 [5.75 to 12.05]	Low
Symptom score - 24 months	30	14	Not applicable	MD 7.00 [4.1 to 9.9]	Low
Quality of life (IPSS question)- 3 months	30	14	Not applicable	MD 1.4 [0.55 to 2.25]	Low
Quality of life (IPSS question)- 6 months (a)	153	132	Not applicable	MD 0.80 [-0.13 to 1.74]	Very Low
Quality of life (IPSS question)- 12 months	30	14	Not applicable	MD 1.6 [0.92 to 2.28]	Low
Quality of life (IPSS question)- 24 months	30	14	Not applicable	MD 1.5 [0.79 to 2.21]	Low
Qmax at follow up - 3 months (a)	164	150	Not applicable	MD -5.75 [-9.42 to -2.09]	Low
Qmax - Longest available follow up (a)	355	347	Not applicable	MD -4.27 [-6.22 to -2.31]	Low
All cause mortality	8/305 (2.6%)	6/310 (0.8%)	RR 1.31 [0.49 to 3.50]	6 more per 1000 [10 fewer to 48 more]	Low
Blood transfusion	1/473 (0.2%)	30/475 (6.3%)	RR 0.12 [0.04 to 0.35]	55 fewer per 1000 [41 to 60 fewer]	Moderate
TUR syndrome	0/124 (0%)	3/133 (2.3%)	RR 0.27 [0.03 to 2.39]	17 fewer per 1000 [22 fewer to 32 more]	Low
Urinary retention	19/145 (13.1%)	9/110 (8.2%)	RR 0.55 [0.27 to 1.12]	37 fewer per 1000 [60 fewer to 10 more]	Low
Urinary tract infections	62/370 (16.8%)	23/362 (6.4%)	RR 2.27 [1.45 to 3.56]	81 more per 1000 [29 to 164 more]	Moderate
Retrograde ejaculation (a)	15/189 (7.9%)	84/177 (47.5%)	RR 0.16 [0.05 to 0.53]	389 fewer per 1000 [223 to 451 fewer]	Low
Urinary incontinence	0/286 (0%)	11/283 (3.9%)	RR 0.16 [0.04 to 0.72]	33 fewer per 1000 [12 to 37 fewer]	Moderate
Strictures	1/195 (0.5%)	14/201 (7%)	RR 0.11 [0.02 to 0.59]	62 fewer per 1000 [29 to 69 fewer]	Moderate
Reoperation	29/311 (9.3%)	2/301 (0.7%)	RR 6.68 [2.44 to 18.24]	40 more per 1000 [10 to 121 more]	Moderate

(b) Random effects analysis were conducted for these outcomes

Fewer patients treated with laser coagulation techniques compared to TURP experienced blood transfusions, strictures, retrograde ejaculation or urinary incontinence.

In AUR patients, there is no statistically significant difference between laser coagulation techniques and TURP in symptom scores or quality of life at 6 months follow up.

In AUR patients, there is no statistically significant difference between laser coagulation techniques and TURP in all cause mortality or number of patients who experienced TUR syndrome, blood transfusion and urinary retention, urinary tract infections, urinary incontinence or reoperations.

Laser Vaporisation Techniques vs TURP

A total of 11 studies were identified comparing laser vaporization techniques with TURP. Two studies used KTP laser vaporization and two used a combination of KTP and NdYAG laser vaporization; the other 7 studies reported laser vaporization techniques using NdYAG.

Table 25-b. Laser coagulation vs TURP in AUR patients - Clinical summary of findings (NICE)

Outcome	Laser coagulation	TURP	Relative risk	Absolute effect	Quality
Symptom score - 6 months	54	48	Not applicable	MD 3.4 [-0.1 to 6.9]	Low
Quality of life score (IPSS question)- 6 months	49	45	Not applicable	MD 0.30 [-0.41 to 1.01]	Low
All cause mortality	8/305 (2.6%)	6/310 (1.9%)	RR 1.31 [0.49 to 3.50]	27 fewer per 1000 [49 fewer to 89 more]	Low
Blood transfusion	0/74 (0%)	4/74 (5.4%)	RR 0.11 [0.01 to 2.03]	48 fewer per 1000 [53 fewer to 56 more]	Low
TUR syndrome	0/74 (0%)	2/74 (2.7%)	RR 0.2 [0.01 to 4.1]	22 fewer per 1000 [27 fewer to 84 more]	Low
Urinary retention	1/74 (1.4%)	0/74 (0%)	RR 3 [0.12 to 72.47]	0 more per 1000 [0 fewer to 0 more]	Very Low
Urinary tract infections	3/74 (4.1%)	4/74 (5.4%)	RR 0.75 [0.17 to 3.24]	14 fewer per 1000 [45 fewer to 121 more]	Low
Urinary incontinence	0/286 (0%)	11/283 (3.9%)	RR 0.16 [0.04 to 0.7]	35 fewer per 1000 [41 fewer to 71 more]	Moderate
Reoperation	29/311 (9.3%)	2/301 (0.7%)	RR 6.68 [2.44to 18.24]	84 more per 1000 [2 fewer to 763 more]	Low

There is no statistically significant difference between laser vaporization techniques and TURP in improving symptom score and improving IPSS QoL score at 3 months, 6 months, 2 years and at 5 years or longer follow up.

Laser vaporization techniques are less effective than TURP in improving symptom score and in improving IPSS QoL score at 1 year and 3 years follow up.

Laser vaporization techniques are less effective than TURP in improving Qmax at 3 months follow up but there is no statistically significant difference at longest available follow up.

Fewer patients treated with laser vaporization techniques compared to TURP experienced transfusions or strictures, however those treated with laser vaporization techniques compared to TURP experienced urinary retention.

There is no statistically significant difference between laser vaporization techniques and TURP in number of patients with all cause mortality, UTI, reoperation, incontinence, TUR syndrome or retrograde ejaculation.

TURP is more effective than TUMT in improving symptom scores at 3, 6, 24 and 36 months post-operatively, however there is no statistically significant difference between TURP and TUMT in improving symptom scores at 12, 48 or 60 months post-operatively.

TURP is more effective than TUMT in improving maximum urinary flow rates at 3 months and longest follow-up post-operatively.

TURP is more effective than TUMT in improving quality of life scores at 24 months post-operatively, however there is no statistically significant difference between TURP and TUMT in improving quality of life scores at 3, 6, 12, 36, 48 or 60 months.

There is no statistically significant difference between TUMT and TURP in number of patients experiencing infection, blood transfusion, TUR syndrome, incontinence, retrograde ejaculation or mortality.

Significantly fewer men treated with TURP experienced acute retention, reoperations compared to TUMT.

Table 25-c. Laser vaporisation vs TURP - Clinical summary of findings (NICE).

