Guidelines on the Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO)

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1. INTRODUCTION

1.1 Aim

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and substantial personal and societal expenditures. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH).

1.2 Publication history

Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. A shorter reference document, the Pocket Guidelines, is also available, both in print and as a mobile application, presenting the main findings of the Non-neurogenic Male LUTS Guidelines. These versions are abridged and therefore may require consultation with the full text version. All are available through the EAU website: http://www.uroweb.org/guidelines/.

For the 2015 Guidelines, the text has been significantly reduced so that only key information is included and re-formatted according to the EAU non-oncology template so that all Guidelines follow a similar format. This document was peer-reviewed prior to publication.

1.3 Panel composition

The Non-neurogenic Male LUTS Guidelines Panel consists of experts with a urological and epidemiological background. Although the Guidelines are written primarily for urologists, they can also be used by general practitioners, patients or other stakeholders.

2. METHODS

A systematic literature search was carried out by the Panel for articles in English language published in the PubMed, Medline, Web of Science, and Cochrane databases between 1966 and 31st December 2013 [1-4]. The search terms included 'lower urinary tract symptoms', 'benign prostatic hyperplasia', 'detrusor overactivity', 'overactive bladder', 'nocturia', and 'nocturnal polyuria', in combination with the pre-specified diagnostic tests, the various treatment modalities and the search limits, 'humans', 'adult men', 'review', 'randomised clinical trials', 'clinical trials', and 'meta-analysis'. References used in this text are graded according to their Level of Evidence (LE) and Guidelines are given a Grade of Recommendation (GR). In this 2015 EAU Guidelines compilation, all standard information on LE and GR has been taken out of the individual Guidelines topics for the sake of brevity. The methodology section (see the introduction chapter of the complete book) and supplementary online material Tables S.1 and S.2 outlines the LE and GR criteria which are used throughout the Guidelines, according to a classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence (modified March 2009) [1].

For Chapter 3B (Diagnostic evaluation), the Panel used the Delphi technique consensus approach. The Delphi method infers that decisions captured systematically from a structured group of individuals (the Panel) are more valid than those from unstructured groups. When published information is scarce, experts can make inferences using other data from comparable contexts. Using bespoke software (www.acord.it), propositions were put to experts who voted their preference. The results for the group were then sent back so participants could review their responses in the context of group-wide results. This was done anonymously, so review was free of peer group pressure. The web-based system offered the option to comment and justify decisions anonymously, and a second round of anonymous voting took place. Three iterations of the process were used, so that opinions of the Panel members converged towards the consensus 'correct' answer. The Panel pre-determined the threshold for consensus at 77% (7 out of 9) in regards to agreeing recommendations. The Panel classified diagnostic tests into three categories: 'must', 'should', and 'may'. 'Must' presents the highest level of obligation. 'Should' presents an intermediate level, and 'may' expresses the lowest level of obligation.

Subsections for the various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing 'mechanism of action', 'efficacy' with a table of high LE trials, 'safety' and 'practical considerations'. 'Grades of Recommendation' (GR) are derived from the relevant articles according to the modified classification system from the Oxford Centre for Evidence-based Medicine [1] (see supplementary online material Table S.2).

Where possible, recommendations are based on the strongest clinically relevant data. When recommendations are graded, there is no automatic relationship between the LE and GR. The availability of randomised controlled trials (RCTs) may not necessarily translate into a Grade A recommendation if there are methodological limitations or a disparity in published results, uncertainty about the balance of desirable and undesirable effects, uncertainty or variability in patients' values and preferences, or uncertainty about whether the intervention represents a wise use of resources. Alternatively, lack of high-level evidence does not preclude a Grade A recommendation where there is considerable clinical experience and consensus, or situations where corroborating studies cannot be performed, perhaps for ethical, financial or other reasons. Such a situation is indictated in the text with an asterisk to denote 'upgraded based on Panel consensus'. The quality of the scientific evidence is a major factor, but it has to be balanced against benefits, burdens, personal values and preferences when a Grade of Recommendation is assigned.

The Working Panel intends to update the content and recommendations regularly, according to the given structure and classification systems.

2.1 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various non-neurogenic and non-malignant conditions, such as LUTS/Benign Prostatic Obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with other contexts of LUT disease (e.g. concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following section. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels (www.uroweb.org).

3. THE GUIDELINE

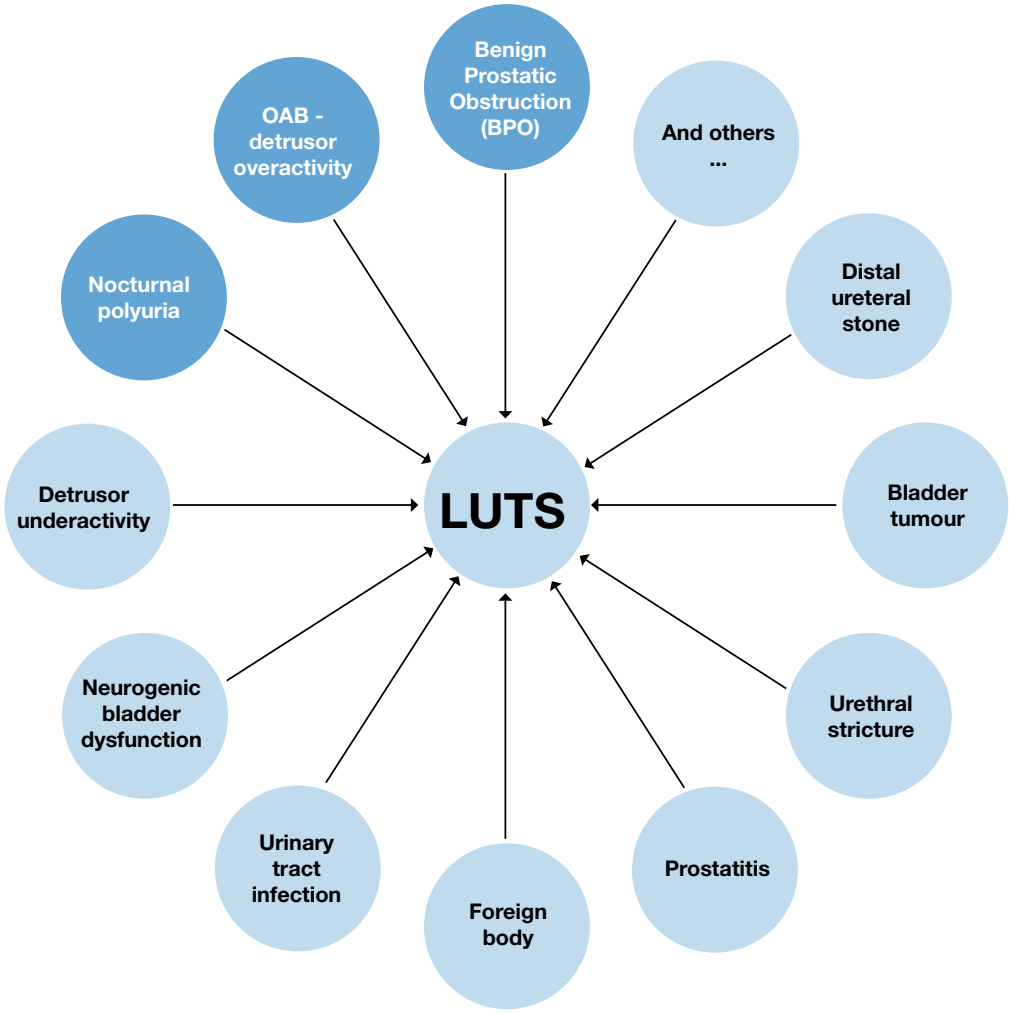
3A EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

LUTS can be divided into storage, voiding and post-micturition symptoms [2]. LUTS are prevalent, cause bother and impair QoL [5-8]. They are strongly associated with ageing [5, 6], so associated costs and burden are likely to continue to increase overall in the future [6, 9].

Most elderly men report having at least one LUTS [6]. However, clinically meaningful prevalences are lower as symptoms may be mild or not very bothersome [8]. LUTS progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [6].

LUTS have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of benign prostatic hyperplasia (BPH) [2, 7]. Recent studies have shown, however, that LUTS are often unrelated to prostate [3, 6]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract [3]. In addition, many non-urological conditions also contribute to LUTS, especially nocturia [6]. Figure 1 illustrates the potential causes of LUTS. In any single person complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male lower urinary tract symptoms (LUTS)



3B DIAGNOSTIC EVALUATION

Tests are useful for diagnosis, monitoring, assessing the prognosis of disease progression, treatment planning, and the prediction of treatment outcome. The clinical assessment of patients with LUTS has two main objectives:

- To consider the differential diagnoses, since the origin of male LUTS are multifactorial. The relevant EAU Guidelines on the management of applicable conditions should be followed in these cases.
- To define the clinical profile of men with LUTS in order to provide appropriate care. The assessment should ascertain treatment options and identify men at risk of disease progression.

3B.1 Medical History

The importance of assessing the patient's history is well-recognised [4, 10, 11].

A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, it is recommended that current medication, lifestyle habits, emotional and psychological factors are reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite relation between LUTS and prostate cancer (PCa) [12, 13].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 3B.2) should be assessed to objectify and quantify LUTS. Voiding diaries are particularly beneficial when assessing patients with nocturia and/or other storage LUTS (see section 3B.3 'frequency volume chart'). When relevant, sexual function should be investigated, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF).

Recommendation	LE	GR
A medical history must always be taken from men with LUTS.	4	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [4, 10, 11]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [14-20]. Symptom scores are helpful in quantifying the patient's LUTS and in identifying which type of symptoms are predominant, yet they are not disease-, age- or gender-specific.

*3B.2.1 **The International Prostate Symptom Score (IPSS)***

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one QoL question [15]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points), and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms, and bother caused by each separate symptom.

*3B.2.2 **The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)***

The ICIQ-MLUTS was created from the ICS Male questionnaire. It is a widely used and validated patient-completed questionnaire [16]. It contains 13 items, with subscales for nocturia and OAB, and is available in 17 languages.

*3B.2.3 **Danish Prostate Symptom Score (DAN-PSS)***

The DAN-PSS [18] is a symptom score used mainly in Denmark and Finland. The IPSS includes only one overall QoL question. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Recommendation	LE	GR
A validated symptom score questionnaire with QoL question(s) should be used for the routine assessment of male LUTS in all patients and should be applied for re-evaluation of LUTS during treatment.	3	B

LUTS = lower urinary tract symptoms; QoL = quality of life.

3B.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of additional information such as fluid intake, use of pads, activities during recording, or symptom scores is termed a bladder diary [2]. Parameters that can be derived from the FVC bladder diary include: day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index [NPi]), and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Likewise, circumstantial influence and intra-individual variation cause FVC parameters to fluctuate, though there is comparatively little data [21, 22]. The FVC diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [23-25]. The use of FVCs may cause a 'bladder training effect', and influence the frequency of nocturnal voids [26].

The duration of observation during FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [27]. A systematic review of the available literature recommended FVC should continue for 3 or more days [28].

Recommendations	LE	GR
Micturition frequency volume charts or bladder diaries should be used to assess male LUTS with a prominent storage component or nocturia.	3	B
Frequency volume charts should be performed for the duration of at least 3 days.	2b	B

LUTS = lower urinary tract symptoms.

3B.4 Physical examination and digital-rectal examination

Physical examination to seek potential influences on LUTS, particularly focussing on the suprapubic area, the external genitalia, the perineum and lower limbs. Urethral discharge, meatal stenosis, phimosis and penile cancer must be identified if present.

*3B.4.1 **Digital-rectal examination and prostate size evaluation***

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but correct estimation is not easy to achieve. Quality-control procedures for DRE have been described [29]. Transrectal ultrasound (TRUS)

is more accurate in determining prostate volume than DRE. Underestimation of prostate volume by DRE increases with increasing TRUS volume, particularly where the volume is > 30 mL [30]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [31]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < than 50 mL [32].

Recommendation	LE	GR
Physical examination including DRE should be a routine part of the assessment of male LUTS.	3	B

DRE = digital-rectal examination; LUTS = lower urinary tract symptoms.

3B.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to determine conditions, such as UTI, microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, including Guidelines on urinary tract cancers and urological infections [33-36].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [37, 38]. There is limited evidence, yet there is general expert consensus that the benefits outweigh the costs [39]. The value of urinary dipstick/microscopy for diagnosing UTI in LUTS without acute frequency and dysuria has recently been questioned [40].

Recommendation	LE	GR
Urinalysis (by dipstick or urinary sediment) must be used in the assessment of male LUTS.	3	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.6 Prostate-specific antigen (PSA)

*3B.6.1 **PSA and the prediction of prostatic volume***

Several reports have demonstrated the reliability of measuring the PSA concentration for predicting prostate volume. The pooled analysis of placebo-controlled BPH trials show that PSA has a good predictive value for assessing prostate volume, with areas under the curve of 0.76 - 0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [41].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [42]. 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%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (± 20%) in > 90% of the cases [43, 44].

*3B.6.2 **PSA and the probability of PCa***

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [45]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed.

*3B.6.3 **PSA and the prediction of BPO-related outcomes***

Serum PSA is a stronger predictor of prostate growth than prostate volume [46]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow rate (Q_{max}) [47]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [48].

In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [49, 50]. An equivalent link was also confirmed by the Olmsted County Study. The risk for treatment was higher in men with a baseline PSA of >1.4 ng/mL [51]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The positive predictive values of PSA for the detection of BPO was recently shown to be 68% [52]. In an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [53].

Recommendation	LE	GR
PSA measurement should be performed only if a diagnosis of PCa will change the management or if PSA can assist in decision-making in patients at risk of progression of BPE.	1b	A

BPE = benign prostate enlargement; PCa = prostate cancer; PSA = prostate-specific antigen.

3B.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [54]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [55].

One study reported 11% of men with LUTS had renal insufficiency [54]. Neither symptom score nor QoL was associated with the serum creatinine concentration, and diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter et al. [56] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch et al. [57] concluded that only those with an elevated creatinine level require investigational ultrasound of the kidney.

In the Olmsted County community-dwelling men, there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [58]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [59]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [60]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [61].

Recommendation	LE	GR
Renal function assessment must be performed if renal impairment is suspected, based on history and clinical examination or in the presence of hydronephrosis or when considering surgical treatment for male LUTS.	3	A*

**Upgraded based on Panel consensus. LUTS = lower urinary tract symptoms.*

3B.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. PVR is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity) [62, 63].

At PVR of 50 mL, the diagnostic accuracy of PVR measurement has a positive predictive value (PPV) of 63% and a negative predictive value (NPV) of 52% to predict BOO [64]. A large PVR measurement is not a contraindication to watchful waiting (WW) or medical therapy, although large PVR may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom deterioration [49, 50].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [50]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α_1-blocker or WW [65]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established and this is a research priority.

