EAU Guidelines on

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

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1. INTRODUCTION

1.1 Aim and objectives

Lower urinary tract symptoms (LUTS) are a common complaint in adult men with a major impact on quality of life (QoL), and have a substantial economic burden. 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). It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

The EAU Non-neurogenic Male LUTS Guidelines Panel consists of an international group of experts with urological and clinical epidemiological backgrounds. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website Uroweb: http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and as an app for iOS and Android devices. These are abridged versions which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: http://www.uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/.

1.4 Publication history

The Non-neurogenic Male LUTS Guidelines was first published in 2000. The standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2020 document presents a limited update of the 2019 publication; the next update of the Non-neurogenic Male LUTS Guidelines will be presented in 2021.

2. METHODS

2.1 Introduction

For the 2020 Management of Non-Neurogenic Male LUTS Guidelines, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between April 30th 2018 and April 1st 2019. A total of 1,254 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://www.uroweb.org/guideline/ treatment-of-non-neurogenic-male-luts/supplementary-material.

For each recommendation within the guidelines there is an accompanying online strength rating form, the bases of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

Additional information can be found in the general Methodology section of this print, and online at the EAU website; http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The Non-Neurogenic Male LUTS Guidelines were peer reviewed prior to publication in 2016.

2.3 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 sections. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [5], they are prevalent, cause bother and impair QoL [6-9]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [10]. Lower urinary tract symptoms are strongly associated with ageing [6, 7], associated costs and burden are therefore likely to increase with future demographic changes [7, 11]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [12]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [13].

Most elderly men have at least one LUTS [7]; however, symptoms are often mild or not very bothersome [9, 10, 14]. Lower urinary tract symptoms can progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [7]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of BPH [5, 8]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [7, 15]. 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 and its surrounding tissues [15]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [16, 17]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [7].

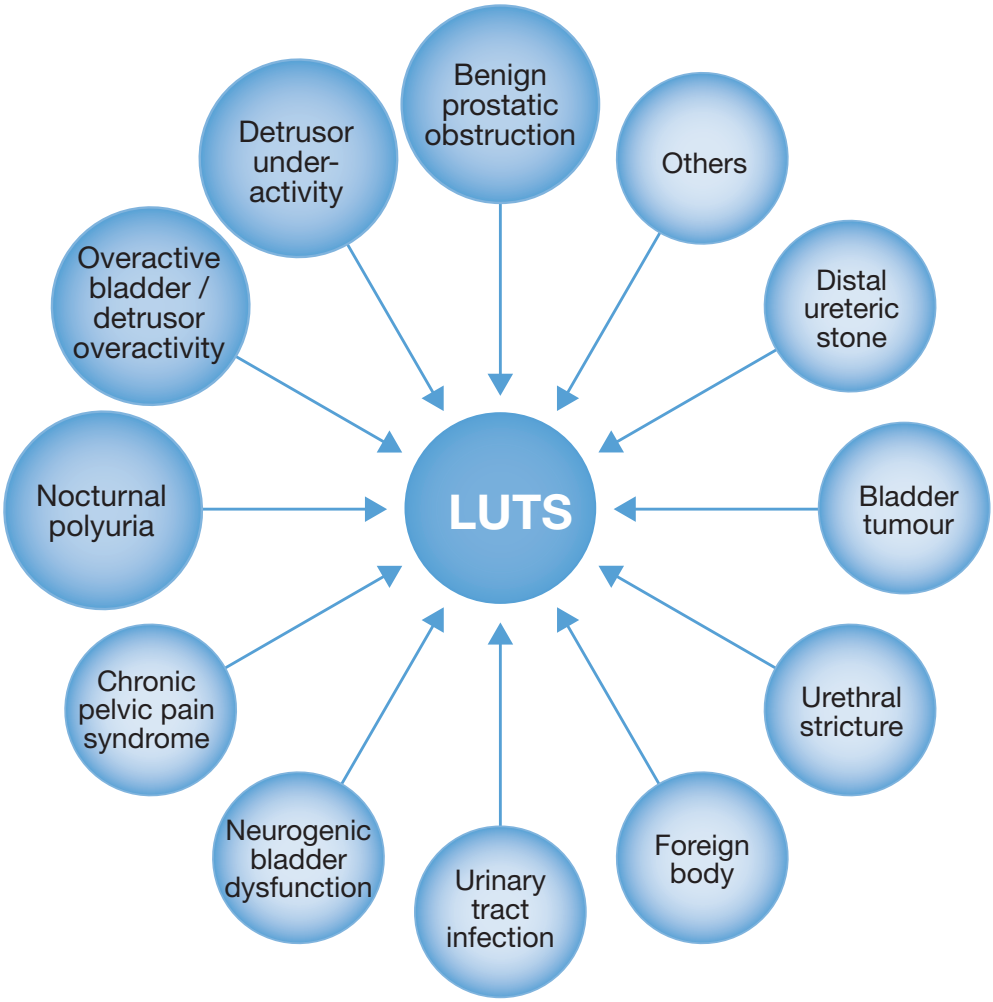
The definitions of the most common conditions related to male LUTS are presented below:

- Acute retention of urine is defined as a painful, palpable or percussible bladder, when the patient is unable to pass any urine [5].
- Chronic retention of urine is defined as a non-painful bladder, which remains palpable or percussible after the patient has passed urine. Such patients may be incontinent [5].
- Bladder outlet obstruction is the generic term for obstruction during voiding and is characterised by increasing detrusor pressure and reduced urine flow rate. It is usually diagnosed by studying the synchronous values of flow-rate and detrusor pressure [5].
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [5]. In the Guidelines the term BPO or BOO is used as reported by the original studies.
- Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease.

- Detrusor overactivity (DO) is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [5].
- Overactive bladder syndrome is characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [18].

Figure 1 illustrates the potential causes of LUTS. In any man complaining of LUTS, it is common for more than one of these factors to be present.

Figure 1: Causes of male LUTS



4. DIAGNOSTIC EVALUATION

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

- to identify the differential diagnoses, since the origin of male LUTS is multifactorial, the relevant EAU Guidelines on the management of applicable conditions should be followed;
- to define the clinical profile (including the risk of disease progression) of men with LUTS in order to provide appropriate care.

4.1 Medical history

The importance of assessing the patient's history is well recognised [19-21]. A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, current medication, lifestyle habits, emotional and psychological factors must be 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 link between LUTS and prostate cancer (PCa) [22, 23].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see section 4.2) should be obtained to objectify and quantify LUTS. Voiding diaries are particularly beneficial when assessing patients with nocturia and/or storage symptoms (see section 4.3). Sexual function should also be assessed, preferably with validated symptom questionnaires such as the International Index for Erectile Function (IIEF) [24].

Summary of evidence	LE
A medical history is an integral part of a patient's medical evaluation.	4
A medical history aims to identify the potential causes of LUTS as well as any relevant comorbidities and to review the patient's current medication and lifestyle habits.	4

Recommendation	Strength rating
Take a complete medical history from men with LUTS.	Strong

4.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [19, 21]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [25-31]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant; however, they are not disease-, or age-specific. A systematic review (SR) evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard), for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [32].

4.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an eight-item questionnaire, consisting of seven symptom questions and one QoL question [26]. 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.

4.2.2 The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)

The ICIQ-MLUTS was created from the International Continence Society (ICS) Male questionnaire. It is a widely used and validated patient completed questionnaire [27]. It contains thirteen items, with subscales for nocturia and OAB, and is available in seventeen languages.

4.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [30] is a symptom score used mainly in Denmark and Finland. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Summary of evidence	LE
Symptom questionnaires are sensitive to symptom changes.	3
Symptom scores can quantify LUTS and identify which types of symptoms are predominant; however, they are not disease- or age-specific.	3

Recommendation	Strength rating
Use a validated symptom score questionnaire including bother and quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	Strong

4.3 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 [5]. Parameters that can be derived from the FVC and bladder diary include: day-time and night-time voiding frequency, total voided volume, the fraction of urine production during the night (nocturnal polyuria index), 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 [33, 34]. The FVC/bladder diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [35-37]. The use of FVCs may cause a 'bladder training effect' and influence the frequency of nocturnal voids [38].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [39]. A SR of the available literature recommended FVCs should continue for three or more days [40].

Summary of evidence	LE
Frequency volume charts and bladder diaries provide real-time documentation of urinary function and reduce recall bias.	3
Three and seven day FVCs provide reliable measurement of urinary symptoms in patients with LUTS.	2b

Recommendations	Strength rating
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	Strong
Tell the patient to complete a bladder diary for at least three days.	Strong

4.4 Physical examination and digital-rectal examination

Physical examination particularly focusing on the suprapubic area, the external genitalia, the perineum and lower limbs should be performed. Urethral discharge, meatal stenosis, phimosis and penile cancer must be excluded.

4.4.1 Digital-rectal examination and prostate size evaluation

Digital-rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [41]. 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 [42]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [43]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50 mL [44].

Summary of evidence	LE
Physical examination is an integral part of a patient's medical evaluation.	4
Digital-rectal examination can be used to assess prostate volume; however, the correlation to actual prostate volume is poor.	3

Recommendation	Strength rating
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	Strong

4.5 Urinalysis

Urinalysis (dipstick or sediment) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions, such as urinary tract infections (UTI), microhaematuria and diabetes mellitus. If abnormal findings are detected further tests are recommended according to other EAU Guidelines, e.g. Guidelines on urinary tract cancers and urological infections [45-48].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [49, 50]. There is limited evidence, but general expert consensus suggests that the benefits outweigh the costs [51]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [52].

Summary of evidence	LE
Urinalysis (dipstick or sediment) may indicate a UTI, proteinuria, haematuria or glycosuria requiring further assessment.	3
The benefits of urinalysis outweigh the costs.	4

Recommendation	Strength rating
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	Strong

4.6 Prostate-specific antigen (PSA)

4.6.1 PSA and the prediction of prostatic volume

Pooled analysis of placebo-controlled LUTS/BPH trials showed that PSA has a good predictive value for assessing prostate volume, with areas under the curve (AUC) 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 [53].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [54]. 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 [55, 56].

4.6.2 PSA and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [57]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.

4.6.3 PSA and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [58]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [59]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [60, 61]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [62, 63]. 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 [64]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The positive predictive value (PPV) of PSA for the detection of BPO was recently shown to be 68% [65]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [66].

Summary of evidence	LE
Prostate-specific antigen has a good predictive value for assessing prostate volume and is a strong predictor of prostate growth.	1b
Baseline PSA can predict the risk of AUR and BPE-related surgery.	1b

Recommendations	Strength rating
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	Strong
Measure PSA if it assists in the treatment and/or decision making process.	Strong

4.7 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 [67]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [68].

One study reported that 11% of men with LUTS had renal insufficiency [67]. Neither symptom score nor QoL was associated with the serum creatinine level. Diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Comiter *et al*. [69] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.* [70] concluded that only those with an elevated creatinine level require investigational ultrasound (US) of the kidney.

In the Olmsted County study community-dwelling men there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [71]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [72]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [73]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [74].

Summary of evidence	LE
Decreased Q_{max} and a history of hypertension and/or diabetes are associated with CKD in patients who present with LUTS.	3
Patients with renal insufficiency are at an increased risk of developing post-operative complications.	3

Recommendation	Strength rating
Assess renal function 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.	Strong

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity [DUA]) [75, 76]. Using a PVR threshold of 50 mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [77]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although it 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 progression [62, 63].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [63]. 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 α1-blockers or WW [78]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established; this is a research priority.

Summary of evidence	LE
The diagnostic accuracy of PVR measurement, using a PVR threshold of 50 mL, has a PPV of 63% and a NPV of 52% for the prediction of BOO.	3
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendation	Strength rating
Measure post-void residual in the assessment of male LUTS.	Weak

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max} and flow pattern. Uroflowmetry parameters should preferably be evaluated with voided volume > 150 mL. As Q_{max} is prone to within-subject variation [79, 80], it is 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 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% [81]. 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 [82], DUA or an under-filled bladder [83]. Therefore, it is limited as a diagnostic test as 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 [84] and correlating symptoms with objective findings.

Summary of evidence	LE
The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. Specificity can be improved by repeated flow rate testing.	2b
Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR.	3

Recommendations	Strength rating
Perform uroflowmetry in the initial assessment of male LUTS.	Weak
Perform uroflowmetry prior to medical or invasive treatment.	Strong

4.10 Imaging

*4.10.1 **Upper urinary tract***

Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [70, 85-87]. Several arguments support the use of renal US in preference to intravenous urography. Ultrasound allows for 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, radiation dose and less side effects [85]. Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.

Summary of evidence	LE
Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population.	3
Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.	4

Recommendation	Strength rating
Perform ultrasound of the upper urinary tract in men with LUTS.	Weak

*4.10.2 **Prostate***

Imaging of the prostate can be performed by transabdominal US, TRUS, computed tomography (CT), and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by transabdominal (suprapubic) US or TRUS [85].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy (OP), enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP), or minimally invasive therapies. It is also important prior to treatment with 5α-reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [87].

Transrectal US is superior to transabdominal volume measurement [88, 89]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach since medial lobe presence can be a contraindication for some minimally invasive treatments (see section 5.3).

Summary of evidence	LE
Assessment of prostate size by TRUS or transabdominal US is important for the selection of interventional treatment and prior to treatment with 5-ARIs.	3

Recommendations	Strength rating
Perform imaging of the prostate when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	Weak
Perform imaging of the prostate when considering surgical treatment.	Strong

*4.10.3 **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. Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures.

4.11 Urethrocystoscopy

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

A prospective study 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 a reduced Q_{max}.

Another study 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, DO 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].

Summary of evidence	LE
Patients with a history of microscopic or gross haematuria, urethral stricture, or bladder cancer, who present with LUTS, should undergo urethrocystoscopy during diagnostic evaluation.	3
None of the studies identified a strong association between the urethrocystoscopic and urodynamic findings.	3

Recommendation	Strength rating
Perform urethrocystoscopy in men with LUTS prior to minimally invasive/surgical therapies if the findings may change treatment.	Weak

4.12 Urodynamics

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

4.12.1 Diagnosing bladder outlet obstruction

Pressure flow studies are the basis for the definition of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outlet obstruction/BPO has to be differentiated from DUA, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [5].

Urodynamic testing may also identify DO. 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 with respect to the outcome of treatment; however, a study has been completed in the UK, but the final results have not yet been published [99, 100].