Outcome	Laser Vaporisation	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months (a)	104	109	Not applicable	MD 1.78 [-2.28 to 5.84]	Very Low
Symptom score at 6 months (a)	171	173	Not applicable	MD 2.39 [-0.31 to 5.09]	Very Low
Symptom score at 1 year (a)	225	228	Not applicable	MD 0.99 [0.14 to 1.85]	Low
Symptom score at 2 years	68	71	Not applicable	MD 1.77 [-0.16 to 3.70]	Very Low
Symptom score at 3 years	76	89	Not applicable	MD 2.49 [0.54 to 4.44]	Very Low
Symptom score at 5 years or more	42	47	Not applicable	MD 2.09 [-0.74 to 4.92]	Very Low
Quality of life (IPSS question) score at 6 months	33	37	Not applicable	MD 0.30 [-0.08 to 0.68]	Very Low
Quality of life (IPSS question score at 1 year	37	41	Not applicable	MD 0.00 [-0.38 to 0.38]	Low
Quality of life (IPSS question at 3 years	10	15	Not applicable	MD 0.90 [0.03 to 1.77]	Very Low
Quality of life (IPSS question) at 5 years or longer	17	15	Not applicable	MD 0.10 [-0.77 to 0.97]	Very Low
Qmax at 3 months	169	173	Not applicable	MD -2.49 [-4.35 to – 0.64]	Low
Qmax at longest available follow up (a)	231	237	Not applicable	MD -0.133 [-3.17 to 2.52]	Very Low
Blood transfusion	1/430 (0.2%)	25/423 (5.9%)	0.13 [0.04 to 0.40]	51 fewer per 1000 [35 fewer to 57 fewer]	Moderate
Urinary retention	26/288 (9%)	5/296 (1.7%)	4.6 [1.93 to 10.95]	61 more per 1000 [16 more to 169 more]	Moderate
UTI	28/270 (10.4%)	23/273 (8.4%)	1.21 [0.73 to 2.02]	18 more per 1000 [23 fewer to 86 more]	Low
Retrograde ejaculation (a)	25/121 (20.7%)	48/117 (41%)	0.38 [0.11, 1.27]	254 fewer per 1000 [365 fewer to 111 more]	Very Low
Urinary incontinence	3/279 (1.1%)	3/272 (1.1%)	0.09 [0.26 to 3.15]	1 fewer per 1000 [8 fewer to 24 more]	Low
Reoperations	33/380 (8.7%)	21/373 (5.6%)	1.58 [0.95 to 2.63]	32 more per 1000 [3 fewer to 91 more]	Low
TUR syndrome	0/133 (0%)	1/134 (0.7%)	0.33 [0.01 to 7.93]	5 fewer per 1000 [7 fewer to 49 more]	Low
Strictures	9/404 (2.2%)	27/397 (6.8%)	0.38 [0.19 to 0.74]	42 fewer per 1000 [18 fewer to 55 fewer]	Moderate
All cause mortality	14/164 (8.5%)	16/177 (9%)	0.94 [0.47 to 1.86]	5 fewer per 1000 [48 fewer to 77 more]	Low

(a) Outcome were analysed using random effects analysis

Significantly fewer men treated with TUMT experienced strictures compared to TURP.

There is no statistically significant difference between TUVP and TURP in improving symptom score at any follow up interval.

TURP is more effective than TUVP in improving quality of life (IPSS question) at 6 months.

TUVP is more effective than TURP in improving quality of life (IPSS question) at 3 years.

Table 26. TUMP vs TURP - Clinical summary of findings (NICE).

Outcome	TUMT	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	173	117	Not available	MD: 5.48 [0.94 to 10.01]	Very low
Symptom score at 6 months	153	93	Not available	MD: 1.25 [0.11 to 2.39]	Moderate
Symptom score at 12 months	178	108	Not available	MD: 2.26 [-0.38 to 4.91]	Very low
Symptom score at 24 months	123	76	Not available	MD: 3.65 [2.1 to 5.2]	Low
Symptom score at 36 months	103	68	Not available	MD: 6.03 [0.45 to 11.62]	Very low
Symptom score at 48 months	56	30	Not available	MD: 0.7 [-2.05 to 3.45]	Low
Symptom score at 60 months	63	34	Not available	MD: 1.4 [-0.88 to 3.68]	Low
Quality of life score at 3 months	84	41	Not applicable	MD: 0.4 [-0.17 to 0.97]	Low
Quality of life score at 6 months	93	42	Not applicable	MD: 0.3 [-0.24 to 0.84]	Low
Quality of life score at 12 months	151	91	Not applicable	MD: 0.62 [-0.76 to 1.99]	Very low
Quality of life score at 24 months	123	76	Not applicable	MD: 0.71 [0.12 to 1.30]	Low
Quality of life score at 36 months	103	68	Not applicable	MD: 1.01 [-0.37 to 2.38]	Very low
Quality of life score at 48 months	56	30	Not applicable	MD: 0.2 [-0.33 to 0.73]	Low
Quality of life score at 60 months	63	34	Not applicable	MD: 0.0 [-0.46 to 0.46]	Moderate
Qmax at 3 months	183	131	Not applicable	MD: -4.92 [-7.34, -2.49]	Moderate
Qmax at long term follow-up	197	158	Not applicable	MD: -5.40 [-7.29, -3.51]	Moderate
All cause mortality	3/246 (1.2%)	4/165 (2.4%)	RR: 0.60 [0.18, 2.01]	10 fewer per 1000 [20 fewer to 24 more]	Low
Infection	32/237 (13.5%)	18/169 (10.7%)	RR: 1.08 [0.64, 1.83]	9 more per 1000 [39 fewer to 89 more]	Low
Re-operation	31/285 (10.9%)	8/205 (3.9%)	RR: 2.81 [1.35, 5.86]	71 more per 1000 [14 to 190 more]	Moderate
TUR syndrome	0/100 (0%)	1/46 (2.2%)	RR: 0.16 [0.01, 3.74]	18 fewer per 1000 [22 fewer to 60 more]	Low
Urinary retention	28/215 (13%)	6/144 (4.2%)	RR: 2.22 [1.04, 4.73]	51 more per 1000 [2 to 157 more]	Low
Blood transfusion	0/98 (0%)	4/83 (4.8%)	RR: 0.11 [0.01, 1.98]	43 fewer per 1000 [48 fewer to 47 more]	Low
Stricture	1/184 (0.5%)	10/168 (6%)	RR: 0.20 [0.05, 0.78]	48 fewer per 1000 [13 to 57 fewer]	Low
Retrograde ejaculation	28/54 (51.9%)	17/61 (27.9%)	RR: 1.41 [0.09, 21.63]	114 more per 1000 [254 fewer to 1000 more]	Very low
Urinary incontinence(a)	11/217 (5.1%)	14/152 (9.2%)	RR: 0.52 [0.12, 2.21]	44 fewer per 1000 [81 fewer to 111 more]	Very Low

(a) *Outcomes analysed using random effects analysis.*

There is no statistically significant difference between TUVP and TURP in improving quality of life (IPSS question) at 3 months, 1 year, 2 years and 5 years or longer follow up.

There is no statistically significant difference between TUVP and TURP in improving Qmax at 3 months or longer follow up.

Significantly more men treated with TUVP than TURP experience urinary retention.