Recommendation	LE	GR
Measurement of post-void residual in male LUTS should be a routine part of the assessment.	3	B

LUTS = lower urinary tract symptoms.

3B.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test that evaluates the functioning of the LUT. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. Q_{max} is prone to within-subject variation [66, 67]; it is therefore useful to repeat uroflowmetry measurements, especially if the voided volume is < 150 mL, or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably, and is substantially influenced by threshold values. A threshold value of Q_{max} of 10 mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% [68]. If Q_{max} is ≥ 15 mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [69], detrusor underactivity or an underfilled bladder [70]. Thus, it is limited as a diagnostic test because it is unable to discriminate between the underlying mechanisms. Specificity can be improved by repeated flow rate testing. Uroflowmetry can be used for monitoring treatment outcomes [71] and correlating symptoms with objective findings.

Recommendation	LE	GR
Uroflowmetry in the initial assessment of male LUTS may be performed and should be performed prior to any treatment.	2b	B

LUTS = lower urinary tract symptoms.

3B.10 Imaging

3B.10.1 ***Upper urinary tract***

Routine imaging of the upper urinary tract in men with LUTS is not recommended, as they are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [57, 72-74].

Several arguments support the use of renal US in preference to intravenous urography (IVU). US allows for a better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, lower radiation dose and less side-effects [72].

Recommendation	LE	GR
Imaging of the upper urinary tract (with US) in men with LUTS should be performed in patients with a large PVR, haematuria or a history of urolithiasis.	3	B

LUTS = lower urinary tract symptoms; PVR = post-void residual; US= ultrasound.

3B.10.2 ***Prostate***

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography, and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by TRUS or transabdominal US [72].

3B.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy, enucleation techniques, transurethral resection, TUIP, or minimally invasive therapies. It is also important prior to treatment with 5-ARIs. Prostate volume predicts the development of progressive symptoms and complications [74].

TRUS is superior to suprapubic (transabdominal) volume measurement [75, 76]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach.

Recommendations	LE	GR
When considering medical treatment for male LUTS, imaging of the prostate (either by TRUS or transabdominal US) should be performed if it assists the choice of the appropriate drug.	3	B
When considering surgical treatment, imaging of the prostate (either by TRUS or transabdominal US) should be performed.	3	B

LUTS = lower urinary tract symptoms; TRUS = transrectal ultrasound.

3B.10.3 ***Prostatic configuration/intravesical prostatic protrusion (IPP)***

Prostatic configuration has been evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [77]. PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward 1 as the prostate becomes more circular. PCAR sensitivity was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [77].

Ultrasound measurement of intravesical prostatic protrusion (IPP) assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with the bladder volume at 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is >10 mm.

IPP correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [78]. IPP may correlate with prostate volume, detrusor overactivity, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [79]. IPP also seems to predict successful outcome of trial without catheter (TWOC) after acute urinary retention [80, 81]. No information with regard to intra- or inter-observer variability and learning curve is yet available. IPP may be a feasible option to infer BPO in men with LUTS. The role of IPP as a non-invasive alternative to pressure flow studies (PFS) in the assessment of male LUTS is under evaluation.

3B.10.4 ***Bladder/detrusor wall thickness and ultrasound-estimated bladder weight***

For bladder wall thickness (BWT) assessment, the distance between the hyperechogenic mucosa and the hyperechogenic adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the hypoechogenic detrusor sandwiched between the hyperechogenic mucosa and adventitia [82].

A significant correlation between BWT and pressure flow studies (PFS) parameters has been reported. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL was best at differentiating between patients with or without BOO [83]. DWT at the anterior bladder wall with a bladder filling ≥ 250 mL (threshold value for BOO ≥ 2 mm) has a PPV of 94% and a specificity of 95%, achieving 89%

agreement with PFS [64]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS is able to identify 81%, 89%, and 100% of patients with BOO, respectively [84].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal urodynamics, BOO or detrusor overactivity; however, the study did not use a specific bladder filling volume for measuring BWT [85]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [86]. Measurement of BWT/DWT is therefore not recommended for the diagnostic work-up of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35 g [87, 88]. Severe LUTS and a high UEBW (≥ 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [89]. The role of BWT, DWT and UEBW as a non-invasive alternative to PFS in the assessment of male LUTS or BOO is under evaluation.

*3B.10.5 **Voiding cysto-urethrogram***

Voiding cysto-urethrogram (VCUG) is not recommended in the routine diagnostic work-up of men with LUTS, but it may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or urethral pathologies in selected patients. Retrograde urethrography may additionally be useful for the evaluation of urethral strictures where suspected.

3B.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture, associated risk factors, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.

Shoukry et al. evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [90]. The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had an 'obstructive' Q_{max}.

Anikwe showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{max} value in 39 symptomatic men aged 53-83 years [91]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [92]. 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 [92].

Recommendation	LE	GR
Urethrocystoscopy should be performed in men with LUTS to exclude suspected bladder or urethral pathology and/or prior to minimally invasive/surgical therapies if the findings may change treatment.	3	B

LUTS = lower urinary tract symptoms.

3B.12 Urodynamics

In male LUTS, the most widespread invasive urodynamic techniques employed are filling cystometry and PFS. The major goal of urodynamics is to explore the functional mechanisms of LUTS and to identify risk factors for adverse outcomes (for informed/shared decision-making). Most terms and conditions (e.g. detrusor overactivity, low compliance, BOO/BPO, detrusor underactivity) are defined by urodynamic investigation.

*3B.12.1 **Diagnosing bladder outlet obstruction***

PFS are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. BOO/BPO has to be differentiated from detrusor underactivity (DUA), which signifies decreased detrusor pressure during voiding in combination with decreased urinary flow rate [2].

Urodynamic testing may also identify detrusor overactivity, which is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Overactive bladder is diagnosed from the patient's symptoms, not urodynamic testing, based on the presence of urgency, usually with increased daytime frequency and nocturia [2]. Studies have described an association between BOO and DO [93, 94]. In men with LUTS attributed to BPE, DO was present in 61% and independently associated with BOO grade and ageing [93].

The prevalence of DUA in men with LUTS is 11-40% [95, 96]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [97, 98].

There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS, but one such study is ongoing in the UK.

Due to the invasive nature of the test, a urodynamic investigation is generally only offered if conservative treatment has failed. The Guidelines Panel attempted to identify specific indications for PFS based on age, findings from the other diagnostic tests, and previous treatments. The Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which may reflect the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10mL/s, although the Panel recognised that with Q_{max} < 10 mL/s, BOO is likely and PFS are not necessarily needed.

Patients with neurological disease, including those with previous radical pelvic surgery should be assessed according to the EAU Guidelines on Neuro-Urology [99].

*3B.12.2 **Videourodynamics***

Videourodynamics provides additional anatomical information and is primarily recommended if there is uncertainty regarding mechanisms of LUTS.

*3B.12.3 **Non-invasive pressure-flow testing***

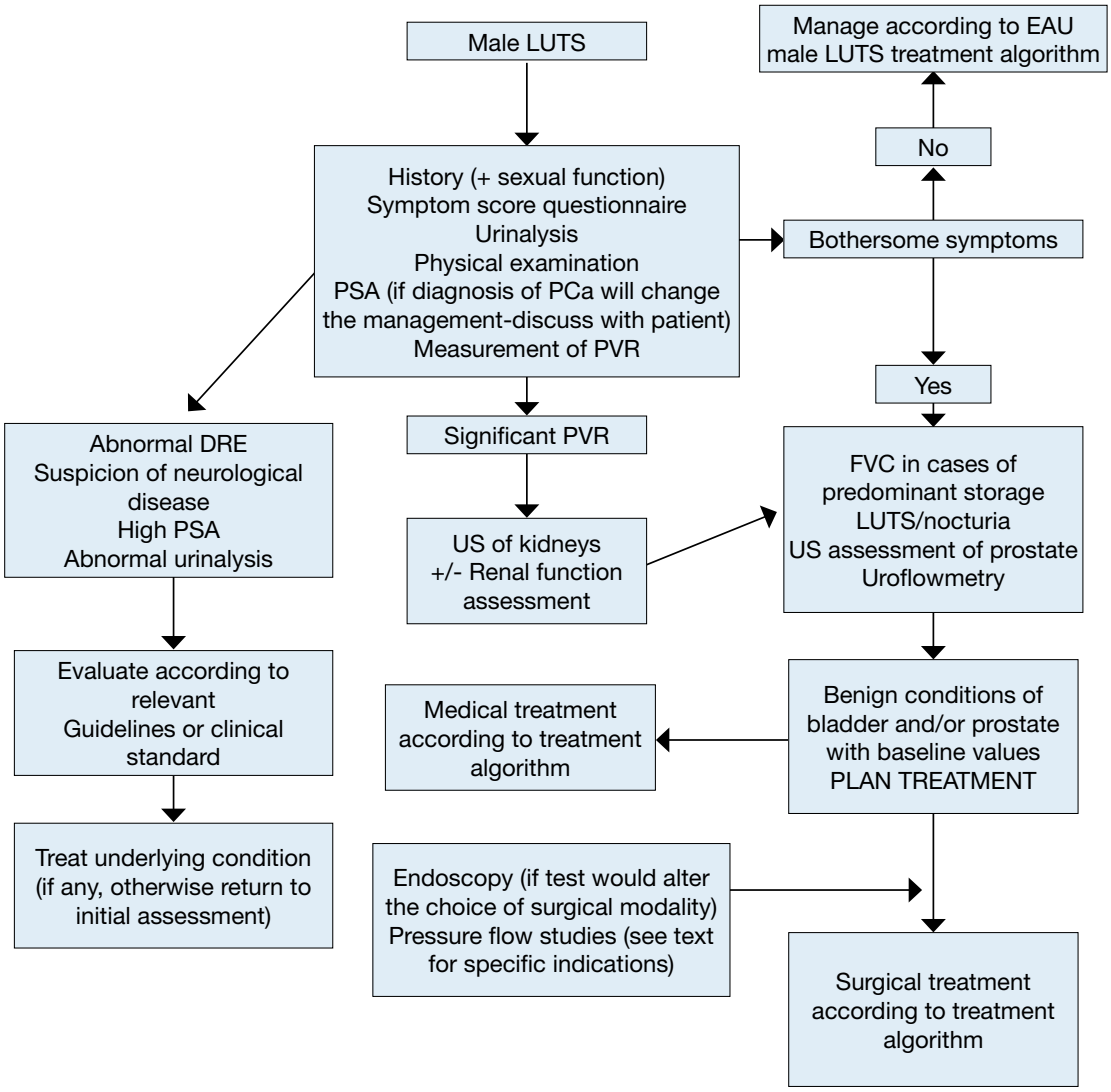
The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure), shows promising data, with good test/retest repeatability [100] and interobserver agreement [101], and a nomogram has been derived [102]. A method in which flow is not interrupted is also under investigation [103].

The data generated with the external condom method [104] correlates with invasive PFS in a high proportion [105]. Resistive index [106] and prostatic urethral angle [107] have also been proposed, but are still experimental.

Recommendations	LE	GR
PFS should be performed only in individual patients for specific indications prior to surgery or when evaluation of the underlying pathophysiology of LUTS is warranted.	3	B
PFS should be performed in men who have had previous unsuccessful (invasive) treatment for LUTS.	3	B
When considering surgery, PFS may be used for patients who cannot void > 150 mL.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS may be performed in men with a PVR > 300 mL.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS may be performed in men aged > 80 years.	3	C
When considering surgery in men with bothersome, predominantly voiding LUTS, PFS should be performed in men aged < 50 years.	3	B

LUTS = lower urinary tract symptoms; PFS = pressure-flow studies, PVR = post-void residual.

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older
Readers are strongly recommended to read the full text that highlights the current position of each test in detail.



DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

3C DISEASE MANAGEMENT

3C.1 Conservative treatment

*3C.1.1 **Watchful waiting***

Many men with LUTS are not troubled enough by their symptoms to need drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting (WW) is a viable option for many men with non-bothersome LUTS as few will progress to acute urinary retention and complications (e.g. renal insufficiency or stones) [108, 109], and others can remain stable for years [110]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [111].

A large study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), especially in those with high levels of bother; 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [112, 113]. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

3C.1.2 ***Behavioural and dietary modifications***

It is customary for this type of management to include the following components:

- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [110, 111, 114, 115] such as:
  - 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);
  - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
  - use of relaxed and double-voiding techniques;
  - urethral milking to prevent post-micturition dribble;
  - distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms;
  - bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids;
  - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
  - providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
  - treatment of constipation.

There now exists evidence (LE: 1b) that self-management as part of WW reduces both symptoms and progression [114, 115] (Table 1). Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only for up to a year [115].

Table 1: Self-management as part of watchful waiting reduces symptoms and progression [115]

Trial	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
Brown et al. (2007) [115]	52	Standard care	67	-1.3	-	-	1b
		Standard care plus self-management	73	-5.7 * †	-	-	

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

3C.1.3 ***Practical considerations***

The components of self-management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [116]. Further research in this area is required.

Recommendations	LE	GR
Men with mild symptoms are appropriate for watchful waiting.	1b	A
Men with LUTS should always be offered lifestyle advice prior to or concurrent with treatment.	1b	A

LUTS = lower urinary tract symptoms.

3C.2 Pharmacological management

3C.2.1 ***α_1-Adrenoceptor antagonists (α_1-blockers)***

Mechanism of action: α_1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [117]. However, α_1-blockers have little effect on urodynamically determined bladder outlet resistance [118], and treatment-associated improvement of LUTS is correlated only poorly with obstruction [119]. Thus, other mechanisms of action may be relevant.

α_1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α_1-adrenoceptor subtypes (α_1B- or α_1D-adrenoceptors) may play a role as mediators of effects. α_1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

α_1-blockers currently available include: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin). α_1-blockers exist in different formulations (see supplementary online material Table S.3). Although different formulations

result in different pharmacokinetic and tolerability profiles, the overall clinical impact of the different formulations is modest.

Efficacy: Indirect comparisons between α_1-blockers and limited direct comparisons demonstrate that all α_1-blockers have a similar efficacy in appropriate doses [120]. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [121].

Controlled studies show that α_1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25% (Table 2). However, considerable improvements also occurred in the corresponding placebo arms [48, 121]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [48, 121].

α_1-blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect α_1-blocker efficacy in studies with follow-up periods of < 1 year, but α_1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [122-125]. α_1-blocker efficacy is similar across age groups [121]. α_1-blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies [49, 123-125]; some patients must therefore be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during α_1-blocker treatment appears to be maintained over at least four years.

Tolerability and safety: Tissue distribution, subtype selectivity, and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α_1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common for alfuzosin and tamsulosin [141]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α_1-blocker-induced vasodilatation [142]. In contrast, the frequency of hypotension with the α_{1A}- selective blocker silodosin is comparable with placebo [132].
An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [143]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all the α_1-blockers [144]. However, the odds-ratio for IFIS was much higher for tamsulosin. It appears prudent not to initiate α_1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α_1-blocker use.