A Cochrane meta-analysis was done to determine whether performing invasive urodynamic investigation reduces the number of men with continuing symptoms of voiding dysfunction. Two trials with 350 patients were included. Invasive urodynamic testing changed clinical decision making. Patients who underwent urodynamics were less likely to undergo surgery; however, no evidence was found to demonstrate whether this led to reduced symptoms of voiding dysfunction after treatment [101]. A more recent meta-analysis of retrospective studies showed that pre-operative urodynamic DOA has no diagnostic role in the prediction of surgical outcomes in patients with male BOO [102].

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 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 reflects 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} > 10 mL/s, although the Panel recognised that with a Q_{max} < 10 mL/s, BOO is likely and PFS is 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 [103].

4.12.2 Videourodynamics

Videourodynamics provides additional anatomical and functional information and may be recommended if the clinician considers this is needed to understand the pathophysiological mechanism of an individual patient's LUTS.

Summary of evidence	LE
There are no RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS with respect to the outcome of treatment.	3

Recommendations	Strength rating
Perform pressure-flow studies (PFS) only in individual patients for specific indications prior to invasive treatment or when evaluation of the underlying pathophysiology of LUTS is warranted.	Weak
Perform PFS in men who have had previous unsuccessful (invasive) treatment for LUTS.	Weak
Perform PFS in men considering invasive treatment who cannot void > 150 mL.	Weak
Perform PFS when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10 mL/s.	Weak
Perform PFS when considering invasive therapy in men with bothersome, predominantly voiding LUTS with a post void residual > 300 mL.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged > 80 years.	Weak
Perform PFS when considering invasive treatment in men with bothersome, predominantly voiding LUTS aged < 50 years.	Weak

4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS

4.13.1 Prostatic configuration/intravesical prostatic protrusion (IPP)

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [104]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [104].

Ultrasound measurement of 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 a bladder volume of 150-250 mL; grade I protrusion is 0-4.9 mm, grade II is 5-10 mm and grade III is > 10 mm.

Intravesical prostatic protrusion correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [105]. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [106]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter after AUR [107, 108]. However, no information with regard to intra- or inter-observer variability and learning curve is yet available. Therefore, whilst IPP may be a feasible option to infer BPO in men with LUTS, the role of IPP as a non-invasive alternative to PFS in the assessment of male LUTS remains under evaluation.

4.13.2 Bladder/detrusor wall thickness and ultrasound-estimated bladder weight

For bladder wall thickness (BWT) assessment, the distance between the mucosa and the adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the detrusor sandwiched between the mucosa and adventitia [109].

A correlation between BWT and 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 [110]. Detrusor wall thickness 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 [73]. Threshold values of 2.0, 2.5, or 2.9 mm for DWT in patients with LUTS are able to identify 81%, 89%, and 100% of patients with BOO, respectively [111].

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 DO. However, the study did not use a specific bladder filling volume for measuring BWT [112]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [113]. 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 [114, 115]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [116].

4.13.3 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 repeatability [117] and inter-observer agreement [118]. A nomogram has also been derived [119] whilst a method in which flow is not interrupted is also under investigation [120].

The data generated with the external condom method [121] correlates with invasive PFS in a high proportion of patients [122]. Resistive index [123] and prostatic urethral angle [124] have also been proposed, but are still experimental.

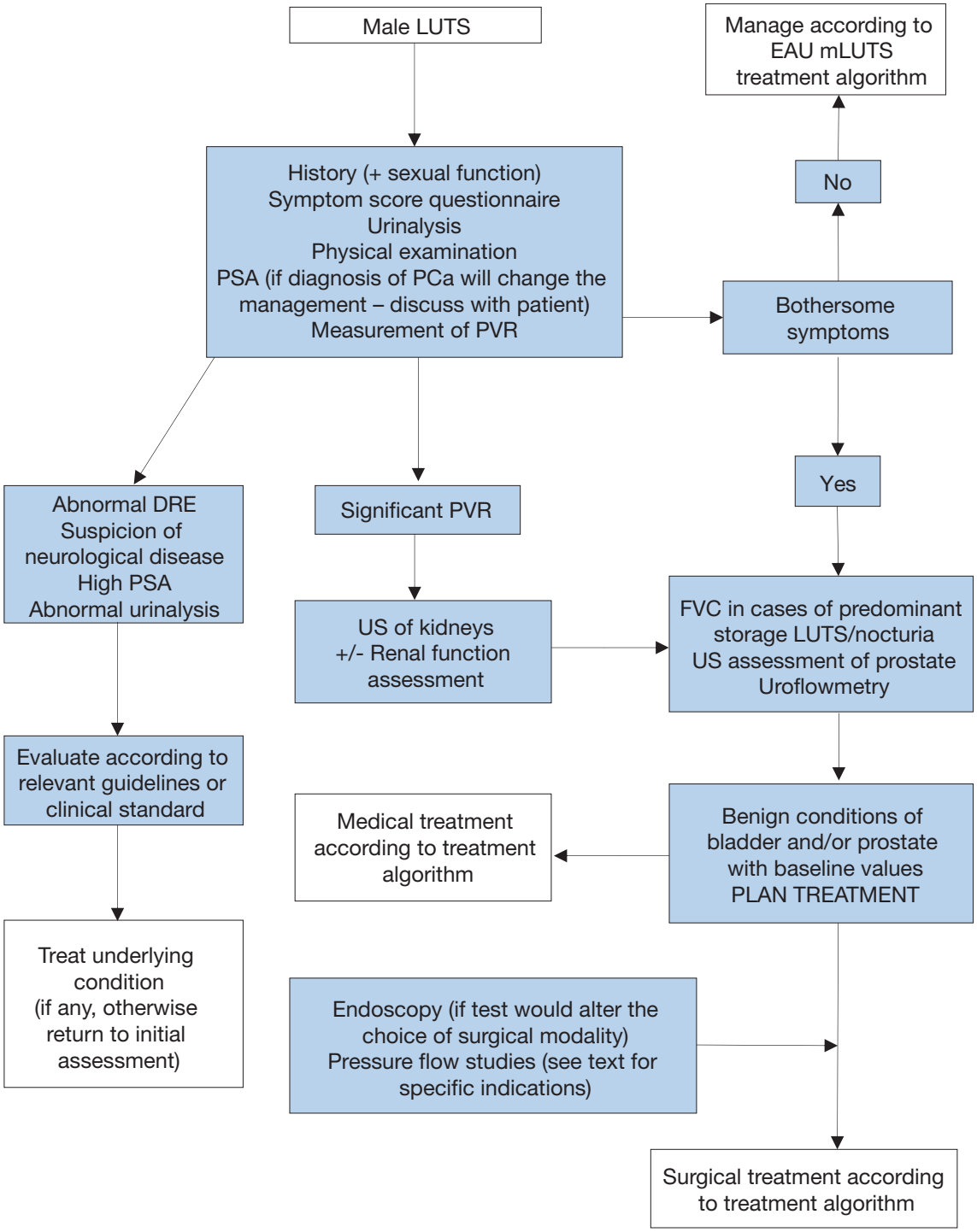
4.13.4 The diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies

The diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with PFS has been investigated in a SR [125]. A total of 42 studies were included is this review. The majority were prospective cohort studies, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; detrusor/bladder wall thickness; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

Summary of evidence	**LE**
Data regarding the diagnostic accuracy of non-invasive tests is limited by the heterogeneity of the studies as well as the small number of studies for each test.	1a
Specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable.	1a

Recommendation	**Strength rating**
Do not offer non-invasive tests as an alternative to pressure-flow studies for diagnosing bladder outlet obstruction in men.	Strong

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.

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting (WW)

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 is a viable option for many men with non-bothersome LUTS as few will progress to AUR and complications (e.g. renal insufficiency or stones) [126, 127], whilst others can remain stable for years [128]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [129].

A 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 [130, 131]. 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.

*5.1.2 **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 [128, 129, 132, 133] 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 that self-management as part of WW reduces both symptoms and progression [132, 133]. 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 [132].

*5.1.3 **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 [134]. Further research in this area is required.

Summary of evidence	**LE**
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21%; 79% of patients were clinically stable.	1b
An additional study reported 81% of patients were clinically stable on WW after a mean follow-up of seventeen months.	2
Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care alone at up to a year. Self-management as part of WW reduces both symptoms and progression.	1b

Recommendations	**Strength rating**
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	Strong
Offer men with LUTS lifestyle advice prior to, or concurrent with, treatment.	Strong

5.2 Pharmacological treatment

5.2.1 α*1-Adrenoceptor antagonists (*α*1-blockers)*

Mechanism of action: α1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [135]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [136], and treatment-associated improvement of LUTS correlates poorly with obstruction [137]. Thus, other mechanisms of action may also be relevant.

Alpha-1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and α1-adrenoceptor subtypes (α1B- or α1D-adrenoceptors) may play a role as mediators of effects. α1-adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system may mediate adverse events.

Currently available α1-blockers are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin); and naftopidil. Alpha-1-blockers exist in different formulations. Although different formulations result in different pharmacokinetic and tolerability profiles, the overall difference in clinical efficacy between the difference formulations seems modest.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [138]. Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [137].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, considerable improvements also occurred in the corresponding placebo arms [60, 139]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [60, 139]. A recent SR and meta-analysis suggested that Q_{max} variation underestimates the real effect of α1-blockers on BPO, as small improvements in Q_{max} correspond to relevant improvements in BOO index in PFS [140].

Alpha-1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [62, 141-144]. The efficacy of α1-blockers is similar across age groups [139]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [142-144]; however, recent evidence suggests that the use of a1-blockers (alfuzosin and tamsulosin) may improve resolution of AUR [145]. Nonetheless, IPSS reduction and Q_{max} improvement during α1-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 α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are less common with alfuzosin and tamsulosin [146]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [147]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [148]. In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR 1.16) was increased, most likely as a result of induced hypotension [149].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [150]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [151]. However, the OR for IFIS was much higher for tamsulosin. It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use.

A SR concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but can cause abnormal ejaculation [152]. 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. In a recent meta-analysis ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR 0.80 and 1.78) were associated with a low risk of EjD [153]. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α1-blocker is the greater the incidence of EjD.

Practical considerations: α1-blockers are usually considered the first-line drug treatment for male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. However, α1-blockers do not prevent occurrence of urinary retention or need for surgery. Ophthalmologists should be informed about α1-blocker use prior to cataract surgery. Elderly patients treated with non-selective α1-blockers should be informed about the risk of orthostatic hypotension. Sexually active patients treated with selective α1-blockers should be counselled about the risk of EjD.

Summary of evidence	LE
α1-blockers are effective in reducing urinary symptoms (IPSS) and increasing the peak urinary flow rate (Q_{max}) compared with placebo.	1a
Alfuzosin, terazosin and doxazosin showed a statistically significant increased risk of developing vascular-related events compared with placebo.	1a
Alfuzosin, doxazosin, tamsulosin or terazosin exposure has been associated with an increased risk of IFIS.	1a
Ejaculatory dysfunction is significantly more common with α1-blockers than with placebo, particularly with more selective α1-blockers such as tamsulosin and silodosin.	1a

Recommendation	Strength rating
Offer α1-blockers to men with moderate-to-severe LUTS.	Strong

*5.2.2 **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 [154], which has two isoforms:

- 5α-reductase type 1: predominant expression and activity in the skin and liver.
- 5α-reductase type 2: predominant expression and activity in the prostate.

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits both 5α-reductase types (dual 5-ARI). 5α-reductase inhibitors induce apoptosis of prostate epithelial cells [155] leading to prostate size reduction of about 18-28% and a decrease in circulating PSA levels of about 50% after six to twelve months of treatment [156]. Mean prostate volume and PSA reduction 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 treatment of at least six months. After two to four years of treatment 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement [62, 143, 144, 157-163]. An indirect comparison and one direct comparative trial (twelve months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [156, 164]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [165]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of AUR, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL [166, 167]. 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 the α1-blocker tamsulosin [143, 163, 168]. The greater the baseline prostate volume (or serum PSA level), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> 1 year) risk of AUR or need for surgery [62, 161, 169]. In the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years, compared with placebo [161]. In the MTOPS study, finasteride reduced the relative risk of AUR by 68% and need for surgery by 64% (absolute risk reduction 2% and 3%, respectively), also at four years [62]. A pooled analysis of three randomised trials with two-year follow-up data, reported that treatment with finasteride decreased the relative risk of AUR by 57%, and surgical intervention by 34% (absolute risk reduction 2% for both) in patients with moderately symptomatic LUTS [170]. 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 [171, 172]. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [173, 174].

Tolerability and safety: The most common adverse events are reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [62, 144, 156, 175]. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients. Two studies have suggested that treatment with 5-ARIs is associated with a higher incidence of high-grade cancers although no causal relationship has been proven [176, 177]. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [178]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [178, 179].

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). They can prevent the risk of AUR and need for surgery. Due to the slow onset of action, they are not suitable for short-term use. Their effect on PSA needs to be considered in relation to PCa screening.

Summary of evidence	**LE**
After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28%, and increase Q_{max} by 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement.	1b
5α-reductase inhibitors can prevent disease progression with regard to AUR and the need for surgery. Due to their slow onset of action, they are suitable only for long-term treatment (years).	1a
The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, ED and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume.	1b

Recommendations	**Strength rating**
Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong
Counsel patients about the onset of action (three to six months) of 5α-reductase inhibitors.	Strong

*5.2.3 **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 and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions [180, 181]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [182, 183].

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [184, 185].

Efficacy: Antimuscarinics were mainly tested in females in the past, as it was believed that LUTS in men were caused by the prostate, so should be treated with prostate-specific drugs. However, there is no scientific data for this assumption [186]. A sub-analysis of an open-label trial of OAB patients showed that age but not gender had an impact on urgency, frequency, or urgency incontinence [187]. In a pooled analysis, which included a sub-analysis of male patients, fesoterodine 8 mg was superior to tolterodine extended release (ER) 4 mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week twelve, the urinary retention rate was around 2% [188].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [189-194]. Most trials lasted only twelve 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 [186, 190, 195]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving 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 [191, 194]. The TIMES RCT reported that tolterodine ER monotherapy significantly improved UUI episodes per 24 hours compared to placebo, at week twelve. Tolterodine ER did not significantly improve urgency, IPSS total or QoL score compared with placebo. A significantly greater proportion of patients in the tolterodine ER plus tamsulosin group reported treatment benefit compared with the other three treatment groups [193].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinics [196]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [194, 197]. In a small RCT propiverine improved frequency and urgency episodes [197].

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) [191]. 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.

Theoretically antimuscarinics might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A twelve week safety study on men with mild-to-moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not AUR (3% in both arms) [198]. 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 [192].

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. Men should be advised to discontinue medication if worsening voiding LUTS or urinary stream is noted after initiation of therapy.

