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). The term BPH is now regarded as inappropriate as it is Benign Prostatic Obstruction (BPO) that is treated if the obstruction is a significant cause of a man's LUTS. 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. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. All sections of the 2022 Male LUTS Guidelines have been fully updated.

2. METHODS

2.1 Introduction

For the 2022 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 (SRs) 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 May 1st 2019 and May 1st, 2021. A total of 2,853 unique records were identified, retrieved, and screened for relevance.

In addition, a new section, 5.6 Management of male urinary incontinence, has been added to the Guidelines. This topic was originally addressed in the now discontinued EAU Guidelines on Urinary Incontinence in Adults [1]. As with the overall Guidelines a broad and comprehensive literature search, limited to studies representing high levels of evidence and published in the English language was performed for this section. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame from May 2017, the previous update cut-off of the EAU Urinary Incontinence Guidelines and June 24th, 2021. A total of 1,054 unique records were identified, retrieved, and screened for relevance. Detailed search strategies are 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 [2, 3]. 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 [4];
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' [5]. 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. The newly added section on management of urinary incontinence in males was peer reviewed prior to the publication in 2022.

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 BPO, detrusor overactivity (DO)/overactive bladder (OAB), or nocturnal polyuria. Men with other associated factors relevant to 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, 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 [6], they are prevalent, cause bother and impair QoL [7-10]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [11]. Lower urinary tract symptoms are strongly associated with ageing [7, 8], associated costs and burden are therefore likely to increase with future demographic changes [8, 12]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [13]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [14].

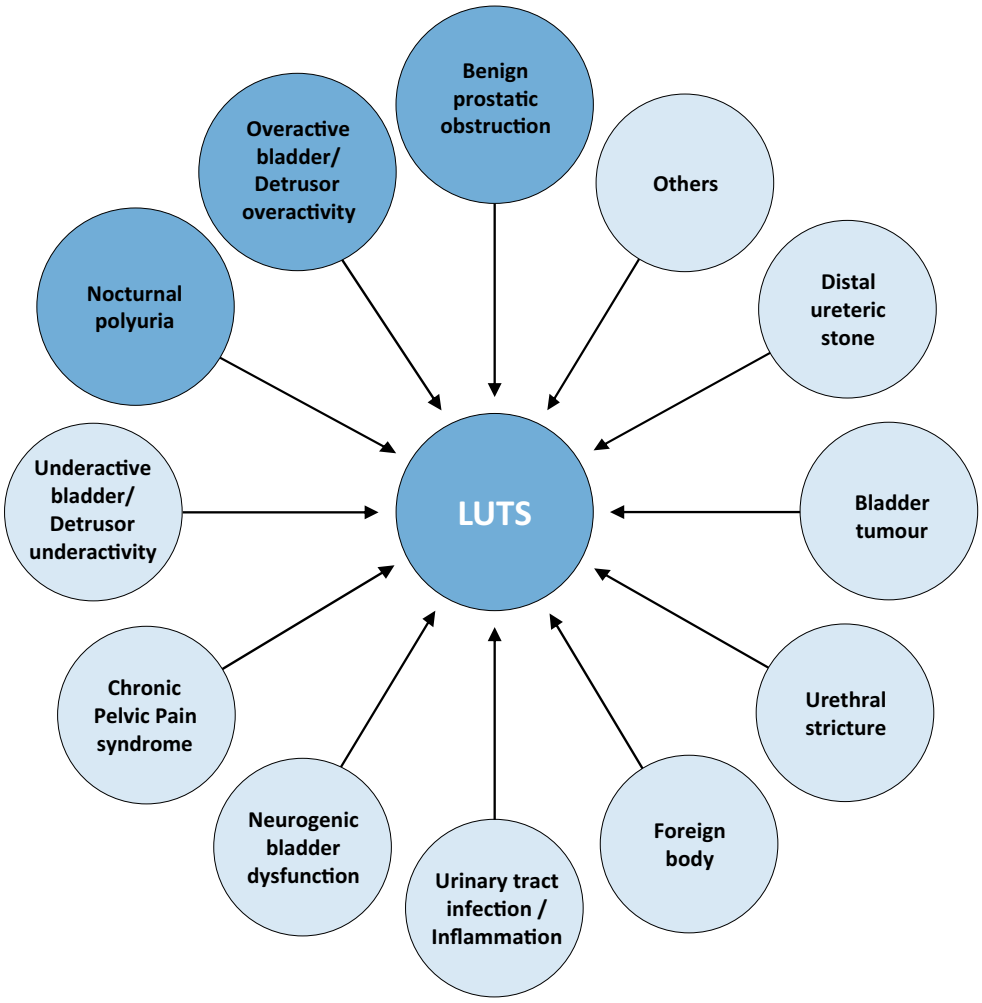
Most elderly men have at least one LUTS [8]; however, symptoms are often mild or not very bothersome [10, 11, 15]. Lower urinary tract symptoms can progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [8]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), most frequently when histological BPH progresses through benign prostatic enlargement (BPE) to BPO [6, 9]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [8, 16]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity (DU)/underactive bladder (UAB), as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [16]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [17, 18]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [8].