Significantly more men treated with TURP than TUVP required blood transfusions.

There is no statistically significant difference between TUVP and TURP in number of men experiencing UTI, incontinence, retrograde ejaculation, TUR syndrome or strictures.

Table 27. TUVP vs TURP-Clinical Summary of findings (NICE).

Outcome	TUVP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	192	205	not applicable	MD -0.03 [-0.62 to 0.55]	Moderate
Symptom score at 6 months	276	292	not applicable	MD 0.34 [-0.14 to 0.82]	Moderate
Symptom score at 1 year	243	266	not applicable	MD 0.40 [-0.09 to 0.88]	Moderate
Symptom score at 2 years (a)	137	124	not applicable	MD -0.50 [-3.54 to -2.54]	Low
Symptom score at 3 years (a)	52	55	not applicable	MD -0.99 [-6.25 to 4.28]	Very Low
Symptom score at 5 years or longer	59	65	not applicable	MD -0.31 [-1.95 to 1.32]	Low
Quality of life (IPSS question) at 3 months	20	20	not applicable	MD -0.40 [-3.49 to 2.69]	Very Low
Quality of life (IPSS question) at 6 months	140	145	not applicable	MD 0.48 [0.14 to 0.82]	Low
Quality of life (IPSS question) at 1 year (a)	108	120	not applicable	MD 0.04 [-0.52 to 0.59]	Very Low
Quality of life (IPSS question) at 2 years (a)	136	127	not applicable	MD -0.25 [-0.94 to 0.43]	Low
Quality of life (IPSS question) at 3 years	52	55	not applicable	MD -0.48 [-0.93 to -0.03]	Low
Quality of life (IPSS question) at 5 years or longer	38	42	not applicable	MD -0.30 [-0.82 to 0.23]	Very Low
Qmax at 3 months	241	250	not applicable	MD -0.52 [-1.15 to 0.11]	Low
Qmax at long term follow-up	217	239	not applicable	MD -0.16 [-1.58 to 1.26]	Very low
Blood transfusion	2/536 (0.4%)	29/566 (5.1%)	RR: 0.19 [0.08 to 0.44]	41 fewer from 29 fewer to 47 fewer	Low
Urinary retention	26/291 (8.9%)	8/316 (2.5%)	RR: 3.10 [1.53 to 6.29]	52 more from 13 more to 132	Low
UTI	13/154 (8.4%)	14/160 (8.8%)	RR: 0.97 [0.48 to 1.98]	3 fewer from 46 fewer to 86 more	Low
Retrograde ejaculation (a)	68/171 (39.8%)	70/174 (40.2%)	RR: 0.97 [0.54 to 1.73]	12 fewer from 185 fewer to 294 more	Very Low
Urinary incontinence	10/301 (3.3%)	5/329 (1.5%)	RR: 2.29 [0.79 to 6.60]	19 more from 3 fewer to 84 more	Low
Reoperations	7/185 (3.8%)	7/198 (3.5%)	RR: 1.05 [0.41 to 2.72]	2 more from 21 fewer to 60 more	Low
TUR syndrome	3/266 (1.1%)	6/278 (2.2%)	RR: 0.59 [0.17 to 2.12]	9 fewer from 18 fewer to 25 more	Low
Strictures	80/578 (13.8%)	77/620 (12.4%)	RR: 1.09 [0.87 to 1.37]	11 more from 16 fewer to 46 more	Low
All cause mortality	6/221 (2.7%)	8/239 (3.3%)	RR: 0.82 [0.33 to 2.08]	6 fewer from 22 fewer to 36 more	Low

(a) *Outcomes analysed using random effects analysis.*

Table 28. Bipolar TUVP vs TURP - Clinical summary of findings (NICE)

Outcome	Bipolar TUVP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	38	37	not applicable	MD -4.00 [-5.43 to -2.57]	Very Low
Symptom score at 6 months	38	37	not applicable	MD -4.00 [-5.20 to -2.80]	Very Low
Symptom score at 1 year	38	37	not applicable	MD -5.00 [-7.89 to -2.11]	Very Low
Symptom score at 2 years	25	15	not applicable	MD 1.90 [1.09 to 2.71]	Very Low
Symptom score at 3 years	25	15	not applicable	MD 1.90 [1.08 to 2.72]	Very Low
Qmax at 3 months	38	37	not applicable	MD -1.00 [-1.97 to -0.03]	Very Low
Qmax at 3 years	25	15	not applicable	MD -7.40 [-9.27 to -5.53]	Very Low
Blood transfusion	0/119 (0%)	6/116 (5.2%)	RR: 0.14 [0.02 to 1.11]	45 fewer from 51 fewer to 6 more	Low
Urinary retention	11/111 (9.9%)	3/100 (3.0%)	RR: 2.01 [0.14 to 28.04]	30 more from 26 fewer to 811 more	Low
Retrograde ejaculation	31/38 (81.6%)	32/37 (86.5%)	RR: 0.94 [0.77 to 1.15]	52 fewer from 199 fewer to 130 more	Very Low
TUR syndrome	0/38 (0%)	0/37 (0%)	not estimable	not estimable	Very Low
Strictures	3/119 (2.5%)	4/116 (3.4%)	RR: 0.73 [0.17 to 3.17]	9 fewer from 28 fewer to 74 more	Low
Catheterisation time (days)	38	37	not applicable	MD -1.30 [-1.68 to -0.92]	Very Low
Length of Stay (days)	119	116	not applicable	MD -0.84 [-1.73 to 0.04]	Very Low

Bipolar TUVP is more effective than TURP in improving symptom score at 3 months, 6 months and 1 year follow up.

Bipolar TUVP is less effective than TURP in improving symptom score at 2 and 3 years follow up.

Bipolar TUVP is less effective than TURP in improving Q_{max} at 3 months and 3 years follow up.

There is no statistically significant difference between bipolar TUVP and TURP in number of men requiring transfusion though the result is borderline in favour of Bipolar TUVP. There is no statistically significant difference between bipolar TUVP and TURP in the number of patients experiencing urinary retention, retrograde ejaculation, TUR syndrome or strictures.

Catheterization time (days) is significantly shorter for those men treated with bipolar TUVP compared to TURP. For the length of stay (in days) there is no statistically significant difference between Bipolar TUVP and TURP though the result is borderline in favour of bipolar TUVP.

TUNA is less effective than TURP in improving symptoms scores at 12 months and 2, 3 and 4 years post-operatively. However the studies concluded that there is no statistically significant difference between and TUNA and TURP in improving symptom scores at 3, 18 months and 5 years, as well as in improving quality of life scores (IPSS question) at 3 and 18 months.

TUNA is less effective than TURP in improving the maximum urinary flow at 3 months or longer follow-up post-operatively.

There is no statistically significant difference between TUNA and TURP in all cause mortality or number of patients who experienced urinary retention or urinary tract infections.

Fewer men treated with TUNA compared to TURP experienced blood transfusion, strictures, retrograde ejaculation or urinary incontinence.