Summary of evidence	**LE**
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	2
Antimuscarinic monotherapy can be associated with increased PVR after therapy, but acute retention is a rare event in men with a PVR volume of < 150 mL at baseline.	2

Recommendations	**Strength rating**
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Strong
Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL.	Weak

*5.2.4 **Phosphodiesterase 5 inhibitors***

Mechanism of action: Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [199]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [200]. Phosphodiesterase 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [201]. The exact mechanism of PDE5Is on LUTS remains unclear.

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 improve QoL. However, Q_{max} did not significantly differ from placebo in most trials.

A recent Cochrane review included a total of sixteen randomised trials that examined the effects

of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [202]. Phosphodiesterase 5 inhibitors led to a small reduction (mean difference (MD) 1.89 lower, 95% CI 2.27 lower to 1.50 lower) in IPSS compared to placebo. There was no difference between PDE5Is and α1-blockers in IPSS. Most evidence was limited to short-term treatment up to twelve weeks and of moderate or low certainty. In earlier [203] and more recent [204] meta-analysis, PDE5Is were also found to improve IPSS and IIEF score, but not Q_{max}.

Tadalafil 5 mg reduces IPSS by 22-37% and improvement may be seen within a week of initiation of treatment [205]. A three point or greater total IPSS improvement was observed in 60% of tadalafil treated men within one week and in 80% within four weeks [206]. The maximum trial (open label) duration was 52 weeks [207]. A subgroup analysis of pooled data from four RCTs 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 [208]. In a recent *post hoc* analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/comorbidities, except for patients receiving more than one antihypertensive medication. The use of diuretics may contribute to patients' perception of a negated efficacy [209]. Among sexually active men > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [208].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%, $p < 0.001$) vs. indirect (7.5%, $p = 0.32$) treatment effects via IIEF-EF improvement [210]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [211]. An integrated analysis of RCTs showed that tadalfil was not superior to placebo for IPSS improvement at twelve weeks in men ≥ 75 years (with varied effect size between studies), but was for men < 75 years [212]. An open label urodynamic study of 71 patients showed improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1; $p < 0.001$), and resolution of DO in 15 (38%) of 38 patients. Flow rate improved from 7.1 to 9.1 mL/s ($p < 0.001$) and mean IPSS from 18.2 to 13.4 [213].

A combination of PDE5Is and α-blockers has also been evaluated. A meta-analysis of five 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 [203]. A Cochrane review found similar findings [202]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms ($p < 0.022$ after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [214]. However, only tadalafil 5 mg has been licensed in the context of LUTS management while data on combinations of PDE5Is and other LUTS medications is emerging.

Tolerability and safety: Reported adverse effects 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 [203]. The discontinuation rate due to adverse effects for tadalafil was 2.0% [215] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [208].

Phosphodiesterase 5 inhibitors are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< three months) or stroke (< six months), 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 ED. The meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [203]. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one year follow-up [207], therefore conclusions about its efficacy or tolerability greater than one year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Summary of evidence	**LE**
Phosphodiesterase 5 inhibitors improve IPSS and IIEF score, but not Q_{max}.	1a
A three point or greater total IPSS improvement was observed in 59.8% of tadalafil treated men within one week and in 79.3% within four weeks.	1b

Recommendation	**Strength rating**
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	Strong

5.2.5 *Plant extracts - phytotherapy*

Potential mechanism of action: Herbal drug preparations are made of roots, seeds, pollen, bark, or fruits. There are single plant preparations (mono-preparations) and preparations combining two or more plants in one pill (combination preparations) [216].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [216]. *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 [216-218]. The *in vivo* effects of these compounds are uncertain, and the precise mechanisms 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; therefore, the effects of one brand cannot be extrapolated to others [219]. In addition, batches from the same producer may contain different concentrations of active ingredients [220]. A review of recent extraction techniques and their impact on the composition/biological activity of available *Serenoa repens* based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [221], as the pharmacokinetic properties of the different preparations can vary significantly.

Heterogeneity and a limited regulatory framework characterise the current status of phytotherapeutic agents. The European Medicines Agency (EMA) has developed the Committee on Herbal Medicinal Products (HMPC). European Union (EU) herbal monographs contain the HMPC's scientific opinion on safety and efficacy data about a herbal substances and their preparations intended for medicinal use. The HMPC evaluates all available information, including non-clinical and clinical data, whilst also documenting long-standing use and experience in the EU. European Union monographs are divided into two sections: a) Well established use (marketing authorisation): when an active ingredient of a medicine has been used for more than ten years and its efficacy and safety have been well established (including a review of the relevant literature); and b) Traditional use (simplified registration): for herbal medicinal products which do not fulfil the requirements for a marketing authorisation, but there is sufficient safety data and plausible efficacy on the basis of long-standing use and experience. Table 1 lists the available EU monographs for herbal medicinal products.

Table 2: European Union monographs for herbal medicinal products

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [222]	Well established use	Symptomatic treatment of BPH	14/01/2016
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [222]	Traditional use	LUTS related to BPH*	14/01/2016
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [223]	Traditional use	LUTS related to BPH or related to OAB*	25/03/2013
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [224]	Traditional use	LUTS related to BPH*	01/09/2017
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [225]	Traditional use	LUTS related to BPH*	05/11/2012
Epilobium angustifolium L. and/or Epilobium parviflorum Schreb., herba (Willow herb) Preparation as defined in the monograph [226]	Traditional use	LUTS related to BPH*	13/01/2016

**after serious conditions have been excluded by a medical doctor*

Panel interpretation: Only hexane extracted *Serenoa reprens* has been recommended for well-established use by the HMPC. A detailed scoping search covering the timeframe between the search cut-off date of the EU monograph and April 2020 will be conducted for the update of the 2021 edition of the Guidelines. Following this a specific recommendation on phytotherapy will be given.

5.2.6 ***Beta-3 agonist***

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. The mode of action of beta-3 agonists is not fully elucidated [227].

Efficacy: Mirabegron 50 mg is the first clinically available beta-3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America and Japan [228-232]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency and UUI and also patient perception of treatment benefit. These studies had a predominantly female study population. A meta-analysis of eight RCTS including 10,248 patients (27% male) found that mirabegron treatment resulted in reduced frequency, urgency and UUI rates, as well as an improved voided volume with a statistically significant improvement of nocturia as compared with both placebo and tolterodine [233].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated with or not associated with BPO confirmed by urodynamics [234]. Mirabegron 25 mg daily led to increased satisfaction and improved QoL, but symptoms assessed by validated questionnaires (IPSS and OAB-SS), only improved in non-obstructed patients. Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [235], again in a predominantly female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition, but did not report the results separately for the genders [236].

In a study of more than 1,000 patients of whom approximately 30% were male, combination therapy of mirabegron 25/50 mg and solifenacin 5/10 mg was associated with statistically significant improvements in patient outcomes and health related QoL vs. solifenacin 5 mg and placebo; however, they did not separate out the effects in men and women [237]. In another study, in which 28% patients were male, mirabegron significantly improved patient reported perception of their condition and QoL whether or not patients were incontinent [238]. A phase IV study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [239].

In an RCT evaluating add-on therapy with mirabegron for OAB symptoms remaining after treatment with tamsulosin 0.2 mg daily in men with BPO, combination therapy was associated with greater improvements in OAB symptom score, in the urinary urgency and daytime frequency part and storage subscore of the IPSS, and in the QoL index compared to monotherapy with tamsulosin [240]. A prospective analysis of 50 elderly men showed that mirabegron add-on therapy was effective for patients whose persistent LUTS and OAB symptoms were not controlled with α1-blocker monotherapy, without causing negative effects on voiding function [241].

An RCT compared the efficacy of mirabegron 50 mg or fesoterodine 4 mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms [242]. At three months, fesoterodine add-on therapy showed a significantly greater improvement then mirabegron add-on therapy in OAB symptom score-total (-2.8 vs.1.5, p = 0.004), IPSS-QoL (-1.5 vs. -1.1, p = 0.04), and OAB symptom score-urgency score (-1.5 vs. -0.9, p = 0.008). Fesoterodine was also superior in alleviating detrusor overactivity (52.6% vs. 28.9%, p = 0.03).

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [228-231]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure $\geq$ 180 mmHg or diastolic blood pressure $\geq$ 110 mmHg, or both). Blood pressure should be measured before starting treatment and monitored regularly during treatment. A combination of thirteen clinical studies including 13,396 patients, 25% of whom were male, showed that OAB treatments (anticholinergics or mirabegron) were not associated with an increased risk of hypertension or cardiovascular events compared to placebo [243]. 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 [228]. 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 [244]. The overall change in PVR with mirabegron is small [244].

A small prospective study (mainly focused on males) has shown that mirabegron 25 mg is safe in patients aged 80 years or more with multiple comorbidities [245]. A pooled analysis of three trials each of twelve weeks and a one year trial showed, in patients aged > 65 years, a more favourable tolerability profile for

mirabegron than antimuscarinics [246]. In an eighteen week study of 3,527 patients (23% male), the incidence of adverse events were higher in the combination (solifenacin 5 mg plus mirabegron 25 mg) group (40%) than the mirabegron 25 mg alone group (32%). Events recorded as urinary retention were low (< 1%), but were reported slightly more frequently in the combined group when compared with the monotherapy and placebo groups. The PVR volume was slightly increased in the combined group compared with solifenacin 5 mg, and the mirabegron monotherapy and placebo groups. Combined therapy with solifenacin 5 mg plus mirabegron 25 mg and solifenacin 5 mg plus mirabegron 50 mg provided improvements in efficacy generally consistent with an additive effect [247].

In a retrospective analysis of persistence and adherence in 21,996 patients, of whom 30% were male, the median time to discontinuation was significantly longer for mirabegron (169 days) compared to tolterodine (56 days) and other antimuscarinics (30-78 days) ($p < 0.0001$). There was no statistical difference between men and women [248]. Data on the safety of combination therapy at twelve months are awaited from the SYNERGY II trial.

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 pending. However, pharmacokinetic interaction upon add-on of mirabegron or tamsulosin to existing tamsulosin or mirabegron therapy does not cause clinically relevant changes in safety profiles [249]. Available studies on mirabegron in combination with antimuscarinics in OAB patients had a predominantly female study population, while further trials are still pending.

Summary of evidence	**LE**
Mirabegron improves the symptoms of OAB, including micturition frequency, urgency and UUI.	2
Patients prescribed mirabegron remained on treatment longer than those prescribed antimuscarinics.	3

Recommendation	**Strength rating**
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	Weak

*5.2.7 **Combination therapies***

5.2.7.1 α1-blockers + 5α-reductase inhibitors

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a 5-ARI (Section 5.2.2). The α1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop full clinical efficacy. Finasteride has been tested in clinical trials with alfuzosin, terazosin, doxazosin or terazosin, and dutasteride with tamsulosin.

Efficacy: Several studies have investigated the efficacy of combination therapy against an α1-blocker, 5-ARI or placebo alone. Initial studies with follow-up periods of six to twelve months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α1-blocker monotherapy [158, 159, 250]. In studies with a placebo arm, the α1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study showed similar results [62].

Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [62, 143, 144].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for AUR and the need for surgery after eight months [144]. Thus, the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [251, 252]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [251], 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 recent trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [252]. Lower urinary tract symptom improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of the studies include the short duration of the studies and the short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, 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) [62]. In addition, finasteride (alone or in combination), but not doxazosin alone, 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 [253]. To prevent one case of urinary retention and/or surgical treatment thirteen patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two year RCT with a total of 742 patients. In both arms detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression, the difference in IPSS at 24 months was 5.4 in the active arm and 3.6 in the placebo arm ($p < 0.001$) [254]. Furthermore, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [255].

More recently, a combination of the 5-ARI, finasteride, and tadalafil 5 mg was tested in a large scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in the chapter on PDE5Is [214].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [62, 143, 144]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy. The MTOPS study demonstrated that the incidence of treatment related adverse events is higher during the first year of combined treatment between doxazosin and finasteride [256]. A meta-analysis measuring the impact of medical treatments for LUTS/BPH on ejaculatory function, reported that combination therapy with α1-blockers and 5-ARIs resulted in a three-fold increased risk of EjD as compared with each of the monotherapies [153].

Practical considerations: Compared with α1-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 a higher rate of 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, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended and patients should be informed about this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Summary of evidence	**LE**
Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery.	1b
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.	1b
The CombAT study found that 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.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and 5-ARIs.	1b

Recommendation	Strength rating
Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL).	Strong

5.2.7.2 α1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α1-blocker together with an antimuscarinic aiming to antagonise both α1-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 four to twelve 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 α1-blocker [193, 253, 257-263]. One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [264]. A high proportion of men with voiding and storage LUTS need to add anticholinergics after α1-blocker monotherapy, particularly those with longer duration of symptoms at presentation, and men with storage symptoms and a small prostate volume [265].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [193, 266]. Symptom improvement is higher regardless of PSA concentration with combination therapy, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [196].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, [253, 257, 263, 267, 268]. Two SRs of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [269, 270]. In a meta-analysis of sixteen studies with 3,548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication improvement storage symptoms and QoL compared to α1-blocker monotherapy without causing significant deterioration of voiding function [271]. There was no difference in total IPSS and Q_{max} between the two groups.

Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [272]. Long term use of combination therapy has been reported in patients receiving treatment for up to one year, showing symptomatic response is maintained, with a low incidence of AUR [273]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150 mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health related quality of life compared with placebo and α1-blocker monotherapy [274].

Tolerability and safety: Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics. The most common side-effect is dry mouth. Some side-effects (e.g.dry mouth 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 up to one year of treatment [269, 275]. Antimuscarinics do not cause evident deterioration in maximum flow rate used in conjunction with an α1-blocker in men with OAB symptoms [266, 276].

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 [277]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased vs. placebo [277].

Practical considerations: Class effects are likely to underlie efficacy and QoL using an α1-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.

Summary of evidence	LE
Combination treatment with α1-blockers and antimuscarinics is effective for improving LUTS-related QoL impairment.	2
Combination treatment with α1-blockers and antimuscarinics is more effective for reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone.	2
Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics.	1
There is a low risk of AUR using α1-blockers and antimuscarinics in men known to have a PVR urine volume of < 150 mL.	2

Recommendations	Strength rating
Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug.	Strong
Do not prescribe combination treatment in men with a post-void residual volume > 150 mL.	Weak

Note: All patients should be counselled about pharmacological treatment related adverse events in order to select the most appropriate treatment for each individual patient.