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 [6].
- 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 [6].
- 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 [6].
- Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [6]. 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 is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [6]. Detrusor overactivity is usually associated with OAB syndrome characterised by urinary urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [19].
- Detrusor underactivity during voiding is characterised by decreased detrusor voiding pressure leading to a reduced urine flow rate. Detrusor underactivity causes OAB syndrome which is characterised by voiding symptoms similar to those caused by BPO [20].

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 [21-23]. 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) [24, 25].

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. Bladder diaries or frequency volume charts (FVC) 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 of Erectile Function (IIEF) [26].

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 recommend using validated symptom score questionnaires [21, 23]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [27-33]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant; however, they are not disease-, gender-, or age-specific. A 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 [34].

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 [28]. 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 including incontinence questions and bother for each symptom [29]. 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 [32] is a symptom score used mainly in Denmark and Finland. The DAN-PSS also has questions on incontinence and measures 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-, gender-, 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 FVC. Inclusion of additional information such as fluid intake, use of pads, activities during recording, or which grades symptom severity and bladder sensation is termed a bladder diary [6]. 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 [35, 36]. The FVC/bladder diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [37-39]. The use of FVCs may cause a 'bladder training effect' and influence the frequency of nocturnal voids [40].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [41]. A SR of the available literature recommended FVCs should continue for three or more days [42]. The ICIQ-Bladder diary (ICIQ-BD) is the only diary that has undergone full validation [43].

Summary of evidence	LE
Frequency volume charts (FVC) 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 [44]. 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 [45]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [46]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50 mL [47].

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 [48-51].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [52, 53]. There is limited evidence, but general expert consensus suggests that the benefits outweigh the costs

[54]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [55].

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

*4.6.1 **Prostate-specific angtigen and the prediction of prostatic volume***

Pooled analysis of placebo-controlled trials of men with LUTS and presumed BPO showed that prostate-specific antigen (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 [56].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [57]. 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 [58, 59].

*4.6.2 **Prostate-specific angtigen and the probability of PCa***

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [60]. 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 **Prostate-specific angtigen and the prediction of BPO-related outcomes***

Serum PSA is a stronger predictor of prostate growth than prostate volume [61]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [62]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [63, 64]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPO-related surgery [65, 66]. 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 [67]. Patients with BPO seem to have a higher PSA level and larger prostate volumes. The PPV of PSA for the detection of BPO was recently shown to be 68% [68]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [69].

Summary of evidence	LE
Prostate-specific antigen (PSA) 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 BPO-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 [70]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [71].

One study reported that 11% of men with LUTS had renal insufficiency [70]. 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.,* [72] reported that non-neurogenic voiding

dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.,* [73] 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) [74]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [75]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [76]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [77].