Table 29. TUNA vs TURP - Clinical summary of findings (NICE).

Outcome	TUNA	TURP	Relative risk	Absolute effect	Quality
Symptom Score at 3 months	26	33	Not applicable	MD 0.8 [-0.66 to 2.26]	Very Low
Symptom score at 6 months	0	0	Not applicable		No Data
Symptom score at 12 months	56	44	Not applicable	MD 3.9 [1.25 to 6.55]	Low
Symptom score at 18 months	26	33	Not applicable	MD -0.1 [-1.47 to 1.27]	Very Low
Symptom score at 2 years	43	35	Not applicable	MD 5.5 [2.17 to 8.83]	Low
Symptom score at 3 years	38	31	Not applicable	MD 5.1 [1.36 to 8.84]	Low
Symptom score at 4 years	24	21	Not applicable	MD 5.6 [1.3 to 9.9]	Very Low
Symptom score at 5 years	18	22	Not applicable	MD -0.1 [-4.25 to 4.05]	Very Low
Quality of life (IPSS question) at 3 months	26	33	Not applicable	0.20 [-0.06 to 0.46]	Very Low
Quality of life (IPSS question) at 18 months	26	33	Not applicable	0.10 [-0.11 to 0.31]	Very Low
Qmax- 3 months	26	33	Not applicable	MD -6.4 [-8.9 to -3.9]	Very Low
Qmax-Longest available follow up	58	67	Not applicable	MD -6.82 [-8.64 to -5]	
All cause mortality (follow-up 18 months)	0/25 (0%)	0/25 (0%)	Not estimable	Not estimable	Very Low
Blood transfusion	0/146 (0%)	22/156 (14.1%)	RR 0.05 [0.01 to 0.32]	134 fewer [96 to 140 fewer]	Very Low
Urinary retention (acute)	5/146 (3.4%)	4/156 (2.6%)	RR 1.25 [0.37 to 4.24]	6 more per 1000 [16 fewer to 84 more]	Low
Urinary tract infection	14/120 (11.7%)	11/123 (8.9%)	RR 1.32 [0.63 to 2.78]	28 more per 1000 [33 fewer to 158 more]	Low
Urinary incontinence	8/211 (3.8%)	19/212 (9%)	RR 0.42 [0.2 to 0.91]	52 fewer per 1000 [8 to 72 fewer]	Low
Retrograde ejaculation	5/191 (2.6%)	78/190 (41.1%)	RR 0.08 [0.03 to 0.17]	378 fewer per 1000 [341 to 399 fewer]	Moderate
Urinary stricture	1/165 (0.6%)	9/157 (5.7%)	RR 0.15 [0.03 to 0.82]	48 fewer per 1000 [10 to 55 fewer]	Very Low
Reoperation	9/165 (5.5%)	1/157 (0.6%)	RR 7.75 [1.01 to 59.33]	41 more per 1000 [0 to 350 more]	Very Low

More men treated with TUNA compared to TURP had reoperations.

TUIP vs TURP

Eleven studies which compared the TUIP against TURP were indentified. One of these studies was conducted solely in patients with acute urinary retention (AUR).

There is no statistically significant difference between TUIP and TURP in improving symptom scores at 3 and 6 months post-operatively, however TUIP is significantly more effective than TURP in improving symptom scores at 24 months post-operatively. After 24 months post-operatively, TUIP is less effective than TURP in improving quality of life scores. No data for TUIP compared TURP at 3, 6, 12, 36, 48 or 60 months post-operatively in improving symptom scores and in improving quality of life scores.

There is no significant difference between TUIP and TURP in improving flow rate (Qmax) at 3 months post-operatively; and in improving peak flow rate (Qmax) at the longest available follow up period reported.

Table 30. TUIP vs TURP - clinical Summary of findings (NICE)

Outcome	TUIP	TURP	Relative risk	Absolute effect	Quality
Symptom score at 3 months	20	21	Not applicable	MD -0.5 [-3.35 to 2.35]	Low
Symptom score at 6 months	20	21	Not applicable	MD 2 [-1.17 to 5.17]	Low
Symptom score at 24 months	50	50	Not applicable	MD -1 [-1.73 to -0.27]	Low
Quality of life (IPSS question) at 24 months	50	50	Not applicable	MD 0.2 [0.01 to 0.39]	Low
Qmax at 3 months	62	65	Not applicable	MD -1.39 [-9.54 to 6.76]	Low
Qmax at longest available follow up	130	134	Not applicable	MD -2.25 [-4.68 to 0.17]	Low
All cause mortality	16/238 (6.7%)	12/233 (52.0%)	RR 1.24 [0.62 to 2.46]	12 more per 1000 [20 fewer to 76 more]	Low
Blood transfusion	1/287 (0.3%)	65/292 (22.3%)	RR 0.05 [0.02 to 0.15]	212 fewer per 1000 [190 to 219 fewer]	Moderate
TUR syndrome	0/110 (0%)	7/110 (6.4%)	RR 0.07 [0 to 1.15]	60 fewer per 1000 [64 fewer to 10 more]	Low
Urinary retention (acute)	12/188 (6.4%)	5/190 (2.6%)	RR 2.28 [0.86 to 6.08]	33 more per 1000 [4 fewer to 132 more]	Low
Urinary tract infection	2/30 (6.7%)	3/31 (9.7%)	RR 0.63 [0.12 to 3.35]	36 fewer per 1000 [85 fewer to 228 more]	Low
Urinary incontinence	2/134 (1.5%)	5/135 (3.8%)	RR 0.46 [0.1 to 2.01]	20 fewer per 1000 [33 fewer to 37 more]	Low
Retrograde ejaculation	48/209 (23%)	96/198 (67.4%)	RR 0.42 [0.24 to 0.75]	281 fewer per 1000 [121 to 369 fewer]	Low
Urinary stricture	6/174 (3.4%)	8/179 (4.5%)	RR 0.82 [0.32 to 2.1]	8 fewer per 1000 [31 fewer to 49 more]	Low
Reoperation	39/197 (19.8%)	16/195 (8.2%)	RR 2.37 [1.38 to 4.07]	112 more per 1000 [31 to 252 more]	Moderate

There is no statistically significant difference between TUIP and TURP in all cause mortality, number of patients experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

Significantly fewer men treated with TUIP compared to TURP required blood transfusions or experienced retrograde ejaculations.

More men treated with TUIP compared to TURP had reoperations.

In men with AUR, there is no statistically significant difference between TUIP and TURP in all cause mortality, number of men experienced TUR syndrome, urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

In men with AUR, significantly fewer men treated with TUIP compared to TURP required blood transfusions.

TUVRP vs TURP

There is no statistically significant difference between TUVRP and TURP in improving symptom scores at 3 months, 6 months and 2 years.

TUVRP is more effective than TURP in improving symptom scores at 1 year.

There is no statistically significant difference between TUVRP and TURP in improving Qmax and in improving quality of life IPSS symptom score at 3 months and 2 years.