5.3 Surgical treatment

Despite the advent of new technologies, monopolar TURP has remained the cornerstone of LUTS/BPO surgical treatment for more than nine decades. Extensive clinical research for a more effective and safer alternative is often hindered by methodological limitations, including inadequate follow up. Based on Panel consensus, timeframes defining short-, mid- and long-term follow up of patients submitted to surgical treatments are 12, 36 and over 36 months, respectively. Clinicians should inform patients that long-term surgical RCTs are lacking.

5.3.1 Monopolar Transurethral resection of the prostate and transurethral incision of the prostate

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

Efficacy: In a meta-analysis of 20 RCTs with a maximum follow-up of five years, M-TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [278]. Monopolar-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 [279]. One study with a mean follow-up of thirteen years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than re-development of BPO [98]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed that the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) remained unchanged during the last decade (0.9%, 3.7%, 9.5% and 12.7% at three months, one year, five years, and eight years, respectively), and that the respective incidence of re-TURP was 0.8%, 2.4%, 6.1% and 8.3% [280, 281].

A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [282]. 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 retreatment rate of 2.6% after a mean follow-up of sixteen months [283]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after M-TURP (7.2%) [282].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [284]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed a 20% reduction in mortality rate over time, to 0.1% at 30 days and 0.5% at 90 days [280, 281].

The risk of TUR-syndrome decreased to < 1.1% [283, 285]. No case has been recorded after TUIP. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% [284]. The risk after TUIP is negligible. Similar results for M-TURP complications were reported by an analysis of contemporary RCTs using M-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 UTI 4.1% (0-22%) [278]. Long-term complications comprise urinary incontinence, urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [283].

Practical considerations: Monopolar-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 M-TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [284]. The upper limit for M-TURP is suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, choice of resectoscope size and resection speed), as surgical duration increases, there is a significant increase in the rate of complications and the procedure is safest when performed in under 90 minutes [286].

5.3.1.1 Modifications of M-TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of 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 resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). Prostatic tissue removal is identical to M-TURP. The various bipolar devices available differ in the way in which current flow is delivered [287, 288]. Prostatic tissue removal is identical to M-TURP.

Efficacy: Bipolar TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from 56 RCTs have been reported [289], of which around half have been pooled in RCT-based meta-analyses [278, 290-294]. Early pooled results concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL score and Q_{max}) [291]. Subsequent meta-analyses supported these conclusions though trial quality was generally poor [278, 290, 292-294]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [295-303].

A meta-analysis was conducted to evaluate the quasi-bipolar transurethral resection in saline (TURis, Olympus Medical) system vs. M-TURP, ten unique RCTs (1,870 patients) were included. It was concluded that TURis was of equivalent efficacy to M-TURP [304].

Tolerability and safety: Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable due to a more favourable peri-operative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [291]. Subsequent meta-analyses supported these conclusions [278, 290, 292-294]. However, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [291]. An RCT based meta-analysis has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP [294]. It was concluded that TURis is associated with improved peri-operative safety, eliminating the risk of TUR syndrome (RR: 0.18; 95% CI, 0.05-0.61; p = 0.006), reducing the risk of blood transfusion/clot retention (RR: 0.34; 95% CI, 0.18-0.61; p = 0.0003 and 0.43; 95% CI, 0.22-0.86; p = 0.0161, respectively), and hospital stay (MD: 0.56 d; 95% CI, 0.77 - 0.35; p < 0.0001). No significant difference was detected in urethral stricture rates.

Data from the vast majority of individual RCTs with mid- to long-term follow-up (up to 60 months), showed no differences in urethral stricture/BNC rates [295-303], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [302, 305]. A significantly higher stricture (urethral stricture + BNC) rate was detected in the B-TURP arm performed with a "quasi" bipolar system (TURis, Olympus Medical) in patients with a prostate volume > 70 mL at 36 months follow up (9/23 [39.1%] vs. 1/22 [4.6%]; p = 0.01) [302]. In addition, a significantly higher BNC, but not urethral stricture, rate was detected in the B-TURP arm performed with a "true" bipolar system (Gyrus PK SuperPulse, Olympus Medical) in 137 patients followed up to twelve months (0.0% vs. 8.5%; p = 0.02) [305].

Randomised controlled trials using the erectile function domain of the IIEF (IIEF-ED) and the ejaculatory domain of the male sexual-health questionnaire (Ej-MSHQ) showed that M-TURP and B-TURP have a similar effect on erectile and ejaculatory function [306, 307]. Comparative evaluations of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at twelve months follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [307, 308].

Practical considerations: Bipolar TURP in patients with moderate-to-severe LUTS secondary to BPO, has similar efficacy with M-TURP, but lower peri-operative morbidity. The duration of improvements with B-TURP were documented in a number of RCTs with mid-term follow-up. Long-term results (up to five years) for 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.

5.3.1.1.1 Modifications of B-TURP: bipolar transurethral vaporisation of the prostate

Mechanism of action: Bipolar transurethral vaporisation of the prostate (B-TUVP) was introduced in the late 1990's ("plasmakinetic" B-TUVP). The technique was derived from plasmakinetic B-TURP and utilised a bipolar electrode and a high-frequency generator to create a plasma effect able to vaporise prostatic tissue [309]. With minimal direct tissue contact (near-contact; hovering technique) and heat production the bipolar electrode produces a constant plasma field (thin layer of highly ionized particles; plasma corona), allowing it to glide over the tissue and vaporise a limited layer of prostate cells without affecting the underlying tissue whilst achieving haemostasis, leaving behind a TURP-like cavity [310]. A distinct difference between B-TUVP and its ancestor (monopolar TUVP), is that B-TUVP displays thinner (< 2 mm) coagulation zones [311], compared to the disproportionate extent of those created by the former (up to 10 mm) [312] that potentially lead to mostly irritative side-effects and stress urinary incontinence [311, 313, 314].

Efficacy: B-TUVP has been evaluated as a TURP alternative for treating moderate-to-severe LUTS in thirteen RCTs to date, including a total of 1,244 men with a prostate size of < 80 mL [298, 315-326]. Early RCTs evaluated the plasmakinetic B-TUVP system [315-319]; however, during the last decade, only the "plasma" B-TUVP system with the "mushroom- or button-like" electrode (Olympus, Medical) has been evaluated [298, 320-326]. Results have been pooled in three RCT-based meta-analyses [278, 327, 328], and a narrative synthesis has been produced in two SRs [278, 329]. The follow up in most RCTs is twelve months [315-318, 320-322, 324, 326]. The longest follow up is 36 months in a small RCT (n = 40) and eighteen months in a subsequent RCT (n = 340); evaluating plasmakinetic [319] and plasma B-TUVP [298], respectively.

Early pooled results concluded that no significant differences exist in short-term efficacy (IPSS, QoL score, Q_{max} and PVR) between plasmakinetic B-TUVP and TURP [278]. However, the promising initial efficacy profile of the former may be compromised by inferior clinical outcomes (IPSS, Q_{max}, re-intervention rate) at mid-term. Larger RCTs with longer follow-up are necessary to draw definite conclusions [278, 319]. A SR of seven RCTs [329] comparing plasmakinetic [315, 317, 318] and plasma B-TUVP [298, 320-322] with TURP concluded that functional outcomes of B-TUVP and TURP do not differ. The poor quality of the included RCTs and the fact that most data was derived from a single institution was highlighted [329]. A similar SR of eight RCTs [278] comparing both B-TUVP techniques with TURP [298, 315, 316, 318-322] concluded that not enough consistent data suitable for a meta-analysis exists; that main functional results are contradictory; and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions. A meta-analysis [328] of six RCTs [298, 320-322, 324, 325] specifically evaluating plasma B-TUVP vs. TURP, concluded that both techniques result in a similar improvement of LUTS.

Tolerability and safety: Early pooled results concluded that no statistically significant differences exist collectively for intra-operative and short-term complications between plasmakinetic B-TUVP and TURP but peri-operative complications are significantly fewer after B-TUVP [278]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [278]. Mid-term safety results (urethral stricture, ED, and retrograde ejaculation) have also been reported to be similar [319], but larger RCTs with longer follow-up are necessary to draw definite conclusions [278, 319]. A SR of seven RCTs [329] comparing plasmakinetic [315, 317, 318] and plasma B-TUVP [298, 320-322] with TURP concluded that most RCTs suggest a better haemostatic efficiency for B-TUVP, resulting in shorter catheterisation (42.5 vs. 77.5 hours) and hospitalisation times (3.1 vs. 4.4 days); however, the poor quality of the included RCTs and the fact that the majority of the data was derived from a single institution was highlighted [329]. A similar SR of eight RCTs [278] comparing both B-TUVP techniques with TURP [298, 315, 316, 318-322] concluded that not enough consistent data suitable for a meta-analysis exists and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions. A meta-analysis [328] of six RCTs [298, 320-322, 324, 325] specifically evaluating plasma B-TUVP vs. TURP, concluded that no significant differences exist between the techniques in overall complication and transfusion rates. However, a statistically significant difference was detected collectively in major complication rates (Clavien 3, 4; including urethral stricture, severe bleeding necessitating re-operation and urinary incontinence) and in the duration of catheterisation favouring plasma B-TUVP.

Practical considerations: B-TUVP and TURP have similar short-term efficacy. Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP. Plasma B-TUVP has a lower short-term major morbidity compared to TURP. Randomised controlled trials of higher quality, multicentre RCTs, and longer follow up periods are needed to evaluate B-TUVP in comparison to TURP.

Summary of evidence	**LE**
Monopolar TURP is the current standard surgical procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO.	1
Transurethral incision of the prostate shows similar efficacy and safety to M-TURP for treating moderate-to-severe LUTS secondary to BPO in men with prostates < 30 mL.	1
No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the re-operation rate is higher compared to M-TURP.	1
Bipolar TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable peri-operative safety profile.	1b
Bipolar TUVP and TURP have similar short-term efficacy.	1
Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1

The choice between TUIP and TURP should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively).	4

Recommendations	Strength rating
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	Strong
Offer bipolar- or monopolar-transurethral resection of the prostate (TURP) to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong
Offer bipolar transurethral vaporisation of the prostate as an alternative to monopolar TURP to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Weak

5.3.2 ***Open prostatectomy***

Mechanism of action: Open prostatectomy 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). It is used for substantially enlarged glands (> 80-100 mL).

Efficacy: Open prostatectomy 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% [330-334]. Efficacy is maintained for up to six years [335].

Two RCT-based meta-analyses evaluated the overall efficacy of OP vs. endoscopic enucleation of the prostate (EEP) for treating patients with large glands [336, 337]. The larger study included RCTs involving 758 patients [337]. Five RCTs compared OP with HoLEP [330, 331, 338] and four RCTs compared OP with EEP using bipolar circuitry [335, 339-341]. Open prostatectomy was performed via a transvesical approach in all RCTs. At 3-, 6-, 12- and 24-month follow-up, there were no significant differences in Q_{max} between EEP and OP. Post-void residual, PSA, IPSS and QoL score also showed no significant difference at 1-, 3-, 6- and 12-months. Furthermore, IIEF also showed no significant difference at 3-, 6- and 12- months. It was concluded that EEP appears to be an effective minimally invasive option for treating large prostates.

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [334]. Data from an Austrian nationwide study of two cohorts totalling 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days. The endourological re-intervention rates after primary OP were 0.9%, 3.0%, 6.0%, and 8.8%, at three months, one year, five years, and eight years, respectively. The respective incidence of re-TURP was 0.5%, 1.8%, 3.7% and 4.3%, respectively [281]. The estimated transfusion rate is about 7-14% [330, 333, 334, 336]. Long-term complications include transient urinary incontinence (up to 10%), BNC and urethral stricture (about 6%) [330-332, 336, 342].

Two recent RCT-based meta-analyses evaluated the overall safety of OP vs. EEP for treating patients with large glands [336, 337]. Operation time was significantly longer for EEP, due to the significantly longer operation time needed for HoLEP (no difference was detected between OP and EEP using bipolar circuitry). Catheterisation and hospitalisation time was significantly shorter with EEP whilst IIEF-5 showed no significant difference between OP and EEP at twelve months. Endoscopic enucleation of the prostate was also associated with fewer blood transfusions but there were no significant differences regarding other complications. It was concluded that EEP appears to be a minimally invasive option for treating large prostates.

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

Summary of evidence	LE
Open prostatectomy is an effective and durable procedure for the treatment of LUTS/BPO but it is the most invasive surgical method.	1b
Endoscopic enucleation of the prostate is an effective minimally invasive alternative for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1
Endoscopic enucleation of the prostate achieves similar short- and mid-term efficacy to OP.	1
Endoscopic enucleation of the prostate has a more favourable peri-operative safety profile compared with OP.	1
Open prostatectomy or EEP such as holmium laser or bipolar enucleation of the prostate are the first choice of surgical treatment in men with a substantially enlarged prostate and moderate-to-severe LUTS.	1

Recommendation	Strength rating
Offer open prostatectomy in the absence of endoscopic enucleation to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong

*5.3.3 **Laser treatments of the prostate***

5.3.3.1 Holmium laser enucleation and holmium laser resection of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140 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 [343].

Efficacy: Meta-analyses of trials on HoLEP vs. TURP found that symptom improvement was comparable [344] and even superior with HoLEP [278, 344, 345]. One RCT comparing HoLEP with TURP in a small number of patients with a seven year follow-up found that the functional long term results of HoLEP were comparable with TURP [346]. Another meta-analysis demonstrated the superiority of HoLEP when compared to TURP with regards to post-operative Q_{max} [278]. A retrospective study of HoLEP with the longest follow-up of up to ten years (mean 62 months) reported durable functional results with low re-operation rates [347]. Randomised controlled trials indicate that HoLEP is as effective as OP for improving micturition in large prostates [330, 331], with similar improvement regarding Q_{max}, IPSS score and re-operation rates after five years [278, 330]. These findings are supported by two meta-analyses [336, 337].

Tolerability and safety: Compared to TURP, HoLEP has shorter catheterisation and hospitalisation times [348, 349]. Three meta-analyses found that HoLEP has shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [344, 345, 350]. 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%) [351]. Holmium laser enucleation of the prostate is superior to OP for blood loss, catheterisation and hospitalisation time [330, 331].