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/DU [78, 79]. 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 [80]. 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 [65, 66].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [81]. 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 BPO-related invasive therapy in patients on α1-blockers or WW [82]. 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 [83, 84], 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% [85]. 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 [86], DU or an under-filled bladder [87]. 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 [88] 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

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 [73, 89-91]. Several arguments support the use of renal ultrasound (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, no radiation dose and less side effects [89]. 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 [89].

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 [91].

Transrectal US is superior to transabdominal volume measurement [92, 93]. 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. The evaluation of a prostatic middle lobe with urethrocystoscopy should be performed when considering interventional treatments for which the presence of middle lobe is a contraindication.

A prospective study evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [94]. 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 [95]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [96]. 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 [96].

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 (UDS) 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, DU) are defined by urodynamic investigation.

*4.12.1 **Diagnosing bladder outlet obstruction***

Pressure flow studies are used to diagnose and define the severity 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 DU, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [6].

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [97, 98]. In men with LUTS attributed to BPO, DO was present in 61% and independently associated with BOO grade and ageing [97].

The prevalence of DU in men with LUTS is 11-40% [99, 100]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [101, 102]. An RCT investigated whether urodynamics would reduce surgery without increasing urinary symptoms. The UPSTREAM study was a non-inferiority, RCT in men with bothersome LUTS, in whom surgery was an option, in 26 hospitals in England. From the 820 men, 153/408 (38%) were in the UDS arm and received surgery compared with 138/384 (36%) in the routine care (RC) arm. A total of 428 adverse events were recorded, with related events similar in both arms and eleven unrelated deaths. The UDS group was non-inferior to the RC group for IPSS, but UDS did not reduce surgical rates. The authors concluded that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively [103]. If urodynamic investigation is performed, a rigorous quality control is mandatory [104].

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 [105].

*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
Urodynamics is not a test for routine use prior to prostate surgery for all patients	3

Recommendations	Strength rating
Perform pressure-flow studies (PFS) only in individual patients for specific indications prior to invasive treatment or when further 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

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [106]. 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 [106].

Ultrasound measurement of intravesical prostatic protrusion (IPP) assesses the distance between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner, with 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% [107]. 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} [108]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter after AUR [109, 110]. However, no information with regards 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 [111].

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 [112]. 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 [113].

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 UDS, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [114]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [115]. 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 [116, 117]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [118].

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 [119] and interobserver agreement [120]. A nomogram has also been derived [121] whilst a method in which flow is not interrupted is also under investigation [122].

The data generated with the external condom method [123] correlates with invasive PFS in a high proportion of patients [124]. Resistive index [125] and prostatic urethral angle [126] 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 [127]. 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; DWT/BWT; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; and 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