A systematic review concluded that α_1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [145]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. Abnormal ejaculation has been observed more frequently with tamsulosin and silodosin than with other α_1-blockers [10, 146]. Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation [146, 147].

Practical considerations: Alpha1-blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. Ophthalmologists should be informed about α_1-blocker use prior to cataract surgery.

Recommendation	**LE**	**GR**
Alpha1-blockers can be offered to men with moderate-to-severe LUTS.	1a	A

Table 2: Randomised, placebo-controlled trials with α_1-blockers in men with LUTS

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) [126]	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) [127]	12	Placebo Alfuzosin 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) [128]	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) [129]	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9[b] (Boyarski)[†] -1.8[b] (IPSS)[†]	+1.2[b]	-	1a
Kirby et al. (2001) [130]	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) [49]	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39[b]	+1.4 +2.5[a,b]	- -	1b
Marks et al. (2009) [131]	12	Placebo Silodosin 1 x 8 mg	457 466	-16.0 -30.0[b]	+1.5 +2.6[b]	- -	1b
Chapple et al. (2011) [132]	12	Placebo Tamsulosin 1 x 0.4 mg Silodosin 1 x 8 mg	185 376 371	-25.0 -35.0[b] -37.0[b]	+2.9 +3.5 +3.7	- - -	1b
Cui et al. (2012) [133]	12	Placebo Tamsulosin 1 x 0.4 mg or 1 x 0.2 mg Silodosin 1 x 8mg or 2 x 4 mg	2543	sign. only vs placebo	sign. only vs placebo	- -	1a
Chapple et al. (1996) [134]	12	Placebo Tamsulosin MR 1 x0.4 mg	185 364	-25.5 -35.1[a,b]	+0.6 +1.6[a,b]	-13.4 -22.4[a]	1b
Lepor (1998) [135]	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) [136]	12	Placebo Tamsulosin MR 1 x0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8mg	350 700 354 707	-32 -43.2[b] -41.7[b] -42.4[b]	- - - -	- - - -	1b
Wilt et al. (2002) [137]	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) [138]	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) [139]	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. (2002) [140]	4-52	Placebo Terazosin (different doses)	5151	-37[b] (-2.9 Boyarski[†]) -38[b] (IPSS[†])	+1.7[b]	-	1a

GITS = gastrointestinal therapeutic system; IPSS = International Prostate Symptom Score; IR = immediate release; MR = modified-release; OCAS = oral-controlled absorption system; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry). [a]significant compared with baseline (indexed wherever evaluated); [b]significant compared with placebo; [†]absolute value.

3C.2.2 ***5α-Reductase inhibitors***

Mechanism of action: Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α-reductase, a nuclear-bound steroid enzyme [148]. Two isoforms of this enzyme exist:

- 5α-reductase type 1, with minor expression and activity in the prostate but predominant activity in extraprostatic tissues, such as skin and liver.
- 5α-reductase type 2, with predominant expression and activity in the prostate.

Two 5α-reductase inhibitors (5-ARIs) are available for clinical use: dutasteride and finasteride (see supplementary online material Table S.4). Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5-ARI). However, the clinical role of dual inhibition remains unclear. 5-ARIs act by inducing apoptosis of prostate epithelial cells [149] leading to prostate size reduction of about 18-28% and circulating PSA levels of about 50% after 6-12 months of treatment [150]. Mean prostate volume reduction and PSA decrease may be even more pronounced after long-term treatment. 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 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after a minimum treatment duration of at least 6-12 months. After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by approximately 18-28%, and increase Q_{max} by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (Table 3) [49, 124, 125, 151-157]. Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [150, 158]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [159]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of acute urinary retention, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL at baseline [160, 161]. Comparative studies with α_1-blockers and a recent meta-analysis have demonstrated that 5-ARIs reduce LUTS slower and that finasteride is less effective than either doxazosin or terazosin, but equally effective compared with tamsulosin [49, 151, 152, 162, 163]. A long-term trial with dutasteride in symptomatic men with prostate volumes >30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as, or even more effectively than, the α_1-blocker tamsulosin [124, 157, 164]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride.

5α-reductase inhibitors, but not α_1-blockers, reduce the long-term (>1 year) risk of acute urinary retention (AUR) or need for surgery [49, 155, 165]. In the Proscar Long-Term Efficacy and Safety Study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo [155]. In the Medical Therapy of Prostatic Symptoms (MTOPS) study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [49].

A pooled analysis of randomised trials with two-year follow-up data, reported that treatment with finasteride significantly decreased the occurrence of AUR by 57%, and surgical intervention by 34%, in moderately symptomatic LUTS [166]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [167, 168].

Table 3: Randomised trials with 5α-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) [151]	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) [152]	52	Placebo	253	-33.1	+1.4	-	1b
		Finasteride 1 x 5 mg	239	-38.6	+1.8	-	
Andersen et al. (1995) [153]	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) [156]	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]	-21.0	
McConnell et al. (1998) [155]	208	Placebo	1503	-8.7	+0.2	+14.0[a]	1b
		Finasteride 1 x 5 mg	1513	-22.0[a,b]	+1.9[a,b]	-18.0[a,b]	
Marberger et al. (1998) [154]	104	Placebo	1452	-9.8[†]	0.8	+9.0	1b
		Finasteride 1 x 5 mg	1450	-21.4[†b]	+1.4[b]	-15.0[b]	
McConnell et al. (2003) [49]	234	Placebo	737	-23.8	+1.4[a]	+24.0[a]	1b
		Finasteride 1 x 5 mg	768	-28.4[a,b]	+2.2[a,b]	-19.0[a,b]	
Roehrborn et al. (2002) [157]	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) [124]	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	-28.0[b]	
Roehrborn et al. (2010) [125]	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	-28.0[b]	

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

Tolerability and safety: The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [49, 125, 150]. The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients.

Data from two trials on prostate cancer chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARIs arms [169, 170]. Although no causal relationship with high-grade prostate cancer has been proven, men taking a 5-ARI should be followed-up regularly using serial PSA testing and any confirmed PSA increase should be evaluated accordingly.

Practical considerations: Treatment with 5-ARIs should be considered in men with moderate-to-severe LUTS and an enlarged prostate (> 40 mL) and/or elevated PSA concentration (> 1.4-1.6 ng/mL). Due to the slow onset of action, they are suitable only for long-term treatment (years). Their effect on the serum PSA concentration needs to be considered for prostate cancer screening. 5α-reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularisation [171].

Recommendations	LE	GR
5α-Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 mL).	1b	A
5α-Reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery.	1b	A

LUTS = lower urinary tract symptoms.

*3C.2.3 **Muscarinic receptor antagonists***

Mechanism of action: The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells.

Muscarinic receptors are also present on other cell types, such as bladder urothelial cells, epithelial cells of the salivary glands, or the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. M2 are more numerous, but the M3 subtype is functionally more important in bladder contractions in healthy humans [172, 173]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by central nervous system [174, 175].

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms (see supplementary online material Table S.5): darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); trospium chloride.

Efficacy: Antimuscarinics were mainly tested in females in the past, because it was believed that LUTS in men are caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for that assumption [176]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender has an impact on urgency, frequency, or urgency incontinence [177].

Efficacy of tolterodine or fesoterodine were tested as single agents in men with OAB in the absence of BOO (Table 4) [178-184]. Most trials lasted only 12 weeks. Four post hoc analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [179, 181, 184, 185]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency, urgency-related voiding, and improve patient perception of treatment benefit. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks [180, 183].

In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety study, men who received tolterodine monotherapy saw improvement only in urgency incontinence, but not urgency, IPSS (total or storage subscore), or the overall percentage of patients reporting treatment benefit compared with placebo [182].

A further analysis showed that men with PSA levels of <1.3 ng/mL (smaller prostates) might profit more from antimuscarinic drugs [186]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [183, 187]. In a small RCT without placebo, propiverine improved frequency and urgency episodes [187]. In an open-label study, tolterodine decreased 24-hour micturition, nocturia and American Urological Association Symptom Index scores [183].

Table 4: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with OAB symptoms

Trials	Duration (weeks)	Treatment	n	Voiding frequency (%)	Nocturia (%)	Urgency incontinence (%)	IPSS (%)	LE
Kaplan et al. (2005) [183]	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) [184]	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4 mg/d	77	-12	-	-71[b]	-	
Kaplan et al. (2006) [181]	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-10.8[b]	-18.8	-	-	
Kaplan et al. (2006) [182]	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) [178]	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-8.7[b]	-18.8	-	-	
Höfner et al. (2007) [180]	12	Tolterodine 1 x 4 mg/d	741	-20[a]	-42.9[a]	-100[a]	-37.9[a]	2b
Herschorn et al. (2010) [179]	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 with baseline (p < 0.01; indexed wherever evaluated); [b]significant compared with placebo (p < 0.05); [c]significant compared with fesoterodine 4 mg (p < 0.05).

Tolerability and safety: Antimuscarinic drug trials generally show approximately 3-10% withdrawals, which is similar to placebo. Drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [179]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%). These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Antimuscarinics theoretically might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A 12-week safety study on men with mild to moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not acute urinary retention (3% in both arms) [188]. The urodynamic effects included larger bladder volumes at first detrusor contraction, higher maximum cystometric capacity, and decreased bladder contractility index. Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [188].

Practical considerations: Not all antimuscarinics have been tested in elderly men, and long-term studies on the efficacy of muscarinic receptor antagonists in men of any age with LUTS are not yet available. In addition, only patients with low PVR volumes at baseline were included in the studies. These drugs should therefore be prescribed with caution, and regular re-evaluation of IPSS and PVR urine is advised.

Recommendations	LE	GR
Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B
Caution is advised in men with BOO.	4	C

BOO = bladder outlet obstruction; LUTS = lower urinary tract symptoms.

3C.2.4 ***Phosphodiesterase 5 inhibitors***

Mechanism of action: PDE type 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDEs might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [189]. Moreover, chronic treatment with PDE5I seems to increase blood perfusion and oxygenation in the LUT [190]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [191].

Available drugs: Although clinical trials of several selective oral PDE5Is have been conducted in men with LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS.

Efficacy: Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and QoL (Table 5). Q_{max} increases in a dose-dependent fashion, but is not significantly different from placebo in most trials. In a meta-analysis, PDE5Is were found to improve IPSS and International Index of Erectile Function (IIEF) score, but not Q_{max} [192].

Tadalafil 5 mg reduces IPSS by 22-37% (Table 5), and improvement may be seen within a week of initiation of treatment [193]; the maximum trial (open label) duration was 52 weeks [194]. A subgroup analysis of pooled data demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α-blockers or PDE5Is, total testosterone level or predicted prostate volume [195]. In a study on sexually active men ≥45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [196]. Another analysis showed a small but significant increase in Q_{max}, and no significant effect on PVR [197].

The combination of PDE5Is and α-blockers has also been evaluated. A meta-analysis of 5 RCTs (two studies with tadalafil 20 mg, two with sildenafil 25 mg, and one with vardenafil 20 mg), showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5 mL/s) compared with α-blockers alone [192]. However, only tadalafil 5 mg has been licensed in the context of LUTS management, so data on combinations of PDE5Is and other LUTS medications are considered insufficient.

Tolerability and safety: Reported adverse effects (AEs) in RCTs comparing the effect of all PDE5Is vs. placebo in men with LUTS include: flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [192]. Discontinuation rate due to AEs for tadalafil is 2.0% [198] and do not differ by age, LUTS severity, testosterone levels, and prostate volume in the pooled data analyses [195].

PDE5Is are contraindicated in patients using nitrates, the potassium channel opener, nicorandil, or α_1-blockers doxazosin or terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (<3 mo) or stroke (<6 mo), myocardial insufficiency (New York Heart Association stage >2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is.

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without erectile dysfunction. The meta-analysis of PDE5Is suggested that younger men with low body mass index and more severe LUTS profit the most from treatment with PDE5Is [192].

Long-term experience with tadalafil in men with LUTS is limited to one trial [194], and therefore conclusions about its efficacy or tolerability >1 year are not possible. There is limited information about reduction of prostate size and none about disease progression.

Recommendations	**LE**	**GR**
PDE5Is reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction. Only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS in Europe.	1a	A

LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

Table 5: Efficacy of PDE5Is in adult men with LUTS who participated in high level clinical trials

Trials	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
PDE5Is in monotherapy							
McVary et al. (2007) [199]‡	12	Placebo	180	-1.93	+0,16	-	1b
		Sildenafil 1 x 50-100 mg/day or 1 x 50-100 mg before sexual intercourse	189	-6.32*	+0.31	-	
McVary et al. (2007) [200]	12	Placebo	143	-1.7 (-9.3%)	+0.9	-2.6	1b
		Tadalafil 1 x 5-20 mg/day	138	-3.8 (-21.7%)*	+0.5	+1.4	
Roehrborn et al. (2008) [201]	12	Placebo	211	-2.3 (-13.3%)	+1.2	+4.81	1b
		Tadalafil 1 x 2.5 mg/day	208	-3.9 (-22.2%)*	+1.4	+12.1	
		Tadalafil 1 x 5 mg/day	212	-4.9 (-28.2%)*	+1.6	+6.6	
		Tadalafil 1 x 10 mg/day	216	-5.2 (-29.1%)*	+1.6	+10.6	
		Tadalafil 1 x 20 mg/day	209	-5.2 (-30.5%)*	+2.0	-4	
Stief et al. (2008) [202]	8	Placebo	113	-3.6 (-20.0%)	+1.0	+1.92	1b
		Vardenafil 2 x 10 mg/day	109	-5.8 (-34.5%)*	+1.6	-1.0	
Porst et al. (2009) [203]‡	12	Placebo	115	-2.1	+1.9	-6.8	1b
		Tadalafil 1 x 2.5 mg/day	113	-3.6*	+1.4	+8.6*	
		Tadalafil 1 x 5 mg/day	117	-4.2*	+1.7	-1.8	
		Tadalafil 1 x 10 mg/day	120	-4.7*	+1.3	+3.8	
		Tadalafil 1 x 20 mg/day	116	-4.7*	+2.0	-14.0	
Egerdie et al. (2012) [204]‡	12	Placebo	200	-3.8 (-20.9%)	+1.2	-3.0	1b
		Tadalafil 1 x 2.5 mg/day	198	-4.6 (-25.3%)	+1.7*	-8.4	
		Tadalafil 1 x 5 mg/day	208	-6.1* (-33,0%)	+1.6	-2.0	
Oelke et al. (2012) [193]‡	12	Placebo	172	-4.2 (-24.1%)	+1.2	-1.2	1b
		Tamsulosin 1 x 0.4 mg/day	168	-5.7* (-33.9%)	+2.2*	-10.2	
		Tadalafil 1 x 5 mg/day	171	-6.3* (-36.6%)	+2.4*	-4.6	
Yokoyama et al. (2012) [205]‡	12	Placebo	154	-3.0 (-17.9%)	+2.2	-1.2	1b
		Tadalafil 1 x 2.5 mg/day	151	-4.8* (-28.9%)	+1.6	-0.1	
		Tadalafil 1 x 5 mg/day	155	-4.7* (-27.3 %)	+1.3	-2.9	
Meta-analysis on PDE5Is							
Gacci et al. (2012) [192]	6-12	Placebo	964				1a
		PDE5I (any)	2250	Δ -2.8*	0.0	-	
		α_1-blocker	107				
		α_1-blocker + PDE5I	109	Δ -1.8•	Δ +1.5•		

*IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine; ‡trial included patients with both erectile dysfunction and LUTS; *significant compared with placebo ($p \leq 0.05$); †significant compared with baseline ($p \leq 0.05$ [indexed wherever evaluated]); °significant compared with PDE5I alone; •significant compared with α_1-blocker alone.*

3C.2.5 ***Plant extracts - phytotherapy***

Mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits of a single plant (mono-preparations); others combine the extracts of two or more plants to one pill (combination preparations). The most widely used plants are: *Cucurbita pepo* (pumpkin seeds), *Hypoxis rooperi* (South African star grass), *Pygeum africanum* (bark of the African plum tree), *Secale cereale* (rye pollen), *Serenoa repens* (syn. *Sabal serrulata*; berries of the American dwarf palm, saw palmetto) and *Urtica dioica* (roots of the stinging nettle).