Holmium laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications [352]. However, current limitations include: a lack of RCTs; limited data on short- and mid-term complications and bridging therapy; data presentation does not allow for separate interpretation of either of the two substantially different topics of antiplatelet (AP) and anticoagulant (AC) therapy. No significant differences in pre-operative characteristics were found between 116 patients who did and 1,558 patients who did not receive AC/AP therapy [352]. Intra-operative characteristics showed shorter enucleation time (51 minutes vs. 65 minutes) for patients under AC/AP vs. no AC/AP, respectively. Post-operative outcomes were comparable except for length of hospital stay (27.8 hrs vs. 24 hrs) and duration of continuous bladder irrigation (15 hrs vs. 13.5 hrs) with both in favor of no AC/AP. No difference was seen between the cohorts for post-operative haemoglobin drop or transfusion rate. With regard to surgical revision two patients (1.9%) in the AC/AP cohort vs. ten patients (0.7%) in the no AC/AP cohort required clot evacuation [352]. Another study of 160 patients on single or dual anti-platelet therapy, who were part of a larger study of > 1000 patients, showed that HoLEP was as effective in patients on anti-platelet therapy with no significant difference in complication rates [353].

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP/OP [331, 354, 355]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP. Data have shown that ejaculation and orgasm perception are the two most impacted domains after HoLEP [356]. Attempts to maintain ejaculatory function with HoLEP have been reported to be successful in up to 46.2% of patients [357].

Practical considerations: HoLEP requires experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [358, 359]. Mentorship programmes are advised to improve surgical performance from both an institutional and personal learning curve perspective [360, 361]. With the advent of HoLEP and the fact that no relevant publications on HoLRP have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.3.1.1 Summary of evidence and recommendations for HoLEP

Summary of evidence	LE
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates higher haemostasis and intra-operative safety when compared to TURP and OP. Peri-operative parameters like catheterisation time and hospital stay are in favour of HoLEP.	1a

Laser enucleation of the prostate using Ho:YAG laser (HoLEP) did not negatively affect erectile function.	1a
The long-term functional results of HoLEP are comparable to OP.	1a

Recommendation	Strength rating
Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate or open prostatectomy.	Strong

5.3.3.2 532 nm ('Greenlight') laser vaporisation of the prostate

Mechanism of action: The Potassium-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. Three "Greenlight" lasers exist, which differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each. The standard Greenlight device is the 180-W XPS laser, but the majority of evidence is published with the former 80-W KTP or 120-W HPS (LBO) laser systems.

Efficacy and safety: A meta-analysis of the nine available RCTs comparing photoselective vaporisation of the prostate (PVP) using the 80-W and 120-W lasers with TURP was performed in 2012 [362]. No differences were found in Q_{max} and IPSS between 80-W PVP and TURP, but only three RCTs provided sufficient twelve month data to be included in the meta-analysis [363-365]. Another meta-analysis from 2016, of four RCTs including 559 patients, on the 120-W laser, demonstrated no significant difference in functional and symptomatic parameters at 6-, 12-, and 24-month follow-up when compared to TURP [366].

The 180-W XPS laser is non-inferior to TURP in terms of IPSS, Q_{max}, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. The 180-W XPS laser prostatectomy is superior to TURP in terms of catheterisation time, length of hospital stay and time to stable health status [367].

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 [368]. The re-operation rate was significantly higher after PVP (11% vs. 1.8%; p = 0.04) [368]. Similar improvements in IPSS, QoL, Q_{max}, or urodynamic parameters were reported from two RCTs with a maximum follow-up of 24 months [364, 369].

The only available RCT for the 180-W laser reported efficacy and safety outcomes similar to TURP with stable results at 24 months follow-up; however, there was a higher retreatment rate after 24 months in the PVP arm [367].

One RCT comparing HoLEP to PVP, in patients with prostates > 60 mL, showed comparable symptom improvement, but significantly higher flow rates and lower PVR volume after HoLEP at short-term follow-up; in addition, PVP showed a 22% conversion rate to TURP [370].

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 [278]. 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 [278]. In a meta-analysis including trials with the 120-W laser, patients in the PVP group demonstrated significantly lower transfusion rates, shorter catheterisation time and shorter duration of hospital stay compared to TURP. Re-operation rates and operation time were in favour of TURP. No significant differences were demonstrated for treatment for urethral stricture, BNC, incidence of incontinence and infection [366].

According to the Goliath Study, 180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications. Re-operation free survival during 24 months follow up was comparable between the TURP-arm and the 180-W XPS laser-arm [367].

Based mostly on case series the 80-,120- and 180-W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [371-374]; however, patients under anticoagulation therapy were either excluded from or represented a very small sample in currently available RCTs. In one study, anticoagulant patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [374]. In contrast, another retrospective study focusing on the 180-W LBO laser did not find any significant differences between patients receiving or not receiving anticoagulants [375]. A retrospective study of a mixed cohort of patients, treated with 80-W KTP PVP and 120-W LBO HPS, revealed that delayed gross haematuria was common in patients (33.8%) during an average follow-up of 33 months [376]. Of these 8.5% presented in the emergency department, 4.8% needed hospitalisation, and surgical revision was required in 4.5%. Multivariate analysis revealed that the odds of bleeding increased with prostate size longer follow-up and anticoagulant use and decreased with increasing age and use of a 5-ARIs

[376]. Available data are further hampered by the absence of details about anticoagulation management in the peri-operative setting (i.e. interruption, bridge or continuation). A retrospective review of a database of patients undergoing 180-W PVP, without interruption of anticoagulation therapy, had a 30.5% rate of peri-operative adverse events with a significant occurrence of high grade Clavien Dindo events [377]. Having significantly more comorbidities, this group of patients also had significantly longer lengths of hospital stay and catheterisation time.

Safety in patients with urinary retention, impaired detrusor contractility, elderly patients or prostates > 80 mL was shown in various prospective short-term non-randomised trials. No RCT including prostates > 100 mL has been reported; therefore, comparison of retreatment rates between prostate volumes of different sizes is not possible [378-380].

An RCT with twelve months follow-up reported a retrograde ejaculation rate of 49.9% following PVP with an 80-W laser vs. 56.7% for TURP, there was no impact on erectile function in either arm of the trial [381]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [382, 383]. However, IIEF-5 scores were significantly decreased at 6-, 12-, and 24- months in patients with pre-operative IIEF-5 greater than 19 [384].

Practical considerations: The 180-W XPS represents the current standard of generators for PVP; however, the number and quality of supporting publications are low, especially for large glands (> 100 mL), with no long-term follow-up.

5.3.3.2.1 Summary of evidence and recommendations for 532 nm ('Greenlight') laser vaporisation of prostate

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 80-W KTP and the 120-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay are in favour of PVP, whereas operation time and risk of re-operation are in favour of TURP. Short-term results for the 80-W KTP laser and mid-term results for the 120-W LBO laser were comparable to TURP.	1a
Laser vaporisation of the prostate using the 180-W LBO laser (PVP) demonstrated higher intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters such as catheterisation time and hospital stay were in favour of PVP, whereas operation time was in favour of TURP. Short- to mid-term results are comparable to TURP.	1b
Laser vaporisation of the prostate using the 80-W KTP and 120-W LBO lasers seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy.	2
Laser vaporisation of the prostate using the 180-W LBO laser seems to be safe for the treatment of patients receiving antiplatelet or anticoagulant therapy; however, the level of available evidence is low.	3

Recommendations	**Strength rating**
Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate (TURP).	Strong
Offer 120-W 532-nm Lithium Borat (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer 180-W 532-nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP.	Strong
Offer laser vaporisation of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL.	Weak

5.3.3.3 Diode laser treatment of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318, and 1,470 nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [385].

Efficacy: Two RCTs for 120-W 980 nm diode laser vaporisation vs. M-TURP are available [386, 387]. The first RCT with 24 month follow-up reported equal symptomatic and clinical parameters at one and six months. However, at 12- and 24-months the results were significantly in favour of TURP, repeat TURP was more frequent in the diode laser group [386]. The second RCT reported equivocal results for both interventions at 3-month follow-up [387].

Three RCTs with a twelve month follow-up compared 980 nm diode laser enucleation with bipolar enucleation and found no significant difference with regard to clinical outcome [388-390]. One small RCT with a six month follow-up comparing laser enucleation using a 1,318 nm diode laser with B-TURP reported similar efficacy [391]. An RCT of 154 patients undergoing 1,470 nm diode laser enucleation of the prostate (DiLEP) or plasmakinetic resection of the prostate (PKRP) revealed no difference in post-operative IPSS, QoL, Q_{max}, and PVR, however DiLEP had decreased risk of hemorrhage, operative time, bladder irrigation time, catheterisation duration, and hospital stay [392].

A one year RCT comparing transurethral endoscopic enucleation of the prostate using a 980 nm diode laser vs. bipolar plasmakinetic enucleation (BEEP) for the treatment of LUTS/BPO in 111 patients showed equivalence for both procedures. Post-operative results for DiLEP were comparable to BEEP regarding Q_{max} (28.0 ± 7.0 vs. 28.1 ± 7.2 mL/s) and IPSS (3.0 ± 2.2 vs. 2.9 ± 2.6) at twelve months. There was also no significant difference in tissue removal (71.8% vs. 73.8%) and complications at twelve months [390].

Tolerability and safety: Published studies on 980 nm laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [393, 394]. In a number of studies, a high rate of post-operative dysuria was reported [386, 393-395]. In an RCT reflecting on peri-operative and post-operative complications no significant differences were demonstrated for clot retention, re-catheterisation, UUI and UTI [386]. Moreover, for late complications no significant differences could be demonstrated for re-operation rate, urethral stricture, bladder neck sclerosis, *de novo* sexual dysfunction and mean time of dysuria [386].

Fibre modifications can potentially reduce surgical time [396]. Early publications on diode vaporisation reported high re-operation rates (8-33%) and persisting stress urinary incontinence (9.1%) [386, 393-395]. In contrast, the four RCTs on diode laser enucleation showed that blood loss, hospitalisation and catheterisation time were in favour of diode laser enucleation, with equivalent clinical outcome for either bipolar enucleation [388-390] or TURP [391] during short-term follow-up.

Practical considerations: Diode laser vaporisation leads to similar improvements in clinical and symptomatic parameters during short-term follow-up and provides good haemostatic properties. Diode laser enucleation seems to offer similar efficacy and safety when compared to either TURP or bipolar enucleation. Based on the limited number, mainly low quality RCTs, and controversial data on the retreatment rate, results for diode laser vaporisation and enucleation should be evaluated in further higher quality RCTs.

5.3.3.3.1 Summary of evidence and recommendations for diode laser treatment of the prostate

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 120-W 980 nm laser demonstrated high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay were in favour of diode lasers. Short-term results are comparable to TURP.	1b
In a number of studies severe post-operative complications such as severe storage symptoms or persisting incontinence occurred with laser vaporisation of the prostate using the 120-W 980 nm diode laser.	3
Laser enucleation of the prostate using the 980 nm laser showed comparable efficacy to bipolar endoscopic enucleation in the short term. Peri-operative parameters like blood loss, catheterisation time and hospital stay were in favour of diode enucleation.	1b
Laser vaporisation using the 120-W 980 nm diode laser seems to be safe with regard to haemostasis in patients receiving anticoagulant therapy.	3

Recommendations	**Strength rating**
Offer 120-W 980 nm diode laser vaporisation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to transurethral resection of the prostate (TURP).	Weak
Offer 120-W 980 nm diode laser or 1,318 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to TURP or bipolar enucleation.	Weak

5.3.3.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG)

Mechanism of action: In the Tm:YAG laser, a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [385, 397]. Different applications, ranging from vaporisation (ThuVAP), vaporesection (ThuVARP), and enucleation (ThuVEP vapoenucleation i.e. excising technique/ThuLEP blunt thereby primarily anatomical enucleation with Tm:YAG support) are published [398-400].

Efficacy: Two meta-analyses compared ThuVARP with TURP. The first meta-analysed data from three RCTs, one quasi-RCT and two case control studies. Studies with mono- or bipolar-TURP were included. Both treatments were efficacious with a difference in IPSS improvement in favour of ThuVARP at twelve months [401]. The second meta-analysis included data from six RCTs and three retrospective studies with different follow-ups and with only B-TURP as the comparator. There was no significant difference in terms of IPSS, Q_{max}, and PVR between the two therapies [402]. An RCT with a four year follow-up comparing ThuVARP to M-TURP, showed comparable efficacy and favourable re-operation rates in the ThuVaRP group [403]. Yang *et al*. demonstrated no significant difference with regard to symptoms and voiding parameters at one, three and five years follow-up [404]. A prospective multicentre study on ThuVARP, including 2,216 patients, showed durable post-operative improvement in IPSS, QoL, Q_{max}, and PVR for the entire eight years of follow-up [405].

There are mainly prospective case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [406-409]. One RCT with eighteen months follow up showed comparable outcomes in both arms for ThuLEP and HoLEP [410]. Furthermore, ThuLEP and bipolar enucleation were compared in one RCT with twelve months follow-up. The outcome showed no difference with regard to efficacy whilst the decrease in haemoglobin level and catheter time were significantly lower for ThuLEP [411]. An RCT with five years follow-up compared ThuLEP with bipolar TURP. No difference was found between the two procedures in terms of Q_{max}, IPSS, PVR, and QoL; however, the attrition rate was 50% at five years [404].

Tolerability and safety: ThuVARP, ThuLEP and ThuVEP show high intra-operative safety in RCTs [403, 412-414], as well as in case series in patients with large prostates [406] and anticoagulation or bleeding disorders [407, 415, 416]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [412, 414, 417, 418]. These results were confirmed in the two meta-analyses comparing ThuVARP with TURP [401, 402]. The rate of post-operative urethral strictures after ThuVARP was 1.9%, the rate of BNC was 1.8%, and the re-operation rate was 0-7.1% during follow-up [412, 417, 419]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall retreatment rate was 3.4% (mean follow-up 16.5 months) [399]. No urethral and bladder neck strictures after ThuLEP were reported during the eighteen months follow-up [413]. Recently, a study focusing on post-operative complications after ThuVEP reported adverse events in 31% of cases, with 6.6% complications greater then Clavien grade 2 [420]. One case control study on ThuVEP with 48-month follow-up reported long-term durability of voiding improvements and overall re-operation rates of 2.4% [415]. Two studies (one case control, one RCT vs. TURP) addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [421, 422]. Another case control study evaluated the impact of thulium laser prostatectomy (resection and vapoenucleation) on erectile function. The IIEF-5 scores dropped significantly during the first three post-operative months and then gradually increased returning to pre-operative levels at the twelve month follow-up assessment [423].

Urethral stricture and BNC was 2.6% and 1.6%, respectively in a prospective multicentered study of ThuVARP. Persistent stress incontinence was found in 0.1% whilst, re-operation due to BPH recurrence was required in 1.2% patients [405].