4.14 Novel assessment

4.14.1 Visual prostate symptom score

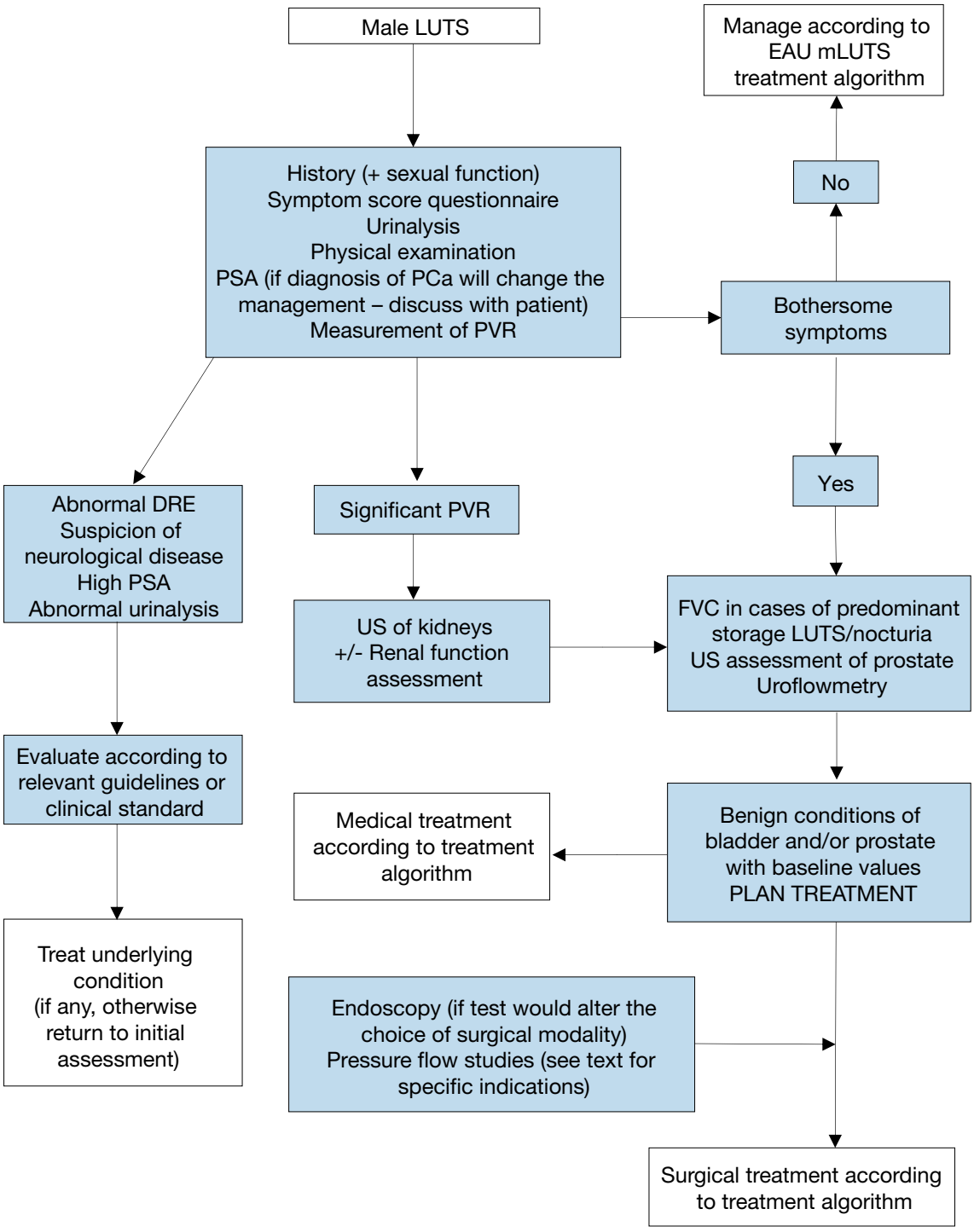
A novel visual prostate symptom score (VPSS) has been prospectively tested vs. the IPSS and correlated positively with the IPSS score [128, 129]. This visual score can be used as an option in men with limited literacy.

4.14.2 Micro-RNA

The use of miR-221 has been shown to have the potential to be used as a biomarker and novel target in the early diagnosis and therapy of BPH [130].

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

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) [131, 132], whilst others can remain stable for years [133]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [134].

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 [135, 136]. Increasing symptom bother and PVR volumes are the strongest predictors of WW 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 [133, 134, 137, 138] 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 OAB symptoms;
    - bladder retraining that encourages men to hold on when they have 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.

Evidence exists that self-management as part of WW reduces both symptoms and progression [137, 138]. Men randomised to three self-care 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 [137]. A SR and meta-analysis found reasonable certainty in estimates that self-management intervention significantly reduced symptom severity in terms of IPSS at six months compared with usual care [139]. The reduction in IPSS score with self-management was similar to that achieved with drug therapy at six to twelve weeks. Self-management had a smaller, additional benefit at six weeks when added to drug therapy [139].