Table 31. TUIP vs TURP in AUR patients - Clinical summary of findings (NICE)

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
All cause mortality	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Blood transfusion	2/29 (6.9%)	13/30 (43.3%)	RR 0.16 [0.04 to 0.64]	364 fewer per 1000 [156 to 416 fewer]	Low
TUR syndrome	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Urinary retention (acute)	0/29 (0%)	0/30 (0%)	not pooled	not pooled	Very Low
Urinary tract infection	5/29 (17.2%)	13/30 (43.3%)	RR 0.4 [0.16 to 0.97]	260 fewer per 1000 [13 to 364 fewer]	Very Low
Urinary incontinence	1/29 (3.4%)	2/30 (6.7%)	RR 0.52 [0.05 to 5.4]	32 fewer per 1000 [64 fewer to 295 more]	Very Low
Urinary stricture	0/29 (0%)	1/30 (3.3%)	RR 0.34 [0.01 to 8.13]	22 fewer per 1000 [33 fewer to 235 more]	Very Low

Table 32. TUVRP vs TURP - Clinical summary of findings (NICE)

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Symptom score at 3 months	65	58	not applicable	MD 0.17 [-0.59 to 0.92]	Very Low
Symptom score at 6 months (a)	84	84	not applicable	MD -0.68 [-1.98 to 0.62]	Low
Symptom score at 1 year	129	119	not applicable	MD -0.20 [-0.32 to -0.08]	Moderate
Symptom score at 2 years	42	30	not applicable	MD 0.60 [-0.72 to 1.92]	Very Low
Quality of life (IPSS question) at 3 months	36	26	not applicable	MD 0.20 [-0.11 to 0.51]	Very Low
Quality of life (IPSS question) at 2 years	36	26	not applicable	MD 0.20 [-0.13 to 0.53]	Very Low
Qmax at 3 months	52	49	not applicable	MD -0.77 [-2.08 to 0.53]	Very Low
Qmax at 2 years	29	21	not applicable	MD -1.60 [-3.37 to -0.17]	Very Low
Blood transfusion	7/296 (2.4%)	12/283 (4.2%)	RR: 0.57 [0.24 to 1.36]	18 fewer [32 fewer to 15 more]	Low
Urinary retention	6/178 (3.4%)	7/166 (4.2%)	RR: 0.72 [0.26 to 2.05]	12 fewer [31 fewer to 44 more]	Low
UTI	0/25 (0%)	0/25 (0%)	not estimable	not estimable	Low
Retrograde ejaculation	2/262 (0.8%)	2/249 (0.8%)	RR: 1.28 [0.78 to 2.08]	127 more [100 fewer to 491 more]	Very Low
Urinary incontinence	62/107 (57.9%)	46/101 (45.5%)	RR: 0.82 [0.14 to 4.88]	1 fewer [7 fewer to 31 more]	Low
Reoperations	11/137 (8.0%)	8/124 (6.5%)	RR: 1.12 [0.33 to 3.80]	8 more [44 fewer to 182 more]	Very Low
TUR syndrome	1/243 (0.4%)	3/229 (1.3%)	RR: 0.37 [0.06 to 2.29]	8 fewer [12 fewer to 17 more]	Low
Strictures	12/336 (3.6%)	15/321 (4.7%)	RR: 0.75 [0.36 to 1.57]	12 fewer [30 fewer to 27 more]	Low
All cause mortality	1/50 (2%)	0/50 (0%)	not estimable	not estimable	Low

(a) Outcomes analysed using random effects analysis

Table 33. Bipolar TUVRP vs TURP - clinical summary of findings (NICE)

Outcome	Intervention	Control	Relative risk	Absolute effect	Quality
Symptom score at 3 months	21	30	not applicable	MD -0.82 [10.02 to 8.38]	Very Low
Quality of life (IPSS question) at 3 months	21	30	not applicable	MD -0.99 [-2.38 to 0.40]	Very Low
Qmax at 3 months	21	30	not applicable	MD 1.86 [-8.91 to 12.63]	Very Low
Urinary retention	4/21 (19.0%)	3/30 (10.0%)	RR: 1.90 [0.47 to 7.64]	90 more [53 fewer to 664 more]	Very Low
UTI	4/21 (19.0%)	4/30 (13.3%)	RR: 1.43 [0.40 to 5.08]	57 more [80 fewer to 543 more]	Very Low
TUR syndrome	0/21 (0%)	0/30 (0%)	not applicable	MD -0.07 [-0.33 to 0.19]	Very Low

Table 34. TEAP vs TURP - clinical summary of findings (NICE).

Outcome	TEAP	TURP	Relative risk	Absolute effect	Quality
Blood transfusions	0/94 (0%)	19/101 (18.8%)	RR 0.03 [0 to 0.45]	182 fewer per 1000 [103 to 188 fewer]	Low
Urinary retention	2/94 (2.1%)	4/101 (4%)	RR 0.54 [0.1 to 2.87]	18 fewer per 1000 [36 fewer to 75 more]	Low
Urinary tract infection	5/94 (5.3%)	7/101 (6.9%)	RR 0.77 [0.25 to 2.34]	16 fewer per 1000 [2 fewer to 92 more]	Low
Urinary Stricture	0/94 (0%)	5/101 (5%)	RR0.1 [0.01 to 1.74]	45 fewer per 1000 [50 fewer to 37 more]	Low
Urinary incontinence	0/94 (0%)	4/101 (4%)	RR 0.12 [0.01 to 2.19]	35 fewer per 1000 [40 fewer to 48 more]	Low

There is no statistically significant difference between TUVRP and TURP in men experiencing incontinence, reoperation, strictures, urinary tract infections, urinary retention, mortality, TUR syndrome or blood transfusions.

BIPOLAR TUVRP vs TURP

There is no statistically significant difference between Bipolar TUVRP and TURP in improving symptom score, IPSS QoL score and improving Qmax from baseline and at 3 months post-operatively.

There is no statistically significant difference between bipolar TUVRP and TURP in the number of men experiencing urinary retention, UTI and TUR syndrome.

TEAP vs TURP

No studies report symptom score, quality of life or peak flow (Qmax) for TEAP compared to TURP at any time point of follow up.

Significantly fewer men had blood transfusions for TEAP compared to TURP.

There is no statistically significant difference between TEAP and TURP in number of men who experienced urinary retention, urinary incontinence, urinary tract infections or urinary strictures.

The EAU regards TURP as the gold standard for the treatment of LUTS secondary to BPO. One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvements in urodynamic parameters following TURP. The study also found that subjective and objective failures were associated with decreased detrusor contractility rather than BPO. A study in 577 men who underwent TURP reported excellent functional outcomes with a mean IPSS of 4.9 and a mean QoL score of 1.2 after 10 years of follow up. A meta-analysis of 29 RCTs reported a mean LUTS improvement of 70.6% (95% CI: 66.4-75.5%) after TURP.