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [206]. In vitro, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects; decrease sexual hormone binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [206-208]. These effects have not been confirmed in vivo, and the precise mechanisms of action of plant extracts remain unclear.

Efficacy: The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects and so the effects of one brand cannot be extrapolated to others [209]. Batches from the same producer might contain different concentrations of active ingredients [210]. Thus the pharmacokinetic properties can vary significantly.

Table 6 presents the trials with the highest LE for each plant extract. In general, no phytotherapeutic agent has been shown to reduce prostate size, and no trial has proven a reduction of BOO or a decrease in disease progression. Analysis of each drug class can be found in the supplementary online material (see www.uroweb.org/guidelines).

Cochrane meta-analyses suggest that a) men treated with *Pygeum africanum* were twice as likely to report symptom improvement, b) men treated with *Secale cereale* were twice as likely to benefit from therapy compared to placebo and c) *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin for IPSS (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [211-213].

Table 6: Trials with plant extracts in patients with BPH-LUTS (selection)

Trials	Duration (weeks)	Treatment	Patients (n)	Change symptoms (IPSS)†	Change Q_{max} (mL/s)	PVR (mL)	LE
Bach (2000) [214]	52	Placebo	243	-5.5	NS	NS	1b
		Cucurbita pepo (Prosta Fink™forte)	233	-6.7[a]	NS	NS	
Berges et al. (1995) [215]	24	Placebo	100	-2.3	+1.1	-16.8	1b
		Hypoxis rooperi (Harzol™)	100	-7.4[a]	+5.2[a]	-35.4[a]	
Klippel et al. (1997) [216]	26	Placebo	89	-2.8	+4.3	-4.1	1b
		Hypoxis rooperi (Azuprostat™)	88	-8.2[a]	+8.8[a]	-37.5[a]	
Wilt et al. (2000) [217]	4-26	Placebo	475	-4.9[b]	+3.9[b]	-28.6[b]	1a
		Hypoxis rooperi					
Wilt et al. (2002) [212]	4-18	Placebo	1562	RR 2.07[b]	+2.5[b]	-13.2[b]	1a
		Pygeum africanum (β-sitosterol)					
Wilt et al. (2000) [213]	12-24	Placebo	444	RR 2.4[b]	-1.6	-14.4	1a
		Secale cereale (Cernilton™)					
Tacklind et al. (2012) [211]	6-18	Placebo	661	-0.16[b] NS	+0.40[b] NS	NA	1a
		Serenoa repens					
Tacklind et al. (2012) [211]	6-18	Tamuslosin	582	-0.52[b] NS	+0.14[b] NS	NA	1a
		Serenoa repens					
Carraro et al. (1996) [218]	26	Finasteride	545	-6.2	+3.2[a]	-	1b
		Serenoa repens (Permixon™)	553	-5.8	+2.7	-	
Safarinejad (2005) [219]	26	Placebo	316	-1.5	+3.4	0	1b
		Urtica dioica	305	-8.0[a]	+8.2[a]	-37	
Lopatkin et al. (2005) [220]	24	Placebo	126	-4.0	+1.9	-	1b
		Sabal serrulata + *Urtica dioica* (Prostatgutt™ forte)	127	-6.0[b]	+1.8	-	
Sökeland and Albrecht (1997) [221]	48	Finasteride	244	-5.6	+2.8	-17.1	1b
		Sabal serrulata + *Urtica dioica* (Prostatgutt™ forte)	245	-4.8	+2.0	-10.2	

IPSS = International Prostate Symptom Score; n = number of patients; NA = not available; NS = not significant; PVR = post-void residual urine; Q_{max} = maximal urinary flow rate (free uroflowmetry); RR = relative risk.
†absolute values; [a]significant reduction compared with placebo/comparison treatment arm ($p < 0.05$);
[b]in favour of plant extract.

Tolerability and safety: Side-effects during phytotherapy are generally mild and comparable to placebo. Serious adverse events were not related to study medication. Gastrointestinal complaints were the most commonly reported. In formulations with *Hypoxis rooperi*, erectile dysfunction appeared in 0.5% of patients.

Practical considerations: Phytotherapeutic agents are a heterogeneous group and may contain differing concentrations of the active ingredient(s). Hence, meta-analyses do not seem to be justified and results of any analyses have to be interpreted with caution.

Recommendations: The Guidelines Panel have not made any specific recommendations on phytotherapy for the treatment of male LUTS because of product heterogeneity, limited regulatory framework, and methodological limitations of the published trials and meta-analyses.

3C.2.6 ***Vasopressin analogue - desmopressin***

Mechanism of action: The antidiuretic hormone arginine vasopressin (AVP) regulates water homeostasis. It controls urine production through the V2 receptor in the renal collecting ducts. AVP increases water re-absorption and urinary osmolality, while decreasing water excretion and total urine volume. AVP also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, so is unsuitable as a treatment for nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties, but has no relevant V1 receptor affinity or hypertensive effects. Desmopressin may be used by intravenous infusion, nasal spray, tablet or 'melt' formulation. Nasally or orally administered desmopressin is rapidly absorbed, and excreted 55% unchanged by the kidneys [222]. Desmopressin has been used for more than 30 years for diabetes insipidus or primary nocturnal enuresis, and it is approved in most European countries for the treatment of nocturia secondary to nocturnal polyuria in adults (see supplementary online material Table S.6).

Efficacy: Desmopressin significantly reduced nocturnal diuresis by approximately 0.6-0.8 mL/min (-40%), decreased the number of nocturnal voids by approximately 0.8-1.3 (-40%), and extended the time until the first nocturnal void by 1.6-2.1 hours (Table 7). Furthermore, desmopressin significantly reduced night-time urine volume, and the percentage of urine volume excreted at night [223-225].

A meta-analysis found that desmopressin significantly reduced the overall number of nocturnal voids and increased hours of undisturbed sleep. However, the RCTs were conducted in heterogeneous populations, using varied dosages [23].

The clinical effects of desmopressin were more pronounced in patients with more severe nocturnal polyuria and normal bladder capacity at baseline. The 24-hour diuresis remained unchanged during desmopressin treatment [226]. The clinical effects were stable over a follow-up period of 10-12 months and returned to baseline values after cessation of the trial [223].

Tolerability and safety: The most frequent adverse events in short-term (up to three weeks) and long-term studies (12 months) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth and hyponatraemia (serum sodium concentration of <130 mmol/L). Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial [223].

Hyponatraemia, not necessarily associated with symptoms, occurs in 5.0-7.6% of patients soon after treatment initiation [235, 236]. The risk of developing hyponatraemia significantly increases with age (odds ratio 1.16 per year of age), lower serum sodium concentration at baseline (odds ratio 0.76), and higher basal 24-hour urine volume per bodyweight (odds ratio 1.09) [235]. The risk of hyponatraemia in patients < 65 years is < 1%; for older patients with normal sodium concentration it is 8%, but it is up to 75% in old patients with low sodium concentration at baseline [235]. A recent subanalysis suggests that oral doses of 50-100µg desmopressin (melt) are safe in men [237].

At the time of treatment initiation or dose change, older men with normal values of serum sodium should be monitored by Na+ measurement at day three and day seven of treatment, and one month later. If serum sodium concentration has remained normal and no dose adjustment is intended, Na+ should be monitored every three to six months thereafter [238]. Patients should be informed about the symptoms of hyponatraemia, (headache, nausea or insomnia).

Practical considerations

Desmopressin is taken once daily before sleeping. Because the optimal dose differs between patients, desmopressin treatment should be initiated at a low dose (0.1 mg/day) and may be gradually increased up to a dosage of 0.4 mg/day every week until maximum efficacy is reached. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below normal.

Recommendation	**LE**	**GR**
Vasopressin analogue can be used for the treatment of nocturia due to nocturnal polyuria.	1b	A

Table 7: Clinical trials with desmopressin in adult men with nocturnal polyuria

Trials	Duration (weeks)	Treatment (oral daily dose before bedtime, unless otherwise indicated)	Patients (n)	Change nocturnal urine volume (mL/min)	Change nocturnal voids (n)	Time to first void (hours)	LE
Asplund et al. (1998) [227]	3	1 x 0.1 mg	23*	-0.5 (-31%)	-	-	2b
		1 x 0.2 mg	23*	-0.7 (-44%)	-	-	
		2 x 0.2 mg	23*	-0.6 (-38%)	-	-	
Cannon et al. (1999) [228]	6	Placebo	20	-	+0.1 (+3%)	-	1b
		1 x 20 µg intranasal	20	-	-0.3 (-10%)	-	
		1 x 40 µg intranasal	20	-	-0.7 (-23%)[a]	-	
Asplund et al. (1999) [226]	2	Placebo	17*	-0.2 (-11%)	-0.2 (-11%)	+0.2	1b
		1 x 0.1-0.4 mg	17*	-0.8 (-44%)[a]	-0.8 (-42%)[a]	+1.6	
Chancellor et al. (1999) [229]	12	1 x 20-40 µg intranasal	12	-	-1.8 (-50%)	-	2b
Mattiasson et al. (2002) [224]	3	Placebo	65	-0.2 (-6%)	-0.5 (-12%)	+0.4	1b
		1 x 0.1-0.4 mg	86	-0.6 (-36%)[a]	-1.3 (-43%)[a]	+1.8[a]	
Kuo 2002 [230]	4	1 x 0.1 mg	30*	-	-2.72 (-48.5)	-	2b
Rembratt et al. (2003) [231]	0.5	1 x 0.2 mg	72*	-0.5	-1.0	+1.9	2b
van Kerrebroeck et al. (2007) [225]	3	Placebo	66	-	-0.4 (-15%)	+0.55	1b
		1 x 0.1-0.4 mg	61	-	-1.25 (-39%)[a]	+1.66[a]	
Lose et al. (2004) [223]‡	52	1 x 0.1-0.4 mg	132	-	-2.0	+2.3	2b
Wang et al. (2011) [232]	52	Placebo	58		-	-	1b
		1 x 0.1 mg	57	Δ141 mL	-	+0.5[a]	
Weiss et al. (2012) [233]‡	4	Placebo	90	-125 mL	-0.84	40 min	1b
		1 x 10 µg	82	-125 mL	-0.54	48 min	
		1 x 25 µg	87	-163 mL	-0.83	61 min	
		1 x 50 µg	77	-286 mL[a]	-1.13	72 min	
		1 x 100 µg	80	-306 mL[a]	-1.38[a]	100 min[a]	
Weiss et al (2013) [234]	12	Placebo	142	-130.9 mL	-0.88	72.9	1b
		1 x 50 µg	119	-208.7 mL[a]	-1.25[a]	111.8[a]	
		1 x 75 µg	124	-217.1 mL[a]	-1.29[a]	115.6[a]	

**The majority of study participants were male; ‡male data only; [a]significant compared with placebo.*

3C.2.7 ***Emerging therapies***

3C.2.7.1 Beta-3 agonists

Mechanism of action: Beta-3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation.

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist and has received approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in three 12-week, RCTs conducted in Europe, Australia, and North America and a further 12-month randomised, double-blind, active treatment-controlled, study in OAB patients [239-242]. Mirabegron at daily doses of 25, 50, and 100 mg demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency and also patient perception of treatment benefit.

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, urinary tract infection, headache and nasopharyngitis [239-242]. The proportion of patients with

dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [239]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{max}, detrusor pressure at maximum flow and bladder contractility index [243].

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are still pending.

Recommendation	LE	GR
Beta-3 agonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms.	1b	B

LUTS = lower urinary tract symptoms.

*3C.2.8 **Combination therapies***

3C.2.8.1 α_1-blockers + 5α-reductase inhibitors

Mechanism of action: Combination therapy consists of an α_1-blocker (Section 3C.2.1) together with a 5-ARI (Section 3C.2.2). The α_1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop significant clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α_1-blocker, 5-ARI or placebo alone (Table 8). Initial studies with follow-up periods of 6-12 months demonstrated that the α_1-blocker was superior to finasteride in symptom reduction, whereas combination was not superior to α_1-blocker alone [151, 152, 162]. In studies with a placebo arm, the α_1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study (published but not specifically analysed for this timepoint), showed similar results [49].

Long-term data (4 years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) trials showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α-blocker in reducing the risk of acute urinary retention or need for surgery [49, 124, 125].

The CombAT study demonstrated that combination treatment is superior to either monotherapy for symptoms and flow rate starting from month nine, and superior to α_1-blocker for acute urinary retention and the need for surgery after month eight [125]. The different results between the CombAT and MTOPS trials may reflect different inclusion and exclusion criteria, rather than the specific drugs used.

Discontinuation of the α_1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [244, 245]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [244], with almost three-quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recently published trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [245]. LUTS improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.44). However, the main limitations of the studies include the short duration and the short follow-up period after discontinuation.

In both the MTOPS and CombAT trials, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, acute urinary retention, urinary tract infection, incontinence, or an increase in creatinine >50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy (vs placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [49]. In addition, finasteride (alone or in combination), but not doxazosin, significantly reduced both the risks of AUR and the need for BPH-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [246].