5.1.3 Practical considerations

The components of self-care management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [140]. 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-care management as part of WW reduces both symptoms and progression.	1b
Self-management achieved a clinically meaningful reduction in symptom severity at six months compared to usual care. There was also a small but significant additional benefit of adding self-management to drug therapy.	1b

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

5.2 Pharmacological treatment

5.2.1 α1-Adrenoceptor antagonists (α1-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 [141]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [142], and treatment-associated improvement of LUTS correlates poorly with obstruction [143]. 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. Alpha 1-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 negligible.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [144]. Clinical effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [143].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, substantial improvements also occurred in the corresponding placebo arms [63, 145]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [63, 145]. 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 [146].

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 [65, 147-150]. The efficacy of α1-blockers is similar across age groups [145]. A pooled analysis of phase III and IV trials of silodosin 8 mg demonstrated that improvements in total, storage, voiding, and QoL IPSS scores were similar for the severe and not severe LUTS cohorts [151]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [148-150]; however, recent evidence suggests that the use of α1-blockers (alfuzosin and tamsulosin) may improve resolution of AUR [152]. 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 [153]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [154]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [155]. 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 [156].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [157]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [158]. 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 [159]. 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 [160]. 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**
Alpha 1-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 [161], 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). The 5-ARIs induce apoptosis of prostate epithelial cells [162] 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 [163]. 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 [65, 149, 150, 164-170]. An indirect comparison and one direct comparative trial (twelve months duration) indicated that dutasteride and finasteride are equally effective in the treatment of LUTS [163, 171]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [172]. 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 [173, 174]. 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 [149, 170, 175]. 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 [65, 168, 176]. 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 [168]. 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 [65]. A pooled analysis of three RCTs 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 [177]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPO-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [178, 179]. Furthermore, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [180, 181].

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 [65, 150, 163, 182]. 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 [183, 184]. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [185]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [185, 186]. In a British-Taiwanese population-based cohort study, the risk of type II diabetes was higher in men with 5-ARIs than in men receiving tamsulosin but did not differ between dutasteride and finasteride [187].

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 5-ARIs 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 (5-ARIs) 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 slow onset of action of 5-ARIs.	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 [188, 189]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [190, 191].

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 [192, 193].

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 [194]. 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 [195]. 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% [196].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [197-202]. 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 [194, 198, 203]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit [204]. 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 UUI episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after twelve to 25 weeks [199, 202]. 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 [201].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinics [205]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [202, 206]. In a small RCT propiverine improved frequency and urgency episodes [206].

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) [199]. 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 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) [207]. 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 [194].

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 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 **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 [208].

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 [209-213]. 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 compared with both placebo and tolterodine [214].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated or not associated with BPO confirmed by urodynamics [215]. 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 [216], 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 [217].

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 [218]. 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 [219]. 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 [220].

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [209-212]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 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 [221]. 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 [209]. 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 [222]. The overall change in PVR with mirabegron is small [222].

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 [223]. 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 [224]. The PILLAR phase IV study also showed that in a large population of 888 patients ≥ 65 years (approx. 30% of males), mirabegron 50 mg was safe and effective [225]. In an eighteen-week study of 3,527 patients (23% male), the incidence of adverse events was 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 [226].

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). There was no statistical difference between men and women [227].

The phase III EMPOWUR trial comparing vibegron to placebo and tolterodine showed once daily 75 mg vibegron provided statistically significant reductions in micturitions, urgency episodes and UUI [228]. Treatment was well tolerated with a favourable safety profile. However, the majority of the study population (85%) were female and vibegron is not yet licenced in Europe.