In two RCTs on ThuLEP vs. TURP [424], one RCT on ThuLEP vs. bipolar enucleation [411] and one RCT on ThuLEP vs. HoLEP [410], ThuLEP appeared to be superior with regard to intra-operative haemostasis. The same was demonstrated for ThuVEP vs. TURP in one RCT [414]; however, in two further RCTs on ThuLEP vs. HoLEP no significant difference could be demonstrated at 6, 12 and 18 months follow up [413, 425].

Practical considerations: As a limited number of RCTs and only a few studies with long-term follow-up support the efficacy of thulium laser prostatectomy, there is a need for ongoing investigation of the technique.

5.3.3.4.1 Summary of evidence and recommendations for the use of the Thulium: yttrium-aluminium-garnet laser (Tm:YAG)

Summary of evidence	**LE**
Laser enucleation of the prostate using either vapoenucleating (ThuVEP) or laser assisted blunt technique (ThuLEP) demonstrates high intra-operative safety with regard to haemostatic properties when compared to TURP. Short-term results are comparable to TURP.	1b
Laser vapoenucleation of the prostate using a Tm:YAG laser (ThuVEP) seems to be safe in patients receiving anticoagulant or antiplatelet therapy.	2b
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) demonstrates high intra-operative safety with regard to haemostatic properties when compared to TURP. Peri-operative parameters like catheterisation time and hospital stay are in favour of thulium lasers. Long-term results are similar to TURP.	1a

Recommendations	Strength rating
Offer laser enucleation of the prostate using Tm:YAG vapoenucleation (ThuVEP) and Tm:YAG laser assisted anatomical enucleation (ThuLEP) to men with moderate-to-severe LUTS as alternatives to TURP and holmium laser enucleation (HoLEP).	Weak
Offer ThuVEP to patients receiving anticoagulant or antiplatelet therapy.	Weak
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Strong
Offer ThuVARP to patients receiving anticoagulant or antiplatelet therapy.	Weak

5.3.4 ***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 extending from the bladder neck to the verumontanum.

Efficacy: In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%) [426-431]. Prostatic urethral lift was initially evaluated vs. sham in a multicentre study with one [428] three [432] and five [433] years follow-up. The primary endpoint was met at three months with a 50% reduction in IPSS. In addition, Q_{max} increased significantly from 8.1 to 12.4 mL/s compared to baseline at three months and this result was confirmed at twelve 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 or sham. At three years, average improvements from baseline were significant for total IPSS, QoL, Q_{max} and individual IPSS symptoms. There were no *de novo*, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL. Improvements in IPSS, QoL, BPH impact index (BPHII), and Q_{max} were durable throughout the five years with improvement rates of 36%, 50%, 52%, and 44%, respectively. The re-treatment rate was 13.6% over five years. Adverse events were mild to moderate and transient. Sexual function was stable over five years with no *de novo*, sustained erectile, or ejaculatory dysfunction.

Another RCT of 80 patients was conducted in three European countries, comparing PUL to TURP. At twelve months, IPSS improvement was -11.4 for PUL and -15.4 for TURP. There was no retrograde ejaculation among PUL patients, while 40% of TURP patients lost the ability to ejaculate. Surgical recovery was measured using a validated instrument and confirmed that recovery from PUL is more rapid and more extensive in the first three to six months [434]. However, TURP resulted in much greater improvements in Q_{max} after twelve months compared to PUL. At 24 months, significant improvements in IPSS, IPSS QoL, BPHII, and Q_{max} were observed in both arms. Change in IPSS and Q_{max} in the TURP arm were superior to the PUL arm [435]. Improvements in QoL and BPHII score were not statistically different between the study arms. Prostatic urethral lift resulted in superior quality of recovery and ejaculatory function preservation. Ejaculatory function and bother scores did not change significantly in either treatment arm.

In a meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS, Q_{max}, and QoL [431]. Sexual function was preserved with a small improvement estimated at twelve months.

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 UTI (2.9-11%) [428, 431-433]. Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure.

Prostatic urethral lift 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 [426-430].

Practical considerations: An obstructed/protruding middle lobe cannot be effectively treated, and the effectiveness in large prostate glands has not been shown yet. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques.

Summary of evidence	LE
Prostatic urethral lift improves IPSS, Q_{max} and QoL; however, these improvements are inferior to TURP at 24 months.	1b

Prostatic urethral lift has a low incidence of sexual side effects.	1b
Patients should be informed that long-term effects including the risk of retreatment have not been evaluated.	4

Recommendation	Strength rating
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strong

*5.3.5 **Intra-prostatic injections***

Mechanism of action: Various substances have been injected directly into the prostate in order to improve LUTS, these include Botulinum toxin-A (BoNT-A), fexapotide triflutate (NX-1207) and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [436]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data associates apoptosis-induced atrophy of the prostate with both drugs [436].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [437, 438]. A recent SR and meta-analysis showed no differences in efficacy compared with placebo and concluded that there is no evidence of clinical benefits in medical practice [439]. The positive results from Phase II-studies have not be confirmed in Phase III-trials for PRX302 [440, 441]. NX-1207 was evaluated in two multicentre placebo controlled double-blind randomised parallel group trials including a total of 995 patients with a mean follow-up of 3.6 years, IPSS change from baseline was significantly higher and AUR rate was significantly reduced in the treatment arm. The authors concluded that NX-1207 is an effective transrectal injectable for long-term treatment for LUTS and that treated patients have reduced need for further intervention [442].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [436]. A recent SR and meta-analysis showed low incident rates of procedure-related adverse events [439]. Two multicentre placebo controlled double-blind randomised parallel group trials with long-term follow up evaluating NX-1207 detected no significant safety differences between the study arms [442].

Practical considerations: Although experimental evidence for compounds such as BoNT-A and PRX302 were promising for their transition to clinical use positive results from Phase II-studies have not be confirmed in Phase III-trials. Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results of NX-1207

Summary of evidence	LE
Results from clinical trials have shown no clinical benefits for BoNT-A compared to placebo for the management of LUTS due to BPO.	1a
Results from clinical trials have shown clinical benefits for NX-1207 compared to placebo for the management of LUTS due to BPO.	1b

Recommendation	Strength rating
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strong

*5.3.6 **Techniques under investigation***

Recommendations on new interventions will only be included in the Guidelines once supported by RCTs looking at both efficacy and safety, with adequate follow-up (> 3 yrs), and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [443]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include (1) proof of concept, (2) RCTs on efficacy and safety, as well as (3) cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [443]. The panel will assess the quality of all RCTs and if they do not meet the standard required the intervention will continue to have no recommendation i.e. a RCT does not guarantee inclusion in the Guidelines. In the current Guideline, a recommendation is given for Aquablation and Prostatic Artery Embolisation (PAE); however, these two techniques should still be considered as under investigation in order to better define their position in the armamentarium of invasive therapies for BPO and to better define the subgroups of patients who will benefit most from them.

5.3.6.1 Minimal invasive simple prostatectomy

Mechanism of action: The term minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy (LSP) and robot-assisted simple prostatectomy (RASP). The technique for LSP was first described in 2002 [444], while the first RASP was reported in 2008 [445]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP. An extraperitoneal approach is mostly used for LSP, while a transperitoneal approach is mostly used for RASP.

Efficacy: A SR and meta-analysis showed that in 27 observational studies including 764 patients, the mean increase in Q_{max} was 14.3 mL/s (95% CI 13.1-15.6), and the mean improvement in IPSS was 17.2 (95% CI 15.2-19.2) [446]. Mean duration of operation was 141 minutes (95% CI 124-159), and the mean intra-operative blood loss was 284 mL (95% CI 243-325). One hundred and four patients (13.6%) developed a surgical complication. In comparative studies to OP, length of hospital stay, length of catheter use and estimated blood loss were significantly lower in the MISP group, while the duration of operation was longer than in OP. There were no differences in improvements in Q_{max}, IPSS and peri-operative complications between both procedures.

Two recent retrospective series on RASP were not included in the meta-analysis which confirm these findings [447, 448]. The largest retrospective series reports 1,330 consecutive cases including 487 robotic (36.6%) and 843 laparoscopic (63.4%) simple prostatectomy cases. The authors confirm that both techniques can be safely and effectively done in selected centres [447].

Tolerability and safety: In the largest series, the post-operative complication rate was 10.6% (7.1% for LSP and 16.6% for RASP), most of the complications being of low grade. The most common complications in the RASP series were haematuria requiring irrigation, UTI and AUR; in the LSP series, the most common complications were UTI, ileus and AUR. In the most recent, largest comparative analysis of robotic vs. open simple prostatectomy (OSP) for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OSP demonstrated a significant shorter average length of stay (1.5 vs. 2.6 days), but longer mean operative time (161 vs. 93 minutes). The robotic approach was also associated with a lower estimated blood loss (339 vs. 587 mL). Improvements in maximal flow rate, IPSS, QoL, PVR and post-operative PSA levels were similar before and after surgery for both groups. There was no difference in complications between the groups [449].

Practical considerations: Minimal invasive simple prostatectomy seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [446]. However, most studies are of a retrospective nature. High quality studies are needed to compare the efficacy, safety, and hospitalisation times of MISP and both OP and endoscopic methods. Long-term outcomes, learning curve and cost of MISP should also be evaluated.

Summary of evidence	**LE**
Minimal invasive simple prostatectomy is feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

5.3.6.2 (i)TIND

Basic principle: The iTIND is a device designed to remodel the bladder neck and the prostatic urethra and is composed of three elongated struts and an anchoring leaflet, all made of nitinol. Under direct visualisation the iTIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis in defined areas of interest. The iTIND is left in position for five days. The resulting incisions may be similar to a Turner Warwick incision. In an outpatient setting the device is removed by standard urethroscopy.

Efficacy: A single-arm, prospective study of 32 patients with a follow up of three years was conducted to evaluate feasibility and safety of the procedure [450]. The change from baseline in IPSS, QoL score and Q_{max} was significant at every follow-up time point [451].

Tolerability and safety: The device has been reported to be well tolerated by all patients. Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%), and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up period.

Practical considerations: Randomised controlled trials comparing iTIND to a reference technique are ongoing.

5.3.6.3 Aquablation – image guided robotic waterjet ablation: AquaBeam

Basic principle: AquaBeam uses the principle of hydro-dissection to ablate prostatic parenchyma while sparing collagenous structures like blood vessels and the surgical capsule. A targeted high velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal ultrasound guidance. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [452].

Efficacy: In a double-blind, multicentre, prospective RCT 181 patients were randomised to TURP or Aquablation [453]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes, p = 0.2752), but resection time was lower for Aquablation (4 vs. 27 minutes, p < 0.0001). At six months patients treated with Aquablation and TURP experienced large IPSS improvements (-16.9 and -15.1, respectively). The study non-inferiority hypothesis was satisfied (p < 0.0001). Larger prostates (50-80 mL) demonstrated a more pronounced benefit. At one year follow-up, mean IPSS reduction was 15.1 in the Aquablation group and 15.1 in the TURP group with a mean percent reduction in IPSS score of 67% in both groups. Ninety three percent and 86.7% of patients had improvements of at least 5 points from baseline, respectively. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was reported between both groups. One TURP subject (1.5%) and three Aquablation subjects (2.6%) underwent re-TURP within one year of the study procedure [454]. In a cohort study of 101 men with a prostate volume between 80-150 mL mean IPSS improved from 23.2 at baseline to 5.9 at six months. Improvement in IPSS, QoL, Q_{max} and reduction of PVR were also significant at six months. No secondary procedures for tissue removal occurred as of the six months [455].

Tolerability and safety: Aquablation was shown to be non-inferior to TURP (26% vs. 42%, p = 0.0149). Among sexually active men the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). There were no procedure-related adverse events after six months [454]. In patients with a prostate volume between 80-150 mL, bleeding related events were observed in fourteen patients (13.9%) of which eight (7.9%) occurred prior to discharge and six (5.9%) occurred within one month of discharge. Blood transfusions were required in eight (7.9%) patients, return to the theatre for fulguration in three (3.0%) patients, and both transfusion and fulguration in two patients (2.0%). Ejaculatory dysfunction occurred in 19% of sexually active men [455].

Practical considerations: During short-term follow-up, Aquablation provides non-inferior functional outcomes compared to TURP in patients with LUTS and a prostate volume between 30-80 mL. Longer term follow up is necessary to assess the clinical value of Aquablation.

Summary of evidence	**LE**
Aquablation appears to be as effective as TURP both subjectively and objectively; however, there are still some concerns about the best methods of achieving post-treatment haemostasis.	1b

Recommendations	**Strength rating**
Offer Aquablation* to patients with moderate-to-severe LUTS and prostates between 30-80 mL as an alternative to TURP.	Weak
Inform patients about the risk of bleeding and the lack of long-term follow up data.	Strong

** Aquablation remains under investigation*

5.3.6.4 Convective water vapour energy (WAVE) ablation: The Rezum system

Basic principle: The Rezum system uses radiofrequency power to create thermal energy in the form of water vapour, which in turn deposits the stored thermal energy when the steam phase shifts to liquid upon cell contact. The steam disperses through the tissue interstices and releases stored thermal energy onto prostatic tissue effecting cell necrosis. The procedure can be performed in an office based setting. Usually, one to three injections are needed for each lateral lobe and one to two injections may be delivered into the median lobe.

Efficacy: In a multicentre, randomised, controlled study 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment (rigid cystoscopy with imitated treatment sounds) [456]. At three months relief of symptoms, measured by a change in IPSS and Q_{max} were significantly improved and maintained compared to the sham arm, although only the active treatment arm was followed up to twelve months. No relevant impact was observed on PVR. Quality of life outcome was significantly improved with a meaningful treatment response of 52% at twelve months (p < 0.0001). Further validated objective outcome measures such as BPHII, Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and International Continence Society Male Item Short Form Survey for male incontinence

demonstrated significant amelioration of symptoms at three months follow-up with sustained efficacy throughout the study period of twelve months. The reported two year results in the Rezum cohort arm of the same study and the recently reported four year results confirmed durability of the positive clinical outcome after convective water vapour energy ablation [457, 458]. Surgical retreatment rate was 4.4% over four years [458].

Tolerability and safety: Safety profile was favourable with adverse events documented to be mild to moderate and resolving rapidly. Preservation of erectile and ejaculatory function after convective water vapour thermal therapy was demonstrated utilising validated outcome instruments such as IIEF and Male Sexual Health Questionnaire-Ejaculation Disorder Questionnaire [456].

Practical considerations: Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapour energy treatment.