Table 8: Randomised trials using α_1-blocker, 5α-reductase inhibitor, and the combination of both drugs in men with LUTS and benign prostatic enlargement due to BPH

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) [151]	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	-39.0[a,b,d]	+3.2[b,d]	-18.8[b,c]	
Debruyne et al. (1998) [162]	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 [152]	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) [49]	234	Placebo	737	-23.8[a]	+1.4[a]	+24.0[a]	1b
		Doxazosin 1 x 1-8 mg	756	-35.3[a,b,d]	+2.5[a,b]	+24.0[a]	
		Finasteride 1 x 5 mg	768	-28.4[a,b]	+2.2[a,b]	-19.0[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]	-19.0[a,b,c]	
Roehrborn et al. (2008) [124]	104	Tamsulosin 1 x 0.4 mg	1611	-27.4	+0.9	0.0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5	+1.9	-28.0[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) [125]	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	-28.0[c]	
		Tamsulosin 1 x 0.4 mg + dutasteride 1 x 0.5 mg	1610	-38.0[c,d]	+2.4[c]	-27.3[c]	

Note: [124] and [125] reflect different timepoints in the same study
IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate (free uroflowmetry).
[a]significant compared with baseline (indexed wherever evaluated); [b]significant compared with placebo; [c]significant compared with α-blocker monotherapy; [d]significant compared with 5α-reductase inhibitor monotherapy.

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [49, 124, 125].The adverse events observed during combination treatment were typical of α_1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy.

Practical considerations: Compared with α_1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max}, and is superior in prevention of disease progression. However, combination therapy is also associated with more adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, etc.). Combination therapy should only be used when long-term treatment (more than 12 months) is intended; this issue should be discussed with the patient before treatment. Discontinuation of the α_1-blocker after six months might be considered in men with moderate LUTS.

Recommendation	LE	GR
Combination treatment with an α_1-blocker together with a 5α-reductase inhibitor can be offered to men with troublesome moderate-to-severe LUTS, enlarged prostate and reduced Q_{max} (men likely to develop disease progression).	1b	A

Q_{max} = maximum urinary flow rate.

3C.2.8.2 α_1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α_1-blocker together with an antimuscarinic aiming to antagonise both α_1-adrenoceptors and muscarinic receptors.The possible combinations have not all been tested in clinical trials yet.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting 4-12 weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α_1-blocker [182, 183, 246-253] (Table 9). One trial used the α_1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [254].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α_1-blockers or placebo alone, and improves QoL [182]. Symptom improvement is higher regardless of PSA concentration, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [186].

Persistent LUTS during α_1-blocker treatment can be reduced by the additional use of an antimuscarinic, especially when detrusor overactivity is demonstrated [183, 246, 250, 253]. Two systematic reviews of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [255, 256].

Table 9: Efficacy of muscarinic receptor antagonists together with α_1-blockers

Trials	Duration (weeks)	Treatment	Patients (n)	Voiding frequency (%)	Nocturia (%)	IPSS (%)	LE
Saito et al. (1999) [247]	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20.0 mg/d	75	-44.7	-44.4[a]	-	
Lee et al. (2005) [249]	8	Doxazosin 1 x 4.0 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4.0 mg/d + propiverine 1 x 20.0 mg/d	131	-27.5[a]	-46.7	-50.7	
Kaplan et al. (2006) [182]	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4.0 mg/d	210	-16.5	-20.1	-54.0	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9[b]	
		Tolterodine 1 x 4.0 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1[b]	-39.9[b]	-66.4[b]	
MacDiarmid et al. (2008) [252]	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynin 1 x 10.0 mg/d	209	-	-	-51.9[b]	
Kaplan et al. (2005) [183]‡	25	Tolterodine 1 x 4.0 mg/d	43	-35.7[a]	-29.3[a]	-35.3	2b
Yang et al. (2007) [253]‡	6	Tolterodine 2 x 2.0 mg/d	33	-	-	-35.7[a]	2b
Chapple et al. (2009) [250]‡	12	Tolterodine ER 4.0 mg/d + α-blocker	283	-15.8[b]	-29.4	-25.1	1b
		Placebo + α-blocker	292	-10.5	-23.5	-23.5	
Kaplan et al. (2009) [251]‡	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2[a]	-	-29.0	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5.0 mg/d	202	-9.1[a]	-	-31.8	
Kaplan et al. (2013) [257]	12	Tamsulosin 0.4 mg + solifenacin 6 mg	74	-17.8	-	-45.7	1b
		Tamsulosin 0.4 mg + solifenacin 9 mg	74	-17.8	-	-39.0	
		Placebo	74	-9.5	-	-36.0	

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

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using

α_1-blockers and antimuscarinics. The commonest side-effect is xerostomia. Some side-effects (e.g. xerostomia or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low [255, 256].

A recent RCT investigated safety in terms of maximum detrusor pressure and Q_{max} for solifenacin (6 mg or 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo [257]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [257].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α_1-blocker and antimuscarinic. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR is recommended during combination treatment.

Recommendations	LE	GR
Combination treatment with an α_1-blocker together with a muscarinic receptor antagonist may be used in patients with troublesome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	1b	B
Combination treatment should be prescribed with caution in men who may have BOO.	2b	B

BOO = bladder outlet obstruction; LUTS = lower urinary tract symptoms.

3C.3 Surgical treatment

*3C.3.1 **Transurethral resection of the prostate and transurethral incision of the prostate***

Mechanism of action: Transurethral resection of the prostate (TURP) removes tissue from the transition zone of the gland. Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without tissue removal. This technique may replace TURP in selected cases, especially in prostate sizes ≤ 30 mL without a middle lobe.

Efficacy: In a recent analysis of 20 contemporary RCTs with a maximum follow-up of 5 years, TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [258]. TURP delivers durable outcomes as shown by studies with a follow-up of 8-22 years. There are no similar data on durability for any other surgical treatment for BPO [259]. One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with detrusor underactivity rather than re-development of BPO [98].

Table 10 presents RCTs comparing TUIP with TURP [260-267]. A meta-analysis of short- and long-term data from 10 RCTs found similar LUTS improvements and lower but insignificant improvements in Q_{max} for TUIP [262]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 ml and three < 60 ml.

A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A review analysing 29 RCTs found a re-treatment rate of 2.6% after a mean follow-up of 16 months [268]. In a large-scale study of 20,671 men, the overall re-treatment rates (re-TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at 1, 5, and 8 years of follow-up, respectively, and the respective incidence of re-TURP was 2.9%, 5.8% and 7.4% [269]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after TURP (7.2%) [262].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [270]. The possibility of increased long-term mortality compared to open surgery [271] has not been verified [272-274]. Data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that short- and long-term procedural mortality was similar (0.7% vs. 0.9% at 90 days, 2.8% vs. 2.7% at 1 year, 12.7% vs. 11.8% at 5 years, 20% vs. 20.9% at 8 years) and that the 8-year myocardial infarction rates were identical (4.8 vs. 4.9%) [269].

The risk of TUR-syndrome decreased to < 1.1% [268, 275]. No case has been recorded after TUIP. Data from 10,654 TURPs reported bleeding requiring transfusion in 2.9% [270]. The risk after TUIP is negligible [268]. Similar results for TURP complications were reported by an analysis of contemporary RCTs using TURP as a comparator: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and urinary tract infection (UTI) 4.1% (0-22%) [258]. Long-term complications comprise urinary incontinence (1.8% after TUIP vs. 2.2% after TURP), urinary retention and UTIs, bladder neck contracture (BNC) (4.7% after TURP), urethral stricture (3.8% after TURP vs. 4.1% after TUIP), retrograde ejaculation (65.4% after TURP vs. 18.2% after TUIP), and erectile dysfunction (6.5% after TURP) [268].

Practical considerations: TURP and TUIP are effective treatments for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [270]. The upper limit for TURP is mostly suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, resection speed, and choice of resectoscope size).

3C.3.1.1 Modifications of TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of monopolar TURP (M-TURP) by allowing performance in normal saline. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectosope tip ("true" bipolar systems) or the sheath ("quasi-" bipolar systems). Prostatic tissue removal is identical to M-TURP. However, B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue. Energy from the loop is transmitted to the saline solution, resulting in excitation of sodium ions to form a plasma; molecules are then easily cleaved under relatively low voltage enabling resection. During coagulation, heat dissipates within vessel walls, creating a sealing coagulum and collagen shrinkage. The various bipolar devices available differ in the way in which current flow is delivered [276, 277].

Efficacy: B-TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from > 40 RCTs [278] have been reported, of which around half have been pooled in three RCT-based meta-analyses [258, 279, 280]. Early pooled results concluded that no clinically relevant differences exist in short-term (up to 12 months) efficacy (IPSS, QoL score and Q_{max}) [280]. Subsequent meta-analyses supported these conclusions [258, 279], though trial quality was generally poor. Data from RCTs with a follow-up of 12-60 months show no differences in efficacy parameters (Table 11) [281-287].

Tolerability and safety: Early pooled results concluded that no differences exist in short-term (up to 12 months) US/BNC rates, but B-TURP is preferable due to a more favourable perioperative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [280]. Subsequent meta-analyses supported these conclusions [258, 279]. However, trial quality is relatively poor and limited follow-up may cause under-reporting of late complications, such as urethral stricture/BNC [280]. Data from individual RCTs with a follow-up of 12-60 months showed no differences in urethral stricture/BNC rates (Table 11) [281-288].

A focused RCT using the erectile function domain of the IIEF (IIEF-ED) showed that M-TURP and B-TURP have a similar effect [289]. A comparative evaluation of the effects on the overall sexual function, quantified with IIEF-15 showed no differences between B-TURP and M-TURP at 12 months of follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [290].

Practical considerations: B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO, with similar efficacy but lower peri-operative morbidity [280]. The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up of >12 months. Mid-term results (up to 5 years) of B-TURP showed that safety and efficacy are comparable to M-TURP. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Recommendations	**LE**	**GR**
M-TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO. M-TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
The morbidity of M-TURP is higher than for drugs or other minimally invasive procedures.	1a	A
B-TURP achieves short- and mid-term results comparable with M-TURP.	1a	A
B-TURP has a more favourable peri-operative safety profile compared with M-TURP.	1a	A
TUIP is the surgical therapy of choice for men with prostate sizes <30 mL, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A

BPO = benign prostatic obstruction; B-TURP = bipolar TURP; LUTS = lower urinary tract symptoms; M-TURP = monopolar TURP; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

Table 10: Efficacy and safety of transurethral resection of the prostate or transurethral incision of the prostate in level 1 trials at 12 or 24 months. Absolute and relative changes compared to baseline with regard to symptoms (Madson-Iverson or IPSS) and maximum urinary flow rate

Trials	Inter-vention	Patients (n)	Decrease in symptoms at 12 months		Q_{max} (mL/s) at 12 months		Blood trans-fusion (%)	Re-operation rate at 12 months (%)	LE
			Absolute	(%)	Absolute	(%)			
Dorflinger et al. 1992 [260]	TURP	31	-11.6[a]	-88[a]	+22.9[a,b]	+294[a,b]	13	3.2[b]	1b
	TUIP	29	-12.6[a]	-85[a]	+16.3[a]	+223[a]	0[c]	20.7	
Jahnson et al. 1998 [261]	TURP	43	-13[a]	-82[a]	+19.5[a,b]	+229[a, b]	2.4	7.1[b]	1b
	TUIP	42	-11.8[a]	-77[a]	+13.8[a]	+148[a]	0	23.2	
Riehmann et al. 1995 [263]	TURP	61	-9.5[a]	-67[a]	No significant difference between groups		16		1b
	TUIP	56	-10[a]	-63[a]			23		
Saporta et al. 1996 [264]	TURP	20	-9.4[a]	-63[a]	+17.3[a]	+266[a]		0[b]	1b
	TUIP	20	-9.3[a]	-64[a]	+14.6[a]	+197[a]		15	
Soonawalla et al. 1992 [265]	TURP	110			+20.1[a]	+251[a]	34.5		1b
	TUIP	110			+19.5[a]	+246[a]	0c		
Tkocz et al. 2002 [266]	TURP	50	-12*[a]	-70*	6.9*[a]	+255[a]			1b
	TUIP	50	-13*[a]	-77*	7.6*[a]	+222[a]			
Lourenco et al. 2009 [262]	TURP	345	no significant difference between groups	no significant difference between groups			28.3	7.2[b]	1a
	TUIP	346					1.1[c]	18	
Yang et al. 2001 [267]	TURP	403	-11.2 to -13	-63 to -82	+17.3 to +22.9[b]	+266 to +352[b]	25.1	5.5	1a
	TUIP	392	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223	0.87[c]	9.3	

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.
** = 24 months post operatively; [a] = significantly different compared to baseline; [b] = significantly different in favour of TURP; [c] = significantly different in favour of TUIP.*

Table 11: Mid-term (follow-up longer than 12 months) results from randomised controlled trials comparing monopolar and bipolar transurethral resection of the prostate

Trials	Inter-vention	Patients (n)	Follow-up (months)	IPSS Decrease		Q_{max} (mL/s)		US/ BNC (%)	LE
				Absolute	(%)	Absolute	(%)		
Autorino et al. 2009 [281]	M-TURP	31	48	-17.9[a]	-74[a]	+15.0[a]	+242[a]	6.5/3.2	1b
	B-TURP (Gyrus)	32		-17.3[a]	-72[a]	+12.7[a]	+179[a]	3.1/3.2	
Chen et al. 2010 [282]	M-TURP	50	24	-18.0[a]	-83[a]	+16.9[a,b]	+214[a]	6.0/4.0	1b
	B-TURP (TURiS)	50		-19.1[a]	-84[a]	+18.4[a]	+259[a]	4.0/2.0	
Geavlette et al. 2011 [284]	M-TURP	170	18	-15.9[a]	-66[a]	+14.2	+222	5.1/4.1	1b
	B-TURP (TURiS)	170		-16.1[a]	-67[a]	+14.5[a]	+238[a]	6.3/3.4	

Xie et al. 2012 [287]	M-TURP	79	60	-16.2[a]	-71[a]	+15.2[a]	+157[a]	5.1/10.1	1b
	B-TURP (Gyrus)	78		-16.6[a]	-70[a]	+16.5[a]	+167[a]	5.1/5.1	
Mamoulakis et al. 2012 [286]	M-TURP	108	36	-16.0[a]	-69[a]	+10.8[a]	+126[a]	9.3/1.9	1b
	B-TURP (Autocon)	122		-15.4[a]	-66[a]	+10.7[a]	+122[a]	8.2/6.6	
Giulianelli et al. 2013 [285]	M-TURP	80	36	-19.4[a]	-83[a]	+13.5[a]	+208[a]	NA/13.3	1b
	B-TURP (Gyrus)	80		-20.3[a]	-91[a]	+14.1[a]	+158[a]	NA/2.5	

BNC = bladder neck contracture; B-TURP = bipolar TURP; IPSS = International Prostate Symptom Score; M-TURP = monopolar TURP; Q_{max} = maximum urinary flow rate; TURP = transurethral resection of the prostate; US = urethral stricture.

[a] = significantly different compared to baseline; NA = not available.