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. 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 storage LUTS, including urinary 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

*5.2.5 **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 [229]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [230]. Phosphodiesterase 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [231]. 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: Randomised controlled trials 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 [232]. A Cochrane review included a total of sixteen RCTs that examined the effects of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [233]. In the updated meta-analysis, PDE5Is led to a small reduction (mean difference (MD) 1.89 lower; 95% CI: 2.27 lower to 1.50 lower; n = 4293) in IPSS compared to placebo [233]. There was no difference between PDE5Is and α1-blockers in IPSS [234]. Most evidence was limited to short-term treatment up to twelve weeks. In other meta-analyses, PDE5Is were also found to improve IPSS and IIEF score, but not Q_{max} [235, 236]. A meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [235].

In a *post hoc* analysis of data pooled from four blinded trials of tadalafil 5 mg vs. placebo once daily, a minimum improvement of 25% in IPSS score was found in 60% in the tadalafil group vs. 44% in the placebo group [237]. The maximum trial duration was 52 weeks [238]. 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 [239]. In a *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. Among sexually active men > 45 years, tadalafil improved both LUTS/BPH and ED [239].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%) vs. indirect (7.5%) treatment effects via IIEF-EF improvement [240]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [241]. 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 [242]. An open label urodynamic study of 71 patients showed significant improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1), and resolution of DO in fifteen (38%) of 38 patients. Significant flow rate improved from 7.1 to 9.1 mL/s and mean IPSS from 18.2 to 13.4 [249].

A multicenter, double blind, placebo controlled RCT compared once daily tadalafil 20 mg vs. placebo during twelve weeks in men with LUTS with or without BOO. Urodynamic measures including detrusor pressure at maximum urinary flow rate, Q_{max}, maximum detrusor pressure, BOO or bladder capacity remained largely unchanged during the study with no statistically significant or clinically adverse event differences between tadalafil and placebo [243].

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 [235]. Both a SR and Cochrane review found similar findings [233, 244]. 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 a significant early improvement in urinary symptoms at four, twelve and 26 weeks as well as a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [245]. 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 [235].

Tadalafil is contraindicated in patients using nitrates or guanylate cyclase stimulators, such as riociguat, and in men with cardiac disease for whom sexual activity is inadvisable [246]. Tadalafil is also contraindicated in patients with myocardial infarction within the last 90 days, - patients with unstable angina or angina occurring during sexual intercourse, - patients with New York Heart Association Class 2 or greater heart failure in the last six months, - patients with uncontrolled arrhythmias, hypotension (< 90/50 mm Hg), or uncontrolled hypertension, - patients with a stroke within the last six months or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is [246]. Detailed information regarding tolerability/safety of all available PDE5Is for the treatment of ED in men treated with α-blockers for LUTS are provided by the EAU Guidelines on Sexual and Reproductive Health [247].

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one-year follow-up [238]; limiting conclusions about efficacy or tolerability greater than one year. There is limited information on reduction of prostate size and no data on disease progression.

Summary of evidence	LE
Phosphodiesterase 5 inhibitors significantly improve IPSS and IIEF score, but not Q_{max}.	1a

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

*5.2.6 **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) [248].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [248]. *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 [248-250]. 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 [251]. In addition, batches from the same producer may contain different concentrations of active ingredients [252]. 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 [253], 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 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.

The HPMC periodically invites all interested parties to submit any scientific data that the Committee should consider during their periodic review of the monographs. Table 1 lists the available EU monographs for herbal medicinal products and the current calls for update.

Table 1: European Union monographs for herbal medicinal products [254]

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [255]	Well established use	Symptomatic treatment of BPH	14/01/2016 Addendum 1/9/21**
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [255]	Traditional use	LUTS related to BPH*	14/01/2016 Addendum 1/9/21**
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [256]	Traditional use	LUTS related to BPH or related to an OAB*	25/03/2013 Call ended 30/4/21
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [257]	Traditional use	LUTS related to BPH*	01/09/2017 No call for update
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [258]	Traditional use	LUTS related to BPH*	05/11/2012 Call ended 30/6/21
Epilobium angustifolium L. and/or *Epilobium parviflorum Schreb., herba (Willow herb)* Preparation as defined in the monograph [259]	Traditional use	LUTS related to BPH*	13/01/2016 No call for update

** After serious conditions have been excluded by a medical doctor.*

*** Addendum concluded that no revision was needed.*

Panel interpretation: Only hexane extracted *Serenoa repens* (HESr) has been recommended for well-established use by the HMPC. Based on this a detailed scoping search covering the timeframe between the search cut-off date of the EU monograph and May 2021 was conducted for HESr.