5.3.6.5 Prostatic artery embolisation

Basic principle: Prostatic artery embolisation can be performed as a day procedure under local anaesthesia with access through the femoral or radial arteries. Digital subtraction angiography displays arterial anatomy and the appropriate prostatic arterial supply is selectively embolised to effect stasis in treated prostatic vessels. Different techniques have been used for PAE. Atherosclerosis, excessive tortuosity of the arterial supply and the presence of adverse collaterals are anatomical obstacles for the technical approach. Cone beam computed tomography can help identify prostatic arteries and prevent off-target embolisation particularly in patients with challenging anatomical configurations [459].

Efficacy: In a prospective multi-centre matched cohort study of 216 PAE patients and 89 TURP patients, PAE achieved a 10-point improvement in primary outcome of IPSS at twelve months compared with a 15-point improvement with TURP and -3.0 in QoL compared with -4.0 with TURP. There was a 28% reduction in prostate volume with PAE [460].

Another retrospective review of 93 patients undergoing PAE for prostates > 80 mL recorded significant changes in prostate volume 141 mL to 98 mL (-31%), IPSS 22 to 7 (-68%) and QoL 4.4 to 1.3 (-71%), Q_{max} 7.7 to 12.8 mL/s (+66%) and PVR 196 mL to 61 mL (-69%) at twelve months. The authors concluded that PAE may be an alternate treatment for patients for whom conventional surgical options are limited or associated with significant morbidity [461].

Two prospective RCTs were conducted for direct comparison of PAE with TURP [462, 463]. Both studies observed significant treatment outcomes for both procedures as compared to baseline values, but TURP was superior when considering urodynamic parameters such as Q_{max} and PVR. Improvement of LUTS as determined by IPSS and QoL was slightly more pronounced after TURP and reduction of prostate volume was significantly more efficient after TURP than PAE.

Another RCT comparing PAE with TURP in 99 patients (48 vs. 51) showed a mean reduction in IPSS from baseline to twelve weeks of –9.23 points after PAE and –10.77 points after TURP. At twelve weeks, PAE was less effective than TURP regarding improvements in Q_{max} (5.19 mL/s vs. 15.34 mL/s), PVR (–86.36 mL vs. –199.98 mL), prostate volume (–12.17 mL vs. –30.27 mL), and desobstructive effectiveness according to pressure flow studies (56% vs. 93%) shift towards less obstructive category; p = 0.003). For secondary outcomes, compared with PAE, procedural time was shorter for TURP, but in PAE patients bladder catheter indwelling time, and duration of hospital stay were significantly shorter [459].

A SR and meta-analysis of thirteen studies of 1,254 PAE patients between 2014 and 2017 showed IPSS improvement of 67%, QoL (64%) and prostate volume reduction of 26%. Quality of life, IPSS, prostate volume, PVR, & IIEF improvements were maintained at three years [464].

Tolerability and safety: In an earlier SR of comparative studies PAE resulted in more adverse events than TURP/OP (41.6% vs. 30.4%, p = 0.044). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%, p = 0.006) [465]. Non-comparative studies reported an improvement in IIEF after PAE (weighted mean difference 1.31, 95% CI: 0.82, 1.81).

Another RCT however, reported fewer adverse events occurred after PAE than after TURP (36 vs. 70 events; p = 0.003). For secondary outcomes, PAE showed favourable results in terms of blood loss [459]. A SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the post-operative complications rate between TURP and PAE [466]. Concerns still exist about non-target embolisation, reported in earlier studies [467]; however, more recent studies report less incidents [460, 468].

Practical considerations: A multidisciplinary team approach of urologists and radiologists is mandatory and patient selection should be done by urologists and interventional radiologists. The investigation of patients with LUTS to indicate suitability for invasive techniques should be performed by urologists only. This technically demanding procedure should only be done by an interventional radiologist with specific mentored training and expertise in PAE [469]. Patients with larger prostates (> 80 mL) may have the most to gain from PAE. The selection of LUTS patients who will benefit from PAE still needs to be better defined. Further data with medium- and long-term follow up are still required and comparison with other minimally invasive techniques would be valuable. However, current evidence of safety and efficacy of PAE appears adequate to support the use of this procedure for men with moderate-to-severe LUTS provided proper arrangements for consent and audit are in place; therefore, a recommendation has been given, but PAE remains under investigation.

Summary of evidence	**LE**
Prostatic artery embolisation is less effective than TURP at improving symptoms and urodynamic parameters such as flow rate.	1a
Procedural time is longer for PAE compared to TURP, but blood loss, catheterisation and hospitalisation time are in favour of PAE.	1b

Recommendations	**Strength rating**
Offer prostatic artery embolisation (PAE)* to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal objective outcomes compared with transurethral resection of the prostate.	Weak
Perform PAE only in units where the work up and follow up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strong

**PAE remains under investigation*

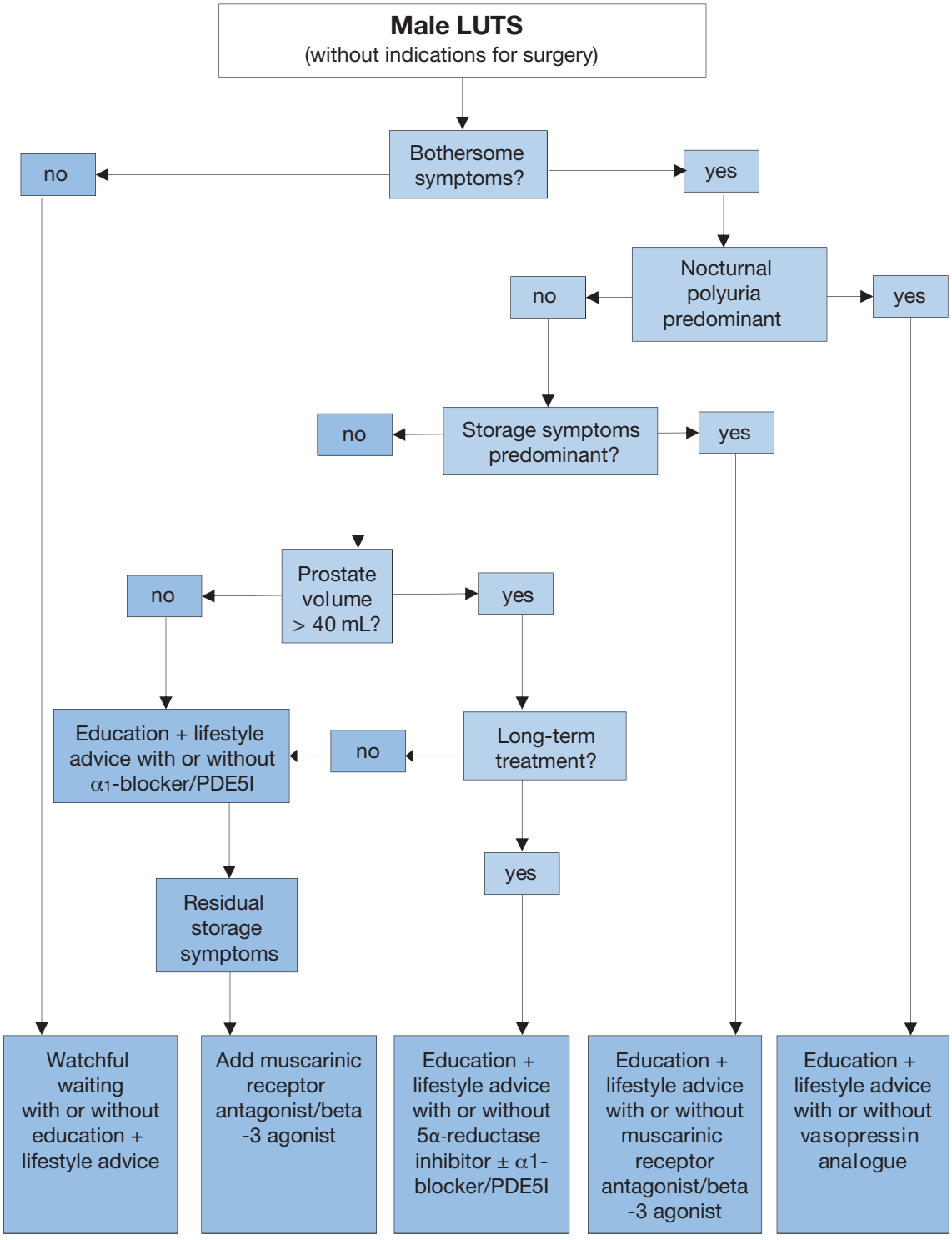
5.4 Patient selection

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.

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).

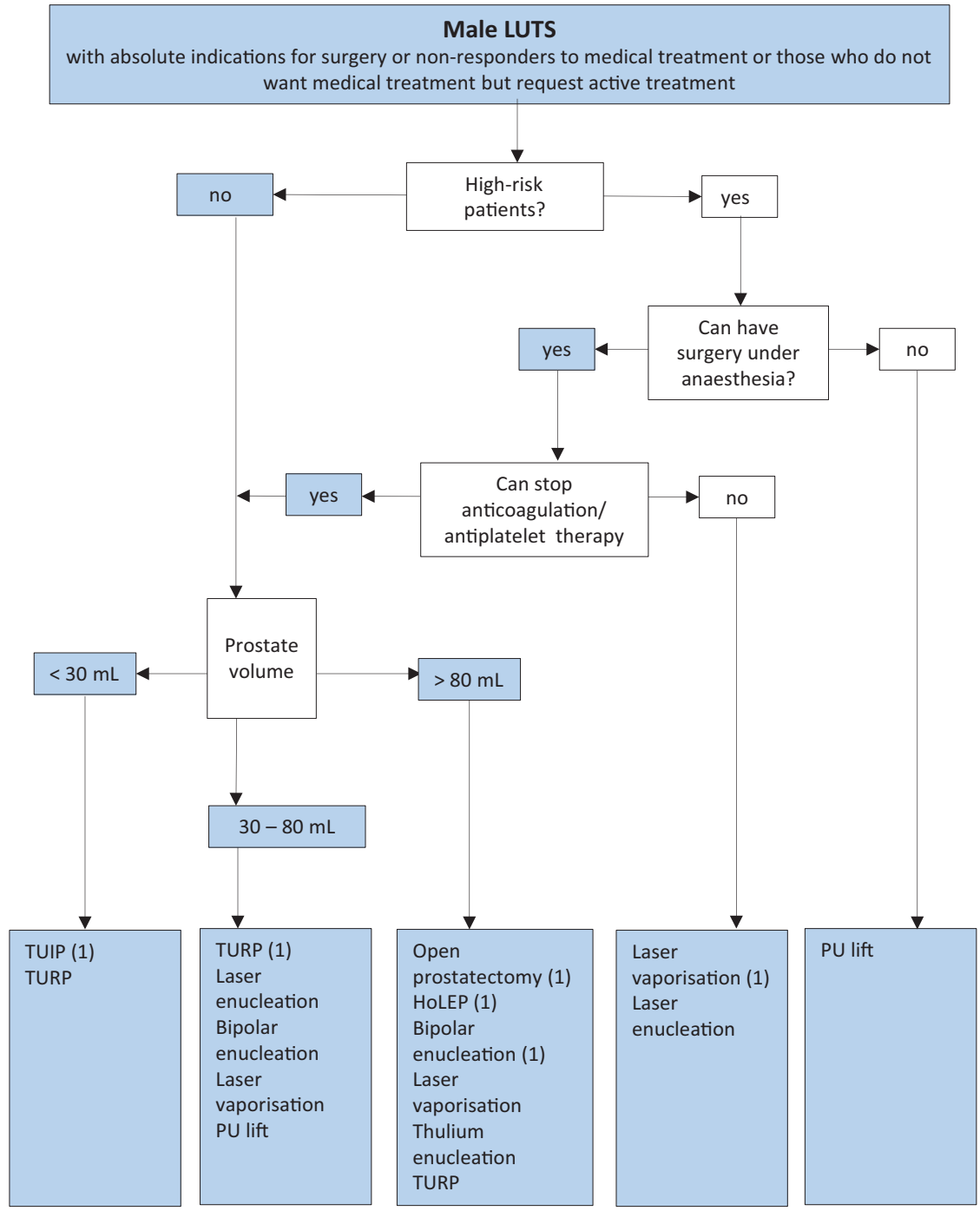
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' 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 the patient's 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.



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 is stratified by the patient's ability to have anaesthesia, their cardiovascular risk and prostate size.



(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Laser vaporisation includes GreenLight, thulium, and diode laser vaporisation. Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate and PU = prostatic urethral.

5.5 Management of Nocturia in men with lower urinary tract symptoms

The following section reports a SR of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia [470].

Nocturia is defined as the complaint of waking at night to void [5]. It reflects the relationship between the amount of urine produced while asleep, and the ability of the bladder to store the urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), such as OAB and chronic pelvic pain syndrome. Nocturia can also occur in association with other forms of LUTD, such as BOO, but here it is debated whether the link is one of causation or simply the co-existence of two common conditions. Crucially, nocturia may have behavioural, sleep disturbance (primary or secondary) or systemic causes unrelated to LUTD (Table 2). Differing causes often co-exist and each has to be considered in all cases. Only where LUTD is contributory should nocturia be termed a LUTS.

Table 2: Categories of nocturia

CATEGORY	Disproportionate urine production (at all times, or during sleep)	Low volume of each void (at all times, or overnight)
Behavioural	Inappropriate fluid intake	"Bladder awareness" due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt output	"Bladder awareness" due to primary sleep disturbance
LUTD		Impaired storage function and increased filling sensation

*5.5.1 **Diagnostic assessment***

Evaluation is outlined in Figure 5;

1. Evaluate for LUTD according to the relevant guidelines. The severity and bother of individual LUTS should be identified with a symptom score, supplemented by directed questioning if needed. A validated bladder diary is mandatory.
2. Review whether behavioural factors affecting fluid balance and sleep are contributing.
3. Review of medical history and medications, including directed evaluation for key conditions, such as renal failure, diabetes mellitus, cardiac failure, and obstructive sleep apnoea. If systemic factors or sleep disorders are potentially important, consider involving appropriate medical expertise (see Figure 6). This is appropriate where a known condition is suboptimally managed, or symptoms and signs suggest an undiagnosed condition.