Eleven RCTs evaluated TURP (and TUIP), and these studies noted mean Q_{max} increase following TURP was 125% with an absolute mean improvement of +9.7 mL/s (95% CI: 8.6-11.2 mL/s), PVR volume decreased by 60.5% (95% CI: 48-71) after TURP. In terms of retreatment, defined as a second prostatic operation, usually performed as TURP again, was reported at a constant rate of approximately 1-2% per year. The review analysing 29 RCTs found a re-treatment rate of 2.6% (96% CI: 0.5-4.7) after a mean follow-up of 16 months.

The incidence of blood transfusion following TURP in the analysis of 29 RCTs was 8.4% (95% CI: 3.9-13.4). In the most recent study of 10,564 men who underwent TURP, peri-operative mortality (during the first 30 days) was 0.1% (17). The risk of transurethral resection (TUR) syndrome has also decreased during the last decades to less than 1.1%. Risk factors associated with TUR syndrome are excessive bleeding with opening of venous sinuses, prolonged operation time, large prostates, and past or present nicotine abuse.

AUA based their recommendations on randomized controlled trials and cohort studies. A total of 11 RCTs compared standard monopolar TURP to various bipolar TURP techniques, one additional RCT compared preoperative treatment with dutasteride to placebo, both followed by standard TURP. Sample size for RCTs ranged between 40 and 240 subjects and follow-up intervals varied between three weeks and 21 months. Patients had baseline I-PSS between 20 and 24, QoL score between two and four, and Qmax between 5.1 and 10.9 mL per second. In the cohort studies, with a Comparison Group AUA identified two cohort studies with comparison groups. Lee and colleagues (2005) compared TURP to TURP plus TUIP over a mean follow-up of 38 months with 1135 patients available for the retrospective analysis; and a study that compared the Gyrus Plasmakinetic system with monopolar TURP. Nineteen single-group cohort studies were identified which examined TURP efficacy, effectiveness, or adverse events.

In these studies, the total I-PSS and QoL improved significantly in studies reporting these outcomes. Erectile function did not change significantly as assessed with the IIEF six months post-TURP. Postvoid residual decreased significantly in all studies and Qmax increased in all studies in the range of 6 to 10 mL per second. Prostate volume decreased by approximately 20 g in two studies. Treatment failure rates were infrequently reported; in one study, 13.3% were operated on for urinary retention post-TURP.

Acute complications of TURP were reported which included, Intracapsular perforation (5%), TUR syndrome (1.1%), transfusions (2- 9% - with the highest rate occurring in a study with prostates estimated between 70 g and 150 g preoperatively), clot retention (2.3%). Longer-term complications include urethral stricture (1.8 - 3.5% in one study, 10% in another study) and bladder neck stenosis (1.5%). Mortality rates were infrequently reported.

Equity issue/Implementation issue(s):

TURP is not cost-effective in men with moderate symptoms but it is cost- effective in men with severe symptoms. This evidence has minor limitations and partial applicability.

17. What is the effectiveness of treatment with treatment with TUIP in patients with LUTS?

Standard:

Offer transurethral incision of the prostate as an alternative surgical treatment to men with a prostate estimated to be smaller than 30 gms, without an enlarged median lobe (i.e, for those with enlarged median lobe, a TURP should be offered)

Transurethral incision of the prostate (TUIP) was initially described by Orandi in 1969. TUIP reduces LUTS secondary to BPO by splitting the bladder outlet with one or two cuts in the prostate and prostate capsule, reducing constriction of the urethra without tissue removal. It is an endoscopic surgical procedure limited to the treatment of smaller prostates (30 mL of resected weight or less) and without prostate middle lobes. The technique has been numerously modified. The

most popular unilateral incision is located at the 6 o'clock position and the most commonly performed bilateral incisions are at the 5 and 7 o'clock positions.

In the appropriate patient, TUIP results in degrees of symptomatic improvement equivalent to those attained after TURP. In addition, compared to TURP, TUIP results in a significantly reduced risk of ejaculatory disturbance. TUIP was also associated with a slightly higher rate of secondary procedures.

Guidelines considered:
NICE: Level 4
EAU: Level
AUA: Level

NICE recommendation was based on expert opinion. There is a high degree of uncertainty with the evidence reviewed (low to very low quality). A comparison between TUIP and TURP was analyzed, results of which are discussed at the TURP section (TUIP versus TURP).

EAU recommendations were based on eleven RCTs comparing TUIP with TURP. Studies that were evaluated reported that all RCTs comparing TUIP with TURP 12 months after the procedure reported a lower mean or median Qmax following TUIP with an overall mean Q_{max} improvement of 70% (95% CI: 27-112); and a lower decrease in post void residual after TUIP compared to TURP. Analyses of RCTs comparing TURP with TUIP showed that re-treatment was more likely following TUIP (17.5%) than after TURP (9%).

Morbidities in TUIP. The risk of bleeding following TUIP is negligible. The median probability of post-operative stress urinary incontinence ranges from 1.8% following TUIP (versus 2.2% in TURP). Recent meta-analysis found no statistically significant differences between TURP and TUIP in the development of urinary retention and UTIs. In terms of risk of developing urethral strictures after TUIP is 4.1% (versus 3.8% in TURP). In terms of sexual dysfuncion; retrograde ejaculation results from resection/destruction of the bladder neck and is reported by 18.2% after TUIP (versus 65.4% of patients after TURP).

AUA based its recommendation on a single RCT comparing TUIP to TURP in 100 subjects with prostate weights not exceeding 30 g with a two-year follow-up. In this study, both TURP AND TUIP groups improved significantly in nocturnal voiding frequency, I-PSS, QoL, and Qmax but there were no statistically significant differences in these outcomes between groups, except for QoL, for which the percentage change was greater with TURP.

Equity issue/Implementation issue(s):
none

18. What is the effectiveness of treatment with laser prostatectomy in patients with LUTS?

Standard:
If offering surgery for managing voiding LUTS presumed secondary to BPE, only consider offering laser prostatectomy as part of a randomized controlled trial in a specialist center.

Option:
Laser prostatectomy may be offered as an alternative surgical treatment in men with very large prostates (>100gms).

Several types of new generation lasers for prostate surgery have emerged during the last decade, including the holmium:YAG, potassium titanyl phosphate:yttrium aluminum garnet (KTP:YAG), thulium: yttrium aluminum garnet (thulium:YAG), light blue optics:yttrium aluminum garnet (LBO: YAG) and the diode lasers.

Laser prostatectomy uses Holmium: YAG laser to dissect in the surgical planes and is conceptually the endoscopic equivalent of open prostatectomy. The procedure requires similar operative and anaesthetic conditions and post operative care to TURP, though it may take a longer hospital stay.

Holium Laser Enucleation (HoLEP) uses holmium:ytrrium-aluminum-garnet (Ho-YAG) laser to deliver the energy to the prostate lobes which are completely enucleated and pushed to the bladder. It uses a morcellator to the completely resected prostate lobes that are pushed in the urinary bladder. It is useful for large prostates that usually require an open prostatectomy.

Thulium resection uses a Thulium YAG fiber to deliver light of 2000nm wavelength light to vaporize and resect or enucleate tissue. These resection techniques can be undertaken using saline as an irrigating solution, thus reducing the risk of "TURP" syndrome, a rare but serious complication of TURP.