3C.3.2 ***Open prostatectomy***

Mechanism of action: OP is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure).

Efficacy: OP is the treatment of choice for large glands (> 80-100 mL). Three RCTs showed that Holmium laser enucleation of the prostate (HoLEP) and photoselective vaporisation of the prostate (PVP) lead to similar outcomes compared to OP in men with large glands (> 70 mL) at a significantly lower complication rate [291-293]. The results of OP studies are summarised in Table 12. OP reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL score by 60-87%, increases mean Q_{max} by 375% (+16.5-20.2 mL/s), and reduces PVR by 86-98% [291-295]. Efficacy is maintained for > 5 years [291, 293, 295] (Table 12).

Tolerability and safety: Mortality has decreased significantly during the past two decades (< 0.25%) [294]. The estimated transfusion rate is about 7-14% [291, 294, 295]. Long-term complications include urinary incontinence (up to 10%), BNC and US (about 6%) [291-293, 296].

Practical considerations: OP is the most invasive but also the most effective and durable procedure for the treatment of LUTS/BPO. In the absence of an endourological armamentarium and a holmium laser, OP is the surgical treatment of choice for men with prostates > 80 mL.

Recommendations	**LE**	**GR**
OP or holmium laser enucleation are the first choice of surgical treatment in men with prostate sizes > 80 mL and bothersome moderate-to-severe LUTS secondary to BPO needing surgical treatment.	1b	A
OP is the most invasive surgical method with significant morbidity.	1b	A

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms; OP = open prostatectomy.

Table 12: Results of OP studies for treating BPH-LUTS or BPO

Studies	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Kuntz et al. 2008 [291]	260	32	-18.2	86	21.4	677	-287	98			1b
Skolarikos et al. 2008 [293]	78	60	-12.5	63	7	86	-77	86	-86	88	1b
Naspro et al. 2006 [292]	104	39	-13.2	62	15.9	291					1b
Varkarakis et al. 2004 [295]	151	232	-23.3	84	16.5	329	-104	90			3
Gratzke et al. 2007 [294]		868			13	218	-128	88	85	88	2b

BPH = benign prostatic hyperlasia; BPO = benign prostatic obstruction; IPSS = International Prostate Symptom Score; LE = level of evidence; LUTS = lower urinary tract symptoms; n = number of patients; OP = open prostatectomy; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry).

*3C.3.3 **Transurethral microwave therapy***

Mechanism of action: Microwave thermotherapy works by emitting microwave radiation through an intra-urethral antenna to deliver heat into the prostate. Tissue is destroyed by being heated at temperatures above cytotoxic thresholds (> 45°C) (coagulation necrosis). The heat may also cause apoptosis and denervation of α-receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

Conceptually, transurethral microwave therapy (TUMT) devices are all similar in delivering microwave energy with some type of feedback system, differing mainly in the design of the urethral applicator. This can have a significant effect on the heating profile [297]. There is also variation in the catheter construction, cooling systems, treatment time, and monitoring of TUMT effects [298].

Efficacy: A systematic review assessed therapeutic efficacy in different devices/software, including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback (Table 13) [299]. It was concluded that TUMT was less effective than TURP in reducing LUTS. Symptom score after TUMT decreased by 65% in 12 months, compared to 77% after TURP. TURP achieved a greater Q_{max} improvement (119% vs. 70%) [299].

A pooled analysis of three studies (two RCTs and one open label) of ProstaLund Feedback TUMT (PLFT) with 12-month follow-up showed the responder rate was 85.3% and 85.9% after PLFT and TURP, respectively [300]. IPSS showed a subjective, non-inferior improvement with PLFT [300]. However, one-sided 95% CI analysis showed that PLFT non-inferiority did not reach the predetermined level, even though both improved Q_{max} significantly.

One RCT compared TUMT with terazosin [301]. After 18 months' follow-up, treatment failure in terazosin-treated patients (41%) was significantly greater compared to TUMT (5.9%), with TUMT achieving a greater improvement in IPSS and Q_{max} [302].

Previously, urinary retention was considered a contraindication for TUMT. Nowadays, LE:2b studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously [303-305]. However, these studies had a short follow-up (≤ 12 months), which makes it difficult to estimate the durability of TUMT outcome in patients with retention. In a study with a longer follow-up, treatment failure was 38% in the retention group, with a cumulative risk of 59% at 5 years [306].

An RCT-based systematic review estimated re-treatment rates [299] (though the trials had different follow-up periods) of 0.075 vs. 0.010 re-treatments per person per year for TUMT and TURP, respectively.

A multicentre RCT with follow-up of 5 years compared TUMT (PLFT; the Core-Therm device) and TURP. No significant differences were found in Q_{max} and IPSS. After TUMT, 10% needed additional treatment, vs. 4.3% after TURP. These data suggest clinical results obtained with PLFT-TUMT were comparable to TURP at five years. Most durability studies have a high attrition rate; in this study, less than half of the patients were analysed at 4-5 years. In addition, patients who remained in the study were likely to represent the best data (responders).

Tolerability and safety: Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency, and require pain medication for therapy. Pooled morbidity data comparing TUMT and TURP have been published [299, 300, 307]. In the Cochrane RCT-based systematic review, catheterisation time, dysuria/urgency and urinary retention rates were significantly less with TURP. Hospitalisation time, haematuria, clot retention, transfusion, TUR syndrome, and urethral stricture rates were significantly less for TUMT [299]. Sexual dysfunction and re-treatment rates for urethral stricture/BNC were higher after TURP.

Practical considerations: Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Due to the low peri- and post-operative morbidity and lack of need for anaesthesia, TUMT is a true outpatient procedure, and an option for older patients, and those with comorbidities or anaesthesia risk [308]. Independent baseline parameters that predict an unfavourable outcome include small prostates, mild-to-moderate BPO, and a low amount of energy delivered during treatment [309]. However, predictive factors for particular devices cannot necessarily be applied to other systems

Recommendations	LE	GR
TUMT achieves symptom improvement comparable with TURP, but TUMT is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP, which has lower re-treatment rates compared to TUMT.	1a	A

TUMT = transurethral microwave therapy; TURP = transurethral resection of the prostate.

Table 13: Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for IPSS, Qmax, PVR and PVol

Trials	Duration (weeks)	Patients (n)	Change in IPSS (absolute [%])	Change in Q_{max} (mL/s, [%])	Change in QoL (absolute [%])	Change in PVR (absolute [%])	Change in PVol (absolute [%])	LE
Hoffman et al. 2007[299]	52	322	-12.7[a] (-65.0)	5.6[a] (70.0)	-2.4[a] (58.5)	NA	NA	1a
Gravas et al. 2005 [300]	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[310]	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. 2001[311]	156	78	-8.0[a] (-40.0)	2.7[a] (29.3)	-2.0[a] (-50.0)	NS	NA	1b
Thalmann et al. 2002[312]	104	200	-20.0[a] (-87.0)	7.0a (116.6)	-4.0[a] (-80.0)	-143[a] (-84.1)	-17.7[a] (-30.7)	2b
Miller et al. 2003 [313]	260	150	-10.6[a] (-47.0)	2.4[a] (37.0)	-2.3[a] (-54.7)	NA	NA	2b
Trock et al. 2004 [314]	208	541	-8.9[a] (-42.7)	2.8[a] (35.0)	-2.1[a] (-50.1)	NA	NA	2b

IPSS = International Prostate Symptom Score; LE = level of evidence; PVol = prostate volume; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry); QoL = quality of life; TUMT = transurethral microwave therapy; [a] = significant compared to baseline (indexed whenever evaluated); n = number of patients; NS = not significant; NA = not available.

*3C.3.4 **Transurethral needle ablation of the prostate***

Mechanism of action: The transurethral needle ablation (TUNA™) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the parenchyma under direct vision using an attachment to the standard cystoscope. The energy induces coagulation necroses in the transition zone resulting in prostate volume reduction and BPO reduction.

Efficacy: A meta-analysis of two RCTs, two non-randomised protocols and 10 single-arm studies showed that TUNA™ achieved a 50% decrease in IPSS and a 70% improvement in Q_{max} at 1 year [315], supported by a more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) [316]. TUNA™ significantly improved IPSS and Q_{max}, but compared to TURP these improvements were significantly lower at 12 months. TURP vs. TUNA™ differences in means were - 4.72 and 5.9 mL/sec for IPSS and Q_{max} respectively [316].

Clinical studies on the impact of TUNA™ on BPO [317, 318] showed a significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max}, but a number of patients were still obstructed.

Most studies were short-to-midterm in duration, and there were concerns about the durability of effects. A study with 5 years' follow-up demonstrated symptomatic improvement in 58% and improved flow in 41%. However, 21% required additional treatment [319]. TUNA™ has a significantly higher re-treatment rate compared with TURP. The overall re-treatment rate after TUNA™ was 19% based on an analysis of 17 non-comparative studies [316].

Tolerability and safety: Post-operative urinary retention with a mean duration of 1-3 days is seen in 13-42% of patients; within 1 week, 90-95% of patients are catheter-free [320]. Storage LUTS are common for the first 4-6 weeks after intervention [321]. TUNA™ is associated with fewer adverse events compared to TURP, including mild haematuria, urinary infections, strictures, incontinence, ED, and ejaculation disorders [316].

Practical considerations: TUNA™ can be performed as a day-case procedure under local anaesthesia or sedation [320]. TUNA™ is unsuitable for prostates > 75 mL or isolated bladder neck obstruction. TUNA™ cannot effectively treat prostatic middle lobes. There is anecdotal evidence for TUNA™ in men receiving aspirin and anti-coagulants. TUNA™ can be performed as a day-case procedure and is associated with fewer side-effects than TURP (e.g. bleeding, ED, urinary incontinence). However, there are concerns about the durability of the effects achieved by TUNA™.

Recommendations	LE	GR
TUNA™ achieves symptom improvement comparable with TURP, but TUNA™ is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP with lower re-treatment rates compared to TUNA™.	1a	A

TUNA™ = transurethral needle ablation; TURP = transurethral resection of the prostate.

Table 14: Summary of comparative LE:1 data for TUNA™ versus TURP [316]

	TUNA™	TURP	TUNA™ vs. TURP (95% CI)	LE
Symptoms (IPSS): mean (% improvement)				
3 months (8,10)	-12 (56%)	-14 (62%)	-2 (-0.9 to 3.1)	1b
1 year (9-11)	-12 (55%)	-15.5 (70%)	3.4 (2.1 to 5.2)[a]	1b
3 years (9,11)	-10 (45%)	-15 (67%)	4.8 (4.2 to 5.4)[a]	1b
Quality of life scores: mean (% improvement)				
3 months (8,10)	-4.5 (54%)	-3.7 (48%)	-0.8 (-1.3 to 0.5)	1b
1 year (9-11)	-4 (50%)	-4.3 (56%)	0.63 (0.1 to 1.2)[a]	1b
3 years (9,11)	-4.2 (50%)	5.2 (67%)	1 (0.2 to 1.9)[a]	1b
Q_{max} (mL/s): mean (% improvement)				
3 months (8,10)	4.7 (54%)	11.5 (150%)	-5.8 (-6.3 to -5.4)[a]	1b
1 year (9-11)	6.5 (76%)	12.2 (160%)	-5.9 (-7.7 to -4.1)[a]	1b
3 years (9,11)	5.6 (66%)	10.8 (141%)	-5.3 (-6.8 to -3.9)[a]	1b
PVR (mL): mean (% improvement)				
1 year (10,11)	-20 (22%)	-42 (41%)	22 (-18 to 27)[a]	1b

IPSS = International Prostate Symptom Score; LE = level of evidence; Q_{max} = maximum urinary flow rate; PVR = post-void residual urine; TUNA™ = transurethral needle ablation; TURP = transurethral resection of the prostate.

[a] = TURP significantly better compared with TUNA™.

*3C.3.5 **Laser treatments of the prostate***

3C.3.5.1 Holmium laser enucleation and holmium laser resection of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2140 nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4 mm, which is enough to obtain adequate haemostasis [322]. Holmium laser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) result in BPO relief and, secondarily, in LUTS reduction.

Efficacy: In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at 6 or 12 months post operatively (Table 15) [323]. One RCT comparing TURP with HoLRP with a minimum follow-up of 4 years showed no difference in urodynamics after 48 months [324]. Three meta-analyses covering trials on HoLEP versus TURP found that symptom improvement was comparable or superior with HoLEP (Table 15) [325-327]. One RCT comparing photoselective vaporisation of the prostate (PVP)

and HoLEP in patients with prostates > 60 mL showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [328]. Another RCT on HoLAP and 80-W PVP showed comparable functional improvement within a median follow-up of 71 months [329].

RCTs indicate that HoLEP is as effective as open prostatectomy for improving micturition in large prostates [291, 292], with similar re-operation rates after 5 years (5% vs. 6.7%, respectively) [291]. One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-year follow-up found that the functional long-term results of HoLEP were comparable with TURP [330]. A retrospective study of HoLEP with the longest follow-up (up to 10 years, mean 62 months) reported durable functional results with low re-operation rates [331].

Tolerability and safety: Dysuria is the most common post-operative complication [322, 325]. Compared to TURP, HoLRP has shorter catheterisation and hospitalisation times [323, 332]. Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP [324]. Three meta-analyses found that HoLEP has a shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [325-327]. In a meta-analysis, no significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress urinary incontinence (1.5% vs. 1.5%), and re-intervention (4.3% vs. 8.8%) [326]. HoLEP is superior to open prostatectomy for blood loss, catheterisation and hospitalisation time [291, 292].

HoLEP has been safely performed in patients using anticoagulant medications [333, 334]. In a study of 83 patients, blood transfusion was required in seven patients (8%) [335]. A retrospective study compared the safety results of HoLEP between 39 patients who were on anticoagulant therapy at the time of their surgery, and 37 controls [334]. No transfusions were required and bleeding complication rates were not significantly different [334]. Short-term studies showed that patients with urinary retention can be treated with HoLEP [336, 337].

The impact on ED and retrograde ejaculation is comparable between HoLEP and TURP/OP [292, 338]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP.

Practical considerations: Holmium laser operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [333, 339].

3C.3.5.2 532 nm ('Greenlight') laser vaporisation of prostate

Mechanism of action: The kalium-titanyl-phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and reduction of LUTS. In 2014, three different Greenlight lasers were in use: the 80-W (KTP), 120-W HPS (LBO), and the 180-W XPS (LBO) laser systems. They differ in maximum power output, fibre design, and maximum energy application.

Efficacy: A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 (Table 15) [340]. No differences were found in Q_{max} and IPSS between PVP and TURP, but only three RCTs provided sufficient 12-month data to be included in the meta-analysis [341-343].

The longest RCT using the 80-W KTP laser has a follow-up of only 12 months [341]. A case series showed durable functional outcomes after the 80-W KTP laser, with an overall re-treatment rate of 8.9% at 5 years [344]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months reported a re-treatment rate of 14.8% [345].

Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated urodynamically [346]. The longest RCT comparing the 120-W HPS laser with TURP had a follow-up of 36 months and showed a comparable improvement in IPSS, Q_{max}, and PVR [347]. Re-operation rate was higher after PVP (11% vs. 1.8%; p = 0.04) [347]. Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months [342, 348].

A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former Greenlight laser systems [349].

Tolerability and safety: A meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but shorter catheterisation time and length of hospital stay after PVP [340]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis [340].

The Greenlight laser appears to be safe in high-risk patients under anticoagulation treatment [350-354]. In one study, anticoagulated patients had significantly higher rate of bladder irrigation (17.2%) compared

with Greenlight laser without taking anticoagulants (5.4%) [353]. Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomised trials [354-356].

The impact of Greenlight laser on sexual function seems to be similar to that of TURP. One RCT comparing TURP and Greenlight PVP reported no significant difference in the rate of retrograde ejaculation [357]. In addition, no difference was reported between OP/TURP and Greenlight PVP for erectile function [358, 359]. IIEF-5 scores are maintained after treatment. However, in patients with preoperative IIEF-5 >19, the post-operative IIEF-5 scores were significantly decreased at 6, 12, and 24 months [360].

Practical considerations: The evolution of the Greenlight laser from 80-W to 120-W and then to 180-W resulted in a wide variation in the degree of maturity of each laser therapy. Long-term results on 120-W and RCTs on 180-W are still pending.

3C.3.5.3 Diode laser vaporisation of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1318, and 1470 nm (depending on the used semiconductor) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [361].

Efficacy: Case series, and two comparative studies of a 980-nm diode laser and the 120 W HPS laser, are available [362-368]. IPSS, QoL, Q_{max}, and PVR improved significantly in all studies compared to baseline and were similar compared to 120-W HPS laser, at 6 and 12 months [362, 363]. However, RCTs and long-term follow up is lacking.

One RCT with a 12 month follow-up compared 980 nm diode laser with plasmakinetic enucleation and found equal clinical outcome (Table 15). Adverse events and catheter time favoured the diode laser group [369]. One small RCT with a 6 months' follow-up comparing laser enucleation using a 1318-nm diode laser with B-TURP reported similar efficacy and safety results (Table 15) [370]. Blood loss and hospitalisation time were in favour of laser enucleation.

Tolerability and safety: Two studies (980 nm) indicate high intraoperative safety, since no bleeding was reported, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% [362, 363]. Post-operatively, a higher rate of dysuria occurs than with 120-W HPS laser [362, 363]. Fibre modifications led to a significant reduction [365]. In summary, high re-operation rates (20-33%) and persisting stress urinary incontinence (9.1%) were reported [362-364].

Practical considerations: Diode lasers lead to immediate improvements of LUTS due to BPO and provide good haemostatic properties. Based on the lack of RCTs and controversial data on the re-treatment rate, diode lasers cannot be recommended as a standard treatment option for BPO.

3C.3.5.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG)

Mechanism of action: In the Tm:YAG laser, a wavelength of 2013 nm is emitted in continuous-wave mode. The laser is primarily used in front-fire applications [361]. Different applications, ranging from vaporisation (ThuVaP), vaporesection (ThuVaRP), and enucleation (ThuVEP/ThuLEP: similar enucleating techniques) are published.

Efficacy: A major drawback is the limited number of RCTs. Maximum follow-up of 4 years (case control study) with cumulative re-operation rates of 6% reported [371]. One RCT and one non-RCT compared ThuVaRP with M-TURP [372, 373], while two RCTs comparing ThuVaRP and B-TURP were published recently [374, 375]. In summary, studies show comparable improvement of symptoms and voiding parameters. There are only a few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [376-379]. ThuLEP and HoLEP were compared in one RCT with 18-months of follow-up with comparable outcome in both arms (Table 15) [380].

Tolerability and safety: Thulium laser prostatectomy shows high intra-operative safety in RCTs [372, 374, 380], as well as in case series in patients with large prostates [376], anticoagulation or bleeding disorders [377]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [372-374]. The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and re-operation rate was 0-7.1% during follow-up [372, 373, 381]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall re-treatment rate was 3.4% (mean follow-up 16.5 months) [382]. No urethral and bladder neck strictures after ThuLEP were reported during the 18-month follow-up [380]. Recently a large series of complications after vapoenucleation reported adverse events in 31% of cases, with 6.6% complications > Clavien grade 2 [383].

Practical considerations: The limited number of RCTs and limited follow-up (up to 18 months) do not permit final conclusions regarding the long-term efficacy of thulium laser prostatectomy.

Recommendations	LE	GR
HoLEP and 532-nm laser vaporisation of the prostate are alternatives to TURP in men with moderate-to-severe LUTS due to BPO leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
The intermediate-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
The long-term functional results of HoLEP are comparable with TURP/open prostatectomy.	1b	A
Diode laser operations lead to short-term objective and subjective improvement.	1b	B
ThuVaRP is an alternative to TURP for small- and medium-size prostates.	1b	A
ThuVEP leads to short-term objective and subjective improvement.	3	C
With regard to intra-operative safety and haemostatic properties, diode and thulium lasers appear to be safe.	3	C
With regard to intra-operative safety, 532-nm laser vaporisation is superior to TURP.	1b	A
532-nm laser vaporisation should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B

BPO = benign prostatic obstruction; HoLEP = holmium laser enucleation; LUTS = lower urinary tract symptoms; TURP = transurethral resection of the prostate; ThuVaRP = Tm:YAG vaporesection; ThuVEP = Tm:YAG vapoenucleation.

Table 15: Efficacy of different lasers for the treatment based on the highest-quality study for each of the treatment options. Absolute and relative changes compared to baseline, with regard to symptoms (AUA-SI/IPSS) and maximum urinary flow rate (Q_{max})

Trials	Duration (months)	Patients (n)	Surgery	Change symptoms (IPSS)			Change Q_{max} (mL/s)			LE
				Absolute	(%)	WMD	Absolute	(%)	WMD	
Tooher et al. 2004 [323]	12	231	HoLRP	NA	NA	-0.4	NA	NA	+4.2	1a
			TURP	NA	NA		NA	NA		
Tan et al. 2007 [326]	12	232	HoLEP	-17.5 to -21.7	-81 to -83	NA	+13.4 to +23.0	+160 to +470	+0.59	1a
		228	TURP	-17.7 to -18.0	-76 to -82		+10.1 to +21.8	+122 to +370		
Lourenco et al. 2008 [325]	12	277	HoLEP	-17.7 to -21.7	-82 to -92	-0.82	+13.4 to +23.0	+160 to +470	+1.48	1a
		270	TURP	-17.5 to -18.7	-81 to -82		+10.1 to +21.8	+122 to +370		
Thangasamy et al. 2012 [340]	12	176	KTP (80 W and 120 W)	-15.9 to -16.1	-64 to -66	-0.7	+9.8 to +14.5	+111 to +181	+1.1	1a
		164	TURP	-14.1 to -14.4	-56 to -63		+10.5 to +13.7	+118 to +154		
Lusuardi et al. 2011 [370]	6	30	Diode laser enuclea-tion	-22.7	-84		+14.8	+218		1b
		30	B-TURP	-21	-83		+15.2	+237		
Xu et al. 2013 [369]	12	40	Diode laser enuclea-tion	-18.6	-79		+15.5	+196		1b
		40	PKERP	-18.5	-77		+15.6	+200		
Xia et al. 2008 [372]	12	52	ThuVaRP	-18.4	-84		+15.7	+196		1b
		48	TURP	-16.9	-81		+15.8	+190		
Peng et al. 2013 [374]	3	50	ThuVaRP	-13.2	-65		+16.2	+205		1b
		50	B-TURP	-12.1	-63		+16.2	+198		
Zhang et al. 2012 [380]	18	71	ThuLEP	-19.4	-79		+16.6	+244		1b
		62	HoLEP	-16.6	-73		+16.9	+232		

Yang et al. 2013 [375]	18	79	ThuLEP	-17	-75		+14.2	+163		1b
		79	B-TURP	-18.2	-78		+14.1	+154		

AUA-SI = American Urological Association Symptom Index; B-TURP = bipolar transurethral resection of the prostate; HoLEP = holmium laser enucleation; HoLRP = holmium laser resection of the prostate; IPSS = International Prostate Symptom Score; KTP = greenlight laser vaporisation; NA = not available; Q_{max} = maximum urinary flow rate; TURP = transurethral resection of the prostate; ThuVaP = Tm:YAG vaporisation of the prostate; ThuVaRP = Tm:YAG vaporesection; ThuLEP = Tm:YAG laser enucleation of the prostate; ThuVEP = Tm:YAG vapoenucleation; WMD = weighted mean difference.

3C.3.6 ***Prostatic stents***

Mechanism of action: The use of an endoprosthesis to preserve luminal patency is a well-established concept. Prostatic stents were primarily designed as an alternative to an indwelling catheter but have also been assessed as a primary treatment option in patients without significant comorbidities [384, 385].

A prostatic stent requires a functioning detrusor [386]. Permanent stents are biocompatible, which allows epithelialisation. Temporary stents do not epithelialise and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery, or after minimally invasive treatment [386].

Efficacy: Several small case studies on a range of stents of different designs and materials have provided low level of evidence for their use. Table 16 describes the most important studies [384, 385, 387-390].

All studies observed a significant attrition rate. There is only one RCT that has compared two versions of a blind-placement prostatic stent (BPS) for BPO [391], and there have been no studies comparing stents with sham or other treatment modalities. The BPS system is temporary, with the difference between BPS-1 and BPS-2 being an additional 2 cm bulbar segment. This bulbar segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%) [391]. BPS-2 also resulted in superior symptom scores and voiding function, but only Q_{max} reached statistical significance [391].

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series, with differing follow ups [392]. These trials reported relevant symptom improvement and Q_{max} increase [392].

The pooled data from studies with patients who were catheter dependent showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment [392, 393].

The best data on non-epithelialising prostatic stents are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent [394], which reduced IPSS by 11-19 points and increased Q_{max} by 3-11 mL/s [394].

Tolerability and safety: In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [386]. The main immediate adverse events include perineal pain or bladder storage symptoms.

A systematic review of the UroLume reported a 16% failure rate within 12 months, mainly due to stent misplacement or migration (37%) or recurrent obstructive or irritative LUTS (14%). The overall failure rate at 5 years was 27% (50/188 stents) [392].

Practical considerations: Due to side effects and a high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS. Prostatic stents are an alternative to catheterisation for men who have (recurrent) urinary retention and are at high risk for surgery. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [386].

Recommendation	LE	GR
Prostatic stents are an alternative to catheterisation for men unfit for surgery.	3	C

Table 16: Efficacy of stents: key studies

Stent	n	Symptoms		Q_{max} (mL/s)		Failure rate (follow-up in months)	LE
		Pre-operative	Post-operative	Pre-operative	Post-operative		
Urolume (P) [384]	91	14.1	4.7	9.3	17.1	Overall	3
	44	R	4.6	R	13.7	15.5% (18)	
Memotherm (P) [387]	123	24.0	6.1*	7.4	16.1*	4% (48)	3
TITAN (P) [388]	85	15.9[a]	9.33[1]	8.59*	11.43[1]	Overall	3
	59	18.0	5.21	R	11.34	19% (24)	
Spanner (T) [385]	30	22.3	7.1	8.2	11.6	0% (2)	3
Memokath (T-P) [389]	211	20.3	8.2[2]	NA	NA	23% (84)	3
Horizon Bell-shaped (T) [390]	108	22.0	15.0	9.1	9.6	46% (3)	3

*Q_{max} = maximum urinary flow rate (free uroflowmetry); (P) = permanent stent; R = retention; (T) = temporary stent; NA = not available. * = immediately after insertion; [a] = Madsen score; [1] = at 2 years; [2] = at 3 months.*

*3C.3.7 **Emerging operations***

3C.3.7.1 Intraprostatic ethanol injections

Mechanism of action: Liquid dehydrated ethanol (95-98%) or ethanol gel is injected into the prostatic parenchyma either transurethrally [395-405], transperineally [400, 406, 407], or transrectally [400]. There is no consensus on the number or volume of injections, which depends on prostate volume, urethral length and/or presence of a median lobe, ranging from 2 to 25 mL in different studies. Most patients need an indwelling catheter after the procedure.

Efficacy: Several open trials without randomisation [395-407] have been published. Mean follow-up varied from 3 - 54 months, showing significant reduction in IPSS (-41% to -71%), PVR (-6% to -99%) and Q_{max} (+35% to +155%) and QoL (-47% to -60%). After an initial strong reduction in prostate volume (-4% to -45%), prostate size increased again by 1-2 years, although LUTS and Q_{max} remained improved [397]. No predictive efficacy parameter or dose-response relationship has been found [399, 404]. Little is known about the durability of clinical effects later than 1 year; one trial with a mean follow-up of 3 years showed a re-treatment rate of 41% [397]. A table with the key studies is available in the supplementary online material, Table S.7.

Tolerability and safety: Adverse events included: perineal or abdominal discomfort/pain, storage LUTS (≤ 40%), haematuria (≤ 40%), UTI or epididymitis, and retention. Less frequently reported (< 5%) were: decreased libido, retrograde ejaculation, urgency urinary incontinence, urethral stenosis, and ED. Two cases of bladder necrosis required cystectomy and urinary diversion were reported [399].

Practical considerations: The mechanism of action, patient selection, and application of ethanol have not been well investigated. In addition, severe adverse events occurred and long-term results are sparse. Intraprostatic ethanol injections are therefore regarded as experimental procedures for use only in trials.

Recommendation	LE	GR
Intraprostatic ethanol injections for men with moderate-to-severe LUTS secondary to BPO are still experimental and should be performed only in clinical trials.	3	C

BPO = benign prostatic obstruction; LUTS = lower urinary tract symptoms.

3C.3.7.2 Intra-prostatic botulinum toxin injections

Mechanism of action: Experience with intra-prostatic injections for the treatment of LUTS/BPO exists only for subtype BTX-A, which reduces LUTS by induction of apoptosis of prostatic (epithelial) cells leading to tissue atrophy and size reduction, and neuronal inhibition [408-412]. Down-regulation of α_1-adrenergic receptors may contribute to smooth muscle cell relaxation [408].

BTX-A can be injected into the prostatic parenchyma transperineally, transurethrally or transrectally. Different doses (100-300 U Botox™ or 300-600 U Dysport™) and dilutions (25-50 U Botox™/mL or 75 U Dysport™/mL) were used.

Efficacy: A review of 20 studies of varying evidence levels showed significant IPSS reduction in 13 studies [413], and significant Q_{max} improvement in 14. The reduction in prostate volume varied and was statistically significant in 18 studies. Durability of the effects ranged from 3 to 30 months [413].