*5.5.2 **Medical conditions and sleep disorders Shared Care Pathway***

Causative categories for nocturia comprise [471]:

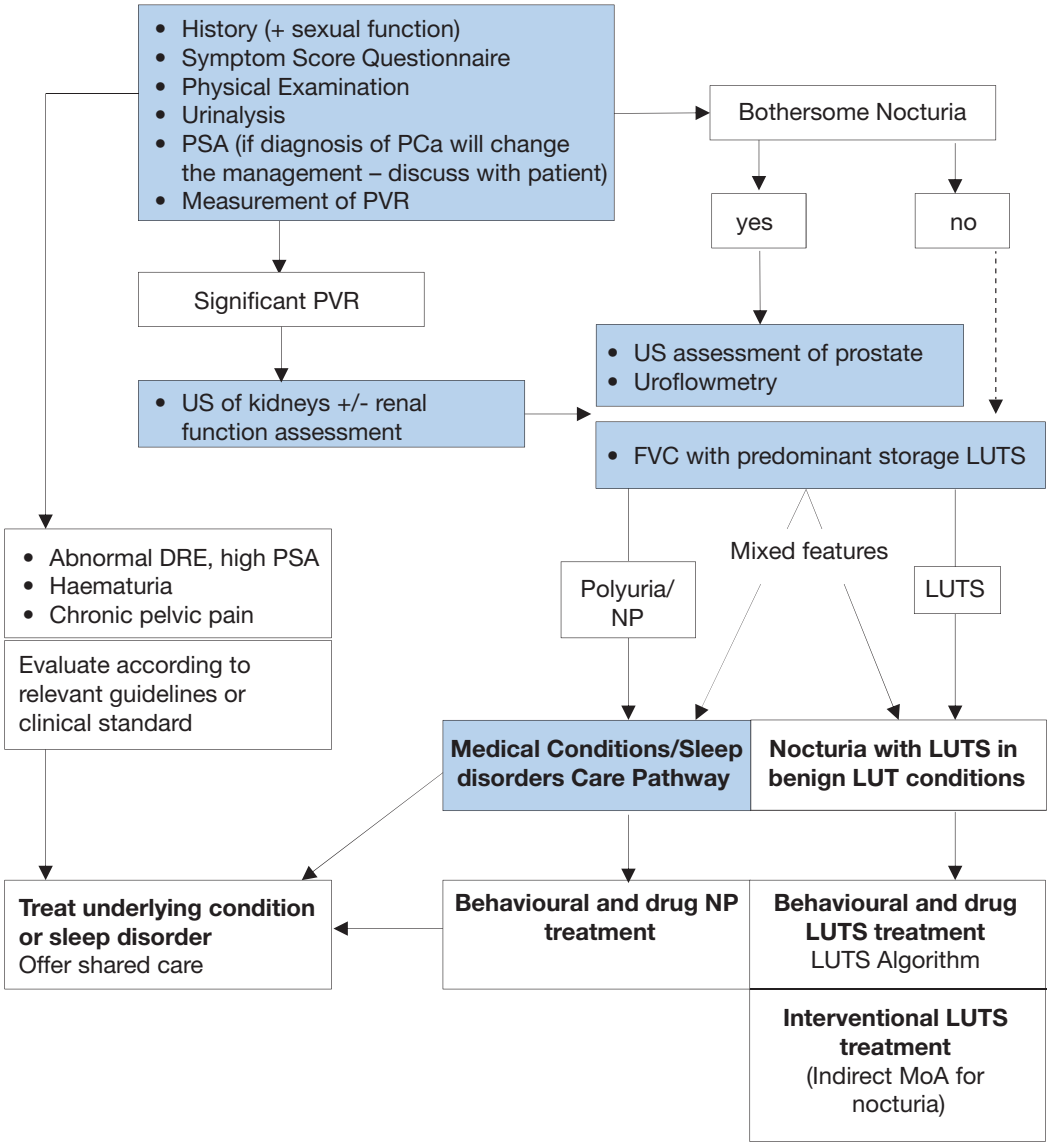
1. bladder storage problems;
2. 24-hour (global) polyuria (> 40 mL/kg urine output over a 24-hour period);
3. nocturnal polyuria (NP; nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [5]);
4. sleep disorders;
5. mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on: levels of free water, salt, other solutes and plasma oncotic pressure; endocrine regulation e.g. by antidiuretic hormone; natriuretic peptides; cardiovascular and autonomic control; renal function; neurological regulation, e.g. circadian regulation of the pineal gland, and renal innervation. As nocturia is commonly referred to the specialty without full insight into cause, the urologist must review the likely mechanisms underlying a presentation with nocturia and instigate review by relevant specialties accordingly. Thus, the managing urologist needs to evaluate nocturia patients in a context where additional medical expertise is available (Table 3). They should not proceed along any LUTD management pathway unless a causative link with LUTD is justifiably suspected, and systemic or sleep abnormalities have been considered.

In patients with non-bothersome nocturia, the medical evaluation (history and physical examination) should consider the possibility of early stages of systemic disease, and whether there is possibility of earlier diagnosis or therapy adjustment.

Some important potentially treatable non-urological causes of nocturia include; obstructive sleep apnoea (OSA), congestive cardiac failure, poorly controlled diabetes mellitus and medications (e.g. diuretics, or lithium).

Figure 5. Evaluation of Nocturia in non-neurogenic Male LUTS.



Assessment must establish whether the patient has polyuria, LUTS, a sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment with a frequency volume chart (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
FVC = frequency volume chart; DRE = digital rectal examination; NP = nocturnal polyuria; MoA = mechanism of action; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound.

Table 3: Shared care pathway for nocturia, highlighting the need to manage potentially complex patients using relevant expertise for the causative factors.

UROLOGICAL CONTRIBUTION	SHARED CARE	MEDICAL CONTRIBUTION
Diagnosis of LUTD • Urological/LUTS evaluation • Nocturia symptom scores • Bladder diary		**Diagnosis of conditions causing NP** • Evaluate patient's known conditions • Screening for sleep disorders • Screening for potential causes of polyuria*
Conservative management Behavioural therapy • Fluid/sleep habits advice • Drugs for storage LUTS • (Drugs for voiding LUTS) • ISC/catherisation Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS	**Conservative management** • Antidiuretic • Diuretics • Drugs to aid sleep	**Management** • Initiation of therapy for new diagnosis • Optimised therapy of known conditions * Potential causes of polyuria NEPHROLOGICAL DISEASE • Tubular dysfunction • Global renal dysfunction CARDIOVASCULAR DISEASE • Cardiac disease • Vascular disease ENDOCRINE DISEASE • Diabetes insipidus/mellitus • Hormones affecting diuresis/natriuresis NEUROLOGICAL DISEASE • Pituitary and renal innervation • Autonomic dysfunction RESPIRATORY DISEASE • Obstructive sleep apnoea BIOCHEMICAL • Altered blood oncotic pressure

5.5.3 ***Treatment for Nocturia***

5.5.3.1 Antidiuretic therapy

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and control of urine production by binding to V2 receptors in the renal collecting ducts. Arginine vasopressin increases water re-absorption and urinary osmolality, so decreasing water excretion and total urine volume. Arginine vasopressin also has V1 receptor mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for treating nocturia/nocturnal polyuria.

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. It has been investigated for treating nocturia [472], with specific doses, titrated dosing, differing formulations, and options for route of administration. Most studies have short follow-up. Global interpretation of existing studies is difficult due to the limitations, imprecision, heterogeneity and inconsistencies of the studies.

A SR of randomised or quasi-randomised trials in men with nocturia found that desmopressin may decrease the number of nocturnal voids by -0.46 compared to placebo over short-term follow-up (up to three months); over intermediate-term follow-up (three to twelve months) there was a change of -0.85 in nocturnal voids in a substantial number of participants without increase in major adverse events [473].

Another SR of comparative trials of men with nocturia as the primary presentation and LUTS including nocturia or nocturnal polyuria found that antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep [470]. Adverse events include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral edema, and nausea. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients (1.3%), with one death. There were seventeen cases of hyponatraemia (3.2%) and seven of hypertension (1.3%). Headache was reported in 53 (10%) and nausea in fifteen (2.8%) [470]. Hyponatremia is the most important concern, especially in patients > 65 years of age, with potential life threatening consequences. Baseline values of sodium over 130 mmol/L have been used as inclusion criteria in some research protocols. Assessment of sodium levels must be undertaken at baseline, after initiation of treatment or dose titration and during treatment. Desmopressin is not recommended in high-risk groups [470].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [474, 475]. Almost 87% of included patients had nocturnal polyuria and approximately 48% of the patients were > 65 years. The co-primary endpoints in both trials were change in number of nocturia episodes per night from baseline and at least a 33% decrease in the mean number of nocturnal voids from baseline during three months of treatment. The mean change in nocturia episodes from baseline was greater with desmopressin ODT compared to placebo (difference: women = -0.3 [95% CI: -0.5, -0.1]; men = -0.4 [95% CI: -0.6, -0.2]). The 33% responder rate was also greater with desmopressin ODT compared to placebo (women: 78% vs. 62%; men: 67% vs. 50%).

Analysis of three published placebo-controlled trials of desmopressin ODT for nocturia showed that clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dosage groups, including those receiving the minimum effective dose for desmopressin (11% of men aged ≥ 65 years vs. 0% of men aged < 65 years receiving 50 mcg; 4% of women ≥ 65 aged years vs. 2% of women aged < 65 years receiving 25 mcg). Severe hyponatraemia, defined as ≤ 125 mmol/L serum sodium, was rare, affecting 22/1,431 (2%) patients overall [476].

Low dose desmopressin (ODT) has been approved in Europe, Canada and Australia for the treatment of nocturia with ≥ 2 episodes in gender-specific low doses 50 mcg for men and 25 mcg for women; however, it initially failed to receive FDA approval, with the FDA citing uncertain benefit relative to risks as the reason. Following resubmission to the FDA in June 2018 desmopressin acetate sublingual tablet, 50 mcg for men and 25 mcg for women, was approved for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void with a boxed warning for hyponatremia.

Desmopressin acetate nasal spray is a new low-dose formulation of desmopressin and differs from other types of desmopressin formulation due to its bioavailability and route of administration. Desmopressin acetate nasal spray has been investigated in two RCTs including men and women with nocturia (over two episodes per night) and a mean age of 66 years. The average benefit of treatment relative to placebo was statistically significant, but low, -0.3 and -0.2 for the 1.5 mcg and 0.75 mcg doses of desmopressin acetate, respectively. The number of patients with a reduction of more than 50% of nocturia episodes was 48.5% and 37.9%, respectively compared with 30% in the placebo group [477]. The reported adverse event rate of the studies was rather low and the risk of hyponatremia was 1.2% and 0.9% for desmopressin acetate 1.5 mcg and 0.75 mcg, respectively. Desmopressin acetate nasal spray was approved by the FDA in 2017 for the treatment of nocturia due to nocturnal polyuria, but it is not available in Europe.

Practical considerations

A complete medical assessment should be made, to exclude potentially non-urological underlying causes, e.g. sleep apnea, before prescribing desmopressin in men with nocturia due to nocturnal polyuria. The optimal dose differs between patients, in men < 65 years 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. Desmopressin is taken once daily before sleeping. Patients should avoid drinking fluids at least one hour before and for eight hours after dosing. Low dose desmopressin may be prescribed in patients > 65 years. In men ≥ 65 years or older, low dose desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatremia. Urologists should be cautious when prescribing low-dose desmopressin in patients under-represented in trials (e.g. patients > 75 years) who may have an increased risk of hyponatremia.

5.5.3.2 Medications to treat LUTD

Where LUTD is diagnosed and considered causative of nocturia, relevant medications for storage (and voiding) LUTS may be considered. Applicable medications include; selective α1-adrenergic antagonists [478], antimuscarinics [479-481], 5-ARIs [482] and PDE5Is [483]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [470]. Data on OAB medications (antimuscarinics, beta-3 agonist) generally had a female-predominant population. No studies specifically addressing the impact of OAB medications on nocturia in men were identified [470]. Benefits with combination therapies were not consistently observed.

5.5.3.3 Other medications

Agents to promote sleep [484], diuretics [485], non-steroidal anti-inflammatory agents (NSAIDs) [486] and phytotherapy [487] were reported as being associated with response or QoL improvement [470]. Effect size of these medications in nocturia is generally small, or not significantly different from placebo. Larger responses have been reported for some medications, but larger scale confirmatory RCTs are lacking. Agents to promote sleep do not appear to reduce nocturnal voiding frequency, but may help patients return to sleep.

Summary of evidence	LE
No clinical trial of pathophysiology-directed primary therapy has been undertaken.	4
No robust clinical trial of behavioural therapy as primary intervention has been undertaken.	4
Antidiuretic therapy reduces nocturnal voiding frequency in men with baseline severity of ≥ two or more voids per night.	1b
There is an increased risk of hyponatremia in patients 65 years of age or older under antidiuretic therapy.	1b
Antidiuretic therapy increases duration of undisturbed sleep.	1b
α1-blocker use is associated with improvements in undisturbed sleep duration and nocturnal voiding frequency, which are generally of only marginal clinical significance.	2
Antimuscarinic medications can reduce night-time urinary urgency severity, but the reduction in overall nocturia frequency is small or non-significant.	2
Antimuscarinic medications are associated with higher incidence of dry mouth compared with placebo.	2
5α-reductase inhibitors reduce nocturia severity in men with baseline nocturia severity of ≥ two or more voids per night.	2
A trial of timed diuretic therapy may be offered to men with nocturia due to nocturnal polyuria. Screening for hyponatremia should be undertaken at baseline and during treatment.	1b

Recommendations	Strength rating
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	Weak
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia, and improve sleep quality.	Weak
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria.	Weak
Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong
Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS.	Weak
Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak
Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at six 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: history, IPSS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six 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 six 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: history, IPSS, uroflowmetry, and PVR volume. Frequency volume charts 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 twelve weeks and six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS, uroflowmetry and PVR volume. Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six 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 three and seven, one month after initiating therapy and periodically during treatment. If serum sodium concentration has remained normal during periodic screening follow-up screening can be carried out every three months subsequently. However, serum sodium concentration should be monitored more frequently in patients $\geq$ 65 years of age and in patients at increased risk of hyponatremia. The following tests are recommended at follow-up visits: serum-sodium concentration and FVC. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

Patients after prostate surgery should be reviewed four to six 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 four to six weeks: IPSS, uroflowmetry and PVR volume.

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

Recommendations	Strength rating
Follow up all patients who receive conservative, medical or surgical management.	Weak
Define follow-up intervals and examinations according to the specific treatment.	Weak

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8. 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: http://www.uroweb.org/guidelines/. 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.

9. CITATION INFORMATION

The format in which to cite the EAU Guidelines will vary depending on the style guide of the journal in which the citation appears. Accordingly, the number of authors or whether, for instance, to include the publisher, location, or an ISBN number may vary.

The compilation of the complete Guidelines should be referenced as:
EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam 2020. ISBN 978-94-92671-07-3.

If a publisher and/or location is required, include:
EAU Guidelines Office, Arnhem, The Netherlands. http://uroweb.org/guidelines/compilations-of-all-guidelines/

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