Guidelines considered:
NICE: Level
EAU: Level
AUA: Level

NICE recommendations on laser prostatectomy used studies that included patients having a first surgery and without prior catheterization, therefore not totally generalisable. NICE recommends HoLEP at a center specializing in the technique, or with mentorship arrangements available. RCT studies comparing laser prostatectomy with TURP were mentioned in the TURP section.

EAU recommendations on HoLEP were based on two meta-analyses, which analyzed available RCTs comparing HoLEP and TURP. It reported a significantly longer operation time with HoLEP. Symptom improvements were comparable, but Q_{max} at 12 months was significantly better with HoLEP. In prostates > 100 mL, HoLEP proved to be as effective as open prostatectomy for improving micturition, with equally low re-operation rates at 5-year follow-up. Both meta-analyses found that HoLEP resulted in a significantly shorter catheterization time and hospital stay, reduced blood loss and fewer blood transfusions, but had a longer operation time than TURP. There exist however limited data that allow firm conclusions with regard to the different laser treatments.

AUA recommendations were based on procedures involving the holmium laser that were examined in eight RCTs, with various comparators: one small (n=40) trial that compared HoLEP to plasmakinetic enucleation of the prostate and followed patients for 12 months, standard monopolar TURP, holmium laser bladder neck incision, and open prostatectomy.

All studies evaluating AUA-SI symptom improvement following laser therapy of the prostate reported improved AUA-SI scores three weeks to six years after therapy; however improvements were not significantly different from the comparison groups. Difference in AUA symptom scores, Q_{max} when compared with open prostatectomy, and TURP did not reach statistical significance in three trials but there was a greater improvement with AUA symptom scores in HoLEP than TURP in one trial with 12 month follow up. In terms of post void residual, in one RCT, HoLEP and TURP achieved similar improvements in the post-void residuals at six months after therapy; however, at 12 months, further improvements in the post-void residuals favored the HoLEP-treated patients. When HoLEP was compared in RCTs to open prostatectomy at three months and five years, both therapies showed improvement in the post-void urinary residuals and there was no significant difference between these therapies.

Equity issue/Implementation issue(s):
Feasibility of implementation would be a big issue for HoLEP. It was felt that patient preference could lean toward HoLEP as it is considered less invasive. Men with religious concerns or on anticoagulants should be offered HoLEP due to lower rates of blood transfusions compared to TURP. However only a few centers offer HoLEP. Appropriate training and adequate number of patients are required to perform the procedure.

19. What is the effectiveness of treatment with TUMT in patients with LUTS?

Standard:
TUMT may be offered as an alternative for older patients with comorbidities and those at risk for anesthesia, otherwise unsuitable for invasive treatment.

Transurethral microwave thermotherapy (TUMT) has evolved through several iterations over the past 15 years, variations are seen in the route of administration (transrectal vs. transurethral), energy levels (low vs. high), and concomitant urethral cooling. TUMT uses microwave energy to induce temperatures of 45 - 70°C in the prostate depending on the device and power setting causing coagulation necrosis. It is also thought that the heat generated by TUMT also causes apoptosis and denervation of α-receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

Treatment may lasts 30-60 minutes under local anaesthesia and oral analgesia together with sedation for high energy protocols.

Guidelines considered:
NICE: Level
EAU: Level
AUA: Level

NICE guidelines based their recommendation on studies on TUMT versus SHAM. Clinical findings from these RCTs showed that TUMT is more effective than SHAM in improving symptom scores at 3 and 6 months, in improving maximum urinary flow rate at 3 months and at longer follow-up and is more effective than SHAM in improving maximum urinary flow rate at longer follow-up. In these studies they noted fewer men treated with TUMT compared to SHAM experienced reoperations, and urinary retention. In moribidities, there is no statistically significant difference between TUMT and SHAM treatment in number of men experiencing strictures, urinary tract infections, urinary incontinence, retrograde ejaculation and mortality.

Comparison was also done with TUMT versus TURP, results of which are discussed at the TURP section (TUMT versus TURP).

EAU based their recommendations on a systematic review of all available RCTs on TUMT which attempted to assess therapeutic efficacy in different TUMT devices and software.

Table 35. TUMT vs SHAM - clinical summary of findings.

Outcome	TUMT	SHAM	Relative risk	Absolute effect	Quality
Symptom score at 3 months	209	89	Not applicable	MD: -5.69 [-7.38, -3.99]	High
Symptom score at 6 months	120	35	Not applicable	MD: -3.80 [-6.27, -1.33]	Low
Qmax at 3 months	264	151	Not applicable	MD: 2.92 [2.03, 3.80]	Moderate
Qmax at longest follow-up	172	84	Not applicable	MD: 1.19 [0.17, 2.20]	Low
Urinary Retention	78/644 (12.1%)	2/354 (0.6%)	RR: 9.57 [3.91, 23.41]	51 more per 1000 [17 more to 134 more]	Moderate
Urinary Tract Infection	5/272 (1.8%)	0/117 (0%)	RR: 1.49 [0.84, 2.67]	38 more per 1000 [12 fewer to 129 more]	Low
Retrograde ejaculation	5/125 (4%)	0/44 (0%)	RR: 3.93 [0.22, 69.96]	Not estimable	Low
Urinary incontinence	5/272 (1.8%)	0/117 (0%)	RR: 3.93 [0.22, 69.96]	Not estimable	Low
Reoperation rate	14/232 (6.0%)	78/145 (53.8%)	RR: 0.16 [0.04, 0.56]	452 fewer per 1000 [37 fewer to 516 fewer]	Low
Blood transfusion	0/125 (0%)	0/144 (0%)	Not estimable	Not estimable	
Strictures	3/246 (1.2%)	0/106 (0%)	RR: 2.50 0.13, 47.46]	Not estimable	Low
All cause mortality	2/172 (1.2%)	0/90 (0%)	RR: 1.83 [0.21, 16.23]	Not estimable	Low

Table 36. Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for symptoms (IPSS), maximum urinary flow rate (Q_{max}) post-void residual urine (PVR), and prostate volume (PVol).

Trials	Duration (weeks)	Patients (n)	Change IPSS (absolute [%])	Change Q_{max} (mL/s, [%])	Change QoL (absolute [%])	Change PVR (absolute [%])	Change PVol (absolute [%])	LE
Hoffman et al. (2007) (3)	52	322	-12.7[a] (-65.0)	5.6[a] (70.0)	-2.4[a] (58.5)	NA	NA	1a
Gravas et al. (2005) (4)	52	183	-14.5[a] (-69.0)	8.4[a] (109.0)	-2.97[a] (70.9)	NA	-17.0 [a] (-33.0)	1b
Mattiasson et al. (2007) (19)	260	100	-13.6[a] (-61.5)	3.8[a] (50.0)	-3.2[a] (-74.4)	-36.0 (-34.0)	-4.0 (-8.1)	1b
Floratos et al. (15)	156	78	-8.0[a] (-40.0)	2.7[a] (29.3)	-2.0[a] (-50.0)	NS	NA	1b
Thalmann et al. (2002) (17)	104	200	-20.0[a] (-87.0)	7.0[a] (116.6)	-4.0[a] (-80.0)	-143 [a] (-84.1)	-17.7 [a] (-30.7)	2b
Miller et al. (2003) (18)	260	150	-10.6[a] (-47.0)	2.4[a] (37.0)	-2.3[a] (-54.7)	NA	NA	2b
Trock et al. (2004) (23)	208	541	-8.9[a] (-42.7)	2.8[a] (35.0)	-2.1[a] (-50.1)	NA	NA	2b

a = significant compared to baseline (indexed whenever evaluated); NS = not significant; NA = not available.