The results from the largest placebo-controlled study of BTX-A (100 U, 200 U, and 300 U) however,

showed no significant difference in terms of IPSS, QoL, and Q_{max} at week 12 [414]. Re-treatment rates with BTX-A were as high as 29% [415].

Tolerability and safety: BoNTA injections were well tolerated in all studies. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis, and grade 2-3 events (unspecified) among 35% of patients in the series [413]. In addition, patients may receive a transurethral catheter or perform clean intermittent catheterisation during the early post-operative period (1 week to 1 month) [416-418]. Intraprostatic injection of BoNTA in patients with BPE seem to have no impact on sexual function [413, 419].

Practical considerations: Initial studies indicated that BoNTA injections into the prostatic parenchyma seem to be a promising and rapid, minimally invasive treatment modality with low morbidity for patients who are refractory to medical treatment or in urinary retention. However, BTX-A has been injected into only a few patients, and all trials have a limited follow-up. Recent studies found no significant difference in the efficacy between BoNTA and placebo arm. Trials with a larger number of patients, randomisation against saline injections, drugs, TURP, or other minimally invasive treatments, systematic evaluation of doses and dilutions, and long-term follow-up are necessary to judge adequately the value of intraprostatic BoNTA injections in the context of other available medical or surgical treatments of LUTS/BPO.

Recommendation	LE	GR
Intraprostatic BTX injections for men with bothersome moderate-to-severe LUTS secondary to BPO or men in urinary retention are still experimental and should be performed only in clinical trials.	3	C

BPO = benign prostatic obstruction; BTX = botulinum toxin ; LUTS = lower urinary tract symptoms.

3C.3.7.3 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes the laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [420], while the first RASP was reported in 2008 [421]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of open simple prostatectomy. An extraperitoneal approach is mostly used for LSP, while a transperitoneal is mostly used for RASP.

Efficacy: In 14 studies (11 case series and 3 comparative retrospective non-randomised case-control studies) with a total of 626 patients with large adenomas treated with LSP were analysed [422] (see supplementary online material Table S.8). Follow-up ranged from one to six months. IPSS, and Q_{max} improved significantly in all studies compared to baseline and improvements were similar compared to OP in the comparative studies [422]. In one retrospective study with a mean follow-up of 30 months, improvement in IPSS and Q_{max} remained durable [423].

Seven non-comparative case series on RASP ranging in size from 3-35 patients (in total 95 cases) are available [421, 424-429]. In all these series with a mean follow-up ranging from 1-13 months, a substantial postoperative improvement in urinary symptoms and Q_{max} was observed. The studies with >10 patients are presented in the supplementary online material Table S.8.

Tolerability and safety: The systematic review on LSP demonstrated that the most frequent complications were bleeding requiring transfusion (5.6%), secondary haematuria/urinary retention requiring re-catheterisation (3%), urogenital tract infection (1.7%), reoperation (1.3%), urosepsis (0.9%), incontinence (0.9%), clot retention (0.9%) and urinary fistula (0.8%). In the three comparative studies, LSP was associated with less blood loss and a reduced irrigation requirement, a shorter catheterisation and hospitalisation time, at the expense of a longer operative time (see online Table S.8). In one study (not included in the systematic review) of 34 cases of single-port transvesical enucleation of the prostate (STEP), there were three complications during STEP (one death, one bowel injury and one haemorrhage) and five afterwards (four bleeding, one epididymo-orchitis) [430].

The studies on RASP mainly focused on the feasibility of the method and reported only major complications. There were two cases of conversion to OP (2.1%). Transfusion was required only in two patients in the earliest series [421, 429]. In addition two cases of urinary leak, one case of postoperative umbilical hernia and a case of a bladder neck stricture were reported [424, 426, 428]. Interestingly, one study reported no significant change in the preservation of sexual activity (mean Sexual Health Inventory: 12.7 pre-operatively vs. 12.5 at 6 months post-operatively) even if a persistent, severe urinary incontinence was recorded in 1 out of 9 patients [426].

Practical considerations: It should be underlined that the available evidence comes from case series and retrospective comparative studies from selected centers. High quality studies are needed to compare the efficacy, safety, and hospitalisation between MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated

Recommendation	LE	GR
MISP seems to be feasible in men with prostate sizes > 80 mL needing surgical treatment. Since more data are required, MISP remains under evaluation.	3	C

MISP = minimal invasive simple prostatectomy.

3C.3.7.4 Prostatic urethral lift

Mechanism of action: The prostatic urethral lift (PUL) represents a novel minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance (Urolift®) resulting in an opening of the prostatic urethra that leaves a continuous anterior channel through the prostatic fossa ranging from bladder neck to the verumontanum.

Efficacy: The available studies on PUL are presented in the supplementary online material Table S.9 [431-435]. In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%). There is only one RCT comparing PUL with sham [433]. The primary endpoint was met at 3 months with a 50% reduction in AUA-SI from 22.1 to 11.0 points and remained stable up to 12 months. Change for AUA-SI was 88% greater for the treatment group than sham control. Also Q_{max} increased significantly from 8.1 to 12.4 mL/s relative to baseline at 3 months and this result could still be confirmed at 12 months. The difference in clinical response for Q_{max} between both groups was of statistical significance. A relevant benefit with regard to PVR was not demonstrated compared to baseline nor relative to sham control.

A multicenter, prospective, non-randomised study on 64 patients evaluated effectiveness of PUL over 2 years [434]. At 2 weeks, IPSS improved by 42% and was maintained for 24 months. A similar therapeutic effect was also observed for Q_{max} which increased significantly by 45% from 8.3 to 12.0 mL/s after 2 weeks. This benefit was stable up to 2 years. However, at the 2 year follow-up, 20% of patients required additional treatment due to initial PUL failure [434].

Tolerability and safety: The most common complications reported post-operatively included haematuria (16–63%), dysuria (25–58%), pelvic pain (5-17.9%), urgency (7.1–10%), transient incontinence (3.6–16%), and urinary tract infection (2.9-11%). Most symptoms were mild to moderate in severity and resolved within two to four weeks after the procedure.

PUL seems to have no significant impact on sexual function. Evaluation of sexual function as measured by IIEF-5, Male Sexual Health Questionnaire-Ejaculatory Dysfunction, and Male Sexual Health Questionnaire-Bother in patients undergoing PUL showed that erectile and ejaculatory function were preserved (supplementary online material Table S.9) [431-435].

Practical considerations: Prostates up to 100 cm^3 with lateral lobe obstruction are appropriate for this technique while an obstructed or protruding medial lobe cannot be effectively treated. Of note, resection or ablation of prostatic tissue is still possible without any limitation after initial treatment with the prostatic urethral lift. High quality studies are needed to compare the efficacy, safety and durability between PUL and established invasive treatments.

Recommendation	LE	GR
Prostatic urethral lift (Urolift™) leads to short-term objective and subjective improvement. RCTs with longer follow-up are needed to confirm these initial promising results	1b	B

RCT = randomised controlled trial.

3C.4 Patient selection

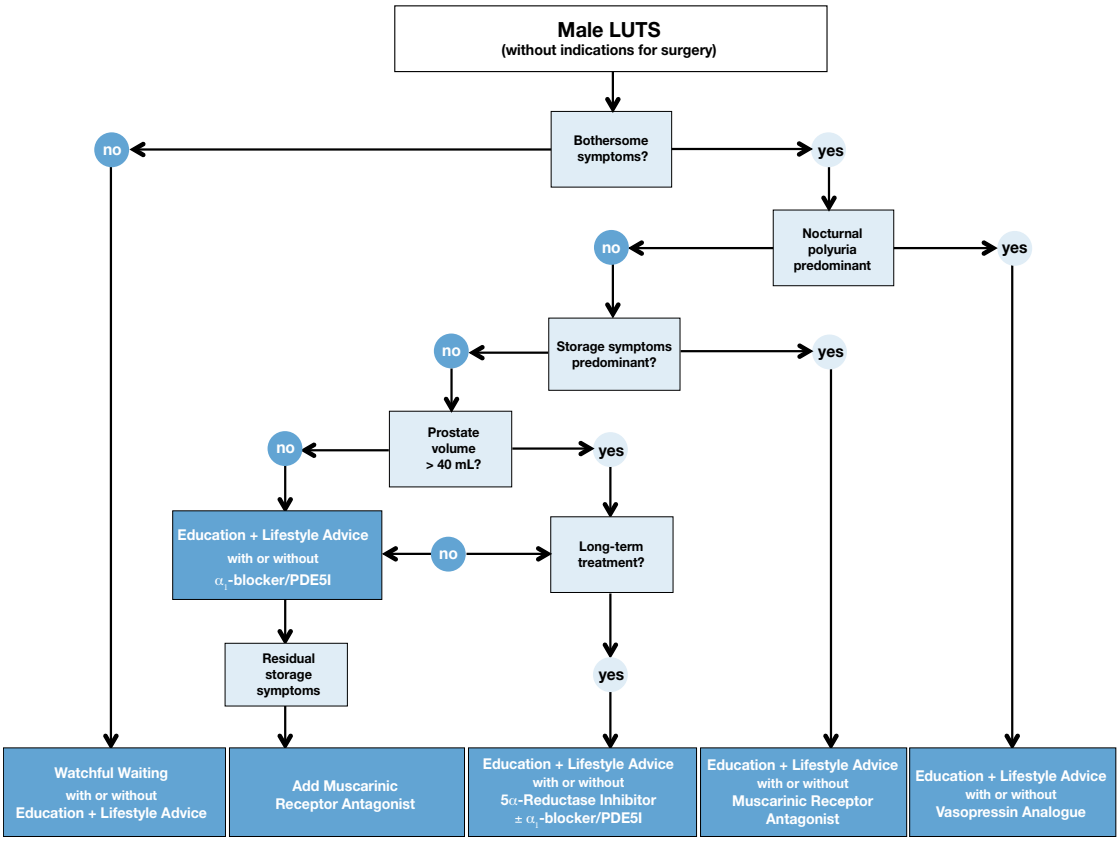
The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL, and disease progression. A table which provides differential information about speed of onset and influence on basic parameters with conservative, medical or surgical treatment options is described in the supplementary online material, Table S.10.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles.

Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

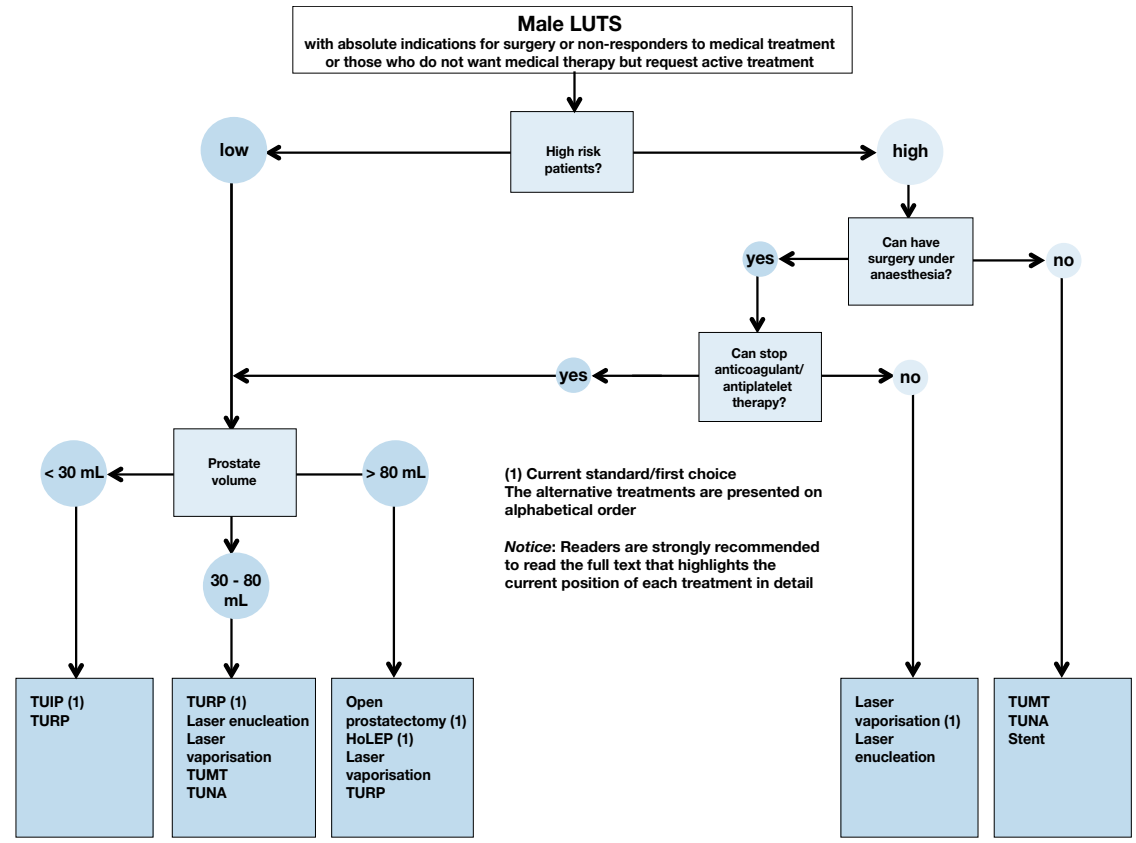
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' preferences, willingness to accept surgery-associated specific side-effects, availability of the surgical armamentarium, and experience of the surgeon with these surgical techniques. An algorithm for surgical approaches according to evidence-based medicine and patient profile is provided in Figure 4.

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation. Note that patients' preferences may result in different treatment decisions.



LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.



Laser vaporisation includes GreenLight, thulium, and diode lasers vaporisation;
Laser enucleation includes holmium and thulium laser enucleation.

HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate.

3D FOLLOW-UP

3D.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy 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 are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume.

3D.2 Medical treatment

Patients receiving α_1-blockers, muscarinic receptor antagonists, PDE5Is or the combination of α_1-blockers + 5-ARIs 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. FVC or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after 12 weeks and 6 months to determine their response and adverse events. The following are recommended at follow-up visits: IPSS, uroflowmetry and PVR volume.

Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is > 10 years and if a diagnosis of prostate cancer could alter management. A new baseline PSA should be determined

at 6 months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month, and if serum sodium concentration has remained normal, every 3 months subsequently. The following tests are recommended at follow-up visits: serum-sodium concentration and frequency volume chart. The follow-up sequence should be restarted after dose escalation.

3D.3 Surgical treatment

Patients after prostate surgery should be reviewed 4-6 weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary.

The following tests are recommended at follow-up visit after 4 to 6 weeks: IPSS, uroflowmetry and PVR volume.

Recommendation	LE	GR
Follow-up for all conservative, medical, or operative treatment modalities is based on empirical data or theoretical considerations, but not on evidence-based studies.	3-4	C

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5. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic Male LUTS Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. This information is publically accessible through the EAU website. These Guidelines were developed with the financial support of the EAU. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.