A large meta-analysis of 30 RCTs with 5,222 men and follow-up ranging from four to 60 weeks, demonstrated no benefit of treatment with *S. repens* in comparison to placebo for the relief of LUTS [260]. It was concluded that *S. repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction; however, the similar improvement in IPSS or Q_{max} compared with finasteride or tamsulosin could be interpreted as treatment equivalence. Importantly, in the meta-analysis all different brands of *S. repens* were included regardless or not of the presence of HESr as the main ingredient in the extract.

Another SR focused on data from twelve RCTs on the efficacy and safety of HESr [261]. It was concluded that HESr was superior to placebo in terms of improvement of nocturia and Q_{max} in patients with enlarged prostates. Improvement in LUTS was similar to tamsulosin and short-term use of finasteride. An updated SR analysed fifteen RCTs and also included twelve observational studies. It confirmed the results of the previous SR on the efficacy of HESr [262]. Compared with placebo, HESr was associated with 0.64 (95% CI: 0.98 - 0.31) fewer voids/night and an additional mean increase in Q_{max} of 2.75 mL/s (95% CI: 0.57 - 4.93), both were significant. When compared with α-blockers, HESr showed similar improvements in IPSS (WMD 0.57, 95% CI: 0.27 - 1.42) and a comparable increase in Q_{max} when compared to tamsulosin (WMD 0.02; 95% CI: 0.71 - 0.66). Efficacy assessed using IPSS was similar after six months of treatment between HESr and 5-ARIs. Analysis of all available published data for HESr showed a mean significant improvement in IPSS from baseline of 5.73 points (95% CI: 6.91 - 4.54) [262].

A network meta-analysis tried to compare the clinical efficacy of *S. repens* (HESr and non-HESr) against placebo and α1-blockers in men with LUTS. Interestingly, only two RCTs on HESr were included in the analysis. It was found that *S. repens* achieved no clinically meaningful improvement against placebo or α1-blockers in short-term follow-up. However, *S. repens* showed a clinical benefit after a prolonged period of treatment, and HESr demonstrated a greater improvement than non-HESr in terms of IPSS [263].

With respect to safety and tolerability data from the SRs showed that HESr had a favourable safety profile with gastrointestinal disorders being the most frequent adverse effects (mean incidence 3.8%) while HESr had very limited impact on sexual function.

A cross-sectional study compared the combination of HESr with silodosin to silodosin monotherapy in patients treated for at least twelve months (mean duration 13.5 months) [264]. It was reported that 69.9% of the combination therapy patients achieved the predefined clinically meaningful improvement (improvement more than three points in baseline IPSS) compared to 30.1% of patients treated only with silodosin. In addition, a greater than 25% improvement in IPSS was found in 68.8% and 31.2% of the patients in the combination and the monotherapy groups, respectively. These data suggest that combination of a α1-blocker with HESr may result in greater clinically meaningful improvements in LUTS compared to α1-blocker monotherapy [264].

Practical considerations: Available RCTs do not use the same endpoints (e.g. IPSS). More studies on the use of HESr in combination with other pharmacotherapeutic agents for male LUTS are pending. There is a need to define the subpopulation of patients who will benefit most from therapy with HESr.

Summary of evidence	**LE**
Hexane extracted Serenoa repens improves Q_{max} and results in fewer voids/night [0.64 (95% CI: 0.98 to 0.31)] compared to placebo.	2
Hexane extracted Serenoa repens has a very limited negative impact on sexual function.	2

Recommendations	**Strength rating**
Offer hexane extracted *Serenoa repens* to men with LUTS who want to avoid any potential adverse events especially related to sexual function.	Weak
Inform the patient that the magnitude of efficacy of HESr may be modest.	Strong

*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 [165, 166, 265]. 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 [65].