The review found that TUMT was somewhat less effective than transurethral resection of the prostate (TURP) in reducing LUTS. The pooled mean symptom score for men undergoing TUMT decreased by 65% in 12 months compared to 77% in men undergoing TURP. TURP achieved a greater improvement in Q_{max} (119%) than TUMT (70%). Urinary retention was previously a contraindication to TUMT, nowadays, however, level 2b evidence studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously, a longer follow up of these patients is still lacking. One RCT compared TUMT with the α1-blocker, terazosin. After 18 months' follow-up, treatment failure in the terazosin-treated patients (41%) was significantly greater than in TUMT patients (5.9%), with TUMT also achieving a greater improvement in IPSS and Q_{max}.

In terms of durability, it is in favor of transurethral resection of the prostate with lower re-treatment rates compared to transurethral microwave therapy as seen in several studies. In terms of morbidity, a pooled morbidity data of randomized studies comparing TUMT and TURP have been published. Catheterization time, incidence of dysuria/urgency and urinary retention were significantly less with TURP, while the incidence of hospitalization, hematuria, clot retention, transfusions, transurethral resection (TUR) syndrome, and urethral strictures were significantly less for TUMT. Pooled data showed

that TUMT had less impact on sexual function (erectile dysfunction, retrograde ejaculation) than TURP.

The reported low morbidity and the absence of any need for anesthesia (spinal or general) make TUMT a true outpatient procedure, providing an excellent option for older patients with co-morbidities at high operative risk and, therefore, unsuitable for invasive treatment. Independent baseline parameters predicting an unfavorable outcome include advanced age of the patient, small prostate volume, mild-to-moderate bladder outlet obstruction and a low amount of energy delivered during treatment.

AUA discussed the evolution of TUMT, mentioning the different TUMT devices. A systematic review of TUMT data reveals a heterogeneous mix of studies of various sizes and TUMT protocols, often using different outcome measures with varying durations of follow-up. This leads to conflicting results, as may be seen in studies of shorter vs. longer follow-up. In general, older, low-energy TUMT devices similarly possess comparatively less clinical efficacy than newer, higher energy counterparts but also carry a lower risk of side effects. The durability of TUMT treatment appears to have improved with the advent of higher energy, later generation devices.

Equity issue/Implementation issue(s):
Availability of this device hinders its use, institutions with available device must be identified for possible referral.

20. What is the effectiveness of treatment with open prostatectomy in patients with LUTS?

Standard:
Offer open prostatectomy only as an alternative to TURP to men with prostates estimated to be larger than 80gms.

Open prostatectomy is the oldest surgical treatment modality for LUTS secondary to BPO. Obstructive prostatic adenomas are enucleated using the index finger, either from the inside of the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure), allowing unobstructed voiding. The most frequent indication for surgical management is bothersome LUTS refractory to medical management. Other strong indications for surgery include refractory urinary retention, recurrent urinary infection, recurrent hematuria refractory to medical management with 5 alpha reductase inhibitors, renal insufficiency secondary to BPO, bladder stones and increased post void residual.

Guidelines considered:
NICE: Level 4
EAU: Level 1b
AUA: Level 1b

NICE recommendation was based on expert opinion. In men with very large prostates, standard TURP and other tissue ablative techniques take a long time to perform. The former may be complicated by increased blood loss and a higher risk of complications. In these circumstances the potential morbidity and longer hospital stay associated with open prostatectomy are felt to be justified by the improved efficacy. One small study found open prostatectomy to be more effective at improving quality of life than HoLEP at three months but this was not seen at later follow up periods. Uncertainties about these results arise as patients following open prostatectomy usually still have pain and continence problems at 3 months. These results leaned towards HoLEP, recommending open prostatectomy as an alternative surgery to HoLEP for men with larger prostates (prostate size more than 70 grams or more than 100 grams).

According to EAU, open prostatectomy is the treatment of choice for large glands (> 80-100 mL). However in three recent RCTs, it has shown that Holmium laser enucleation and PVP lead to similar outcomes compared to open prostatectomy in men with large glands (> 70, 80 and 100 mL) at a significantly lower complication rate. Results of open prostatectomy, showed improvement in LUTS of 63-86 % and IPSS Quality of Life score of 60-87%. The mean increase in Qmax is 375% (16.5-20.2 ml/s), and a

reduction in PVR of 86-98%. A favorable long-term outcome is common after open prostatectomy. A secondary prostatic operation has not been reported in the open prostatectomy arm in randomized studies up to 5 years follow-up. Long-term complications are incontinence bladder neck contracture and urethral stricture. The risk of developing stress incontinence is up to 10%, while the risk for developing bladder neck contracture and urethral stricture is about 6%.

AUA guidelines recommend open prostatectomies only for men with very enlarged prostate glands (it may be more effective than TURP in relieving the blockage of urine flow), and for men with bladder diverticula (pockets), or stones. RCTs were studied in review for efficacy of open prostatectomy. I-PSS or AUA-SI and QoL scores improved in all studies reporting this outcome, with follow-up between three months and more than three years. IIEF and the Madsen-Iversen score improved significantly at 6 and 12 months, respectively. Postvoid residual and Q_{max} also improved significantly in all studies examining this outcome at mean follow-up up to three years. In the only study of sexual function after surgery, a significant increase in sexual desire and overall satisfaction was observed. Reoperation for treatment failure was rarely reported. Incontinence was reported at rates between 0.5% and 8%, with several studies reporting much lower rates of permanent incontinence. Bladder neck contracture was reported at 3% to 6%and in one of six subjects undergoing perineal open prostatectomy in a single series. Mortality was infrequently reported in these studies and perioperative death rates were low (≤1%) and generally related to cardiovascular disease.

Equity issue/Implementation issue(s):
Open prostatectomy requires a longer hospital stay and a longer catheterization among patients.

ERRATUM

The name of **Dr. Kenneth T. Tan**, also an author of the article *Multi-Parametric Magnetic Resonance Imaging (*MpMRI*) Based Prostate Imaging and Reporting Archiving Data System (PIRADS): Utility In Improving Cancer Detection, Localization and Characterization* [PJU 2016; 26(1): 24-31] was inadvertently omitted in the final print. The PJU editorial board sincerely apologizes for the oversight.