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 [65, 149, 150].

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 [150]. 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 in an RCT and an open-label multicentre trial [266, 267]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [266], 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 [267]. 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) [65]. In addition, finasteride (alone or in combination), but not doxazosin alone, significantly reduced both the risks of AUR and the need

for BPO-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPO-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [268]. 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 [269]. 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 [270].

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 section 5.2.5 [245].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [65, 149, 150]. 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 [271]. 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 compared with each monotherapy [160].

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 who 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 of 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 to date.

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, 204, 268, 272-279]. Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [204, 279]. A SR showed that combination therapy of tolterodine and an α1-blocker was significantly more efficacious than either monotherapy for 24-hours and night voiding frequency, and 24-hours urgency episodes [204].

One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [280]. 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 [281].

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 [205].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, [268, 272, 278, 282, 283]. Two SRs of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [284, 285]. 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 [286]. 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 [287]. 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 [288]. 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 QoL compared with placebo and α1-blocker monotherapy [289].

The intake of fixed-dose combination tablet containing solifenacin 6 mg and tamsulosin 0.4 mg improved OAB-q symptom bother in > 80% of LUTS/BPH patients not adequately responding to monotherapy, with a high treatment persistence (77% at weeks 40 to 52), and a low risk of AUR [290]. Combined behavioural and drug therapy yielded greater improvements in OAB symptoms than drug therapy alone, but not behavioural therapy alone, in a RCT evaluating the effectiveness of combined behavioural strategies and drug therapy for OAB symptoms in men [291].

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 [201, 284, 292]. Antimuscarinics do not cause evident deterioration in Q_{max} used in conjunction with an α1-blocker in men with OAB symptoms [279, 293].

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 [294]. The combination therapy was non-inferior to placebo for the primary urodynamic variables; Q_{max} was increased vs. placebo [294].

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

5.2.7.3 α1-blockers + Beta-3 agonist

Mechanism of action: Combination therapy consists of an α1-blocker (Section 5.2.1) together with a beta-3 agonist (Section 5.2.4) as an add-on therapy in males receiving α1-blockers with persisting OAB symptoms.

Efficacy: The MATCH study explored the effect of the addition of mirabegron 50 mg to tamsulosin 0.2 mg compared to tamsulosin plus placebo in 544 patients [295]. A statistically significant difference of 0.52 voids per day was seen in favour of mirabegron. Total IPSS score also improved, but was not significant between the groups. Another RCT evaluated add-on therapy with mirabegron for OAB symptoms persisting after treatment with tamsulosin 0.2 mg daily in men with BPO [296]. Combination therapy was associated with greater improvements in OAB symptom score, in urinary urgency and daytime frequency as well as the storage sub-score of IPSS and QoL index compared to monotherapy with tamsulosin [297].

The PLUS phase IV trial [296] compared mirabegron and placebo in a population of males treated with a standard dose of tamsulosin 0.4 mg. After a four-week run-in period of treatment with tamsulosin 0.4 mg alone, 715 patients were randomised between placebo and mirabegron 25 mg, upgraded to 50 mg after one month. While mean number of micturition's were significantly reduced in the experimental arm, the effect size was deemed as low (mean adjusted difference of 0.39 voids per day). Similar results were seen for mean voided volume and urgency episodes, but total IPSS, IPSS sub-scores and OAB-q symptom score were not significantly different between the groups.

A RCT comparing the efficacy of mirabegron 50 mg or fesoterodine 4 mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms reported that at three months, fesoterodine add-on therapy showed a significantly greater improvement than mirabegron add-on therapy in OAB symptom score and urgency score and IPSS-QoL score [218]. Fesoterodine was also superior in alleviating DO.

Tolerability and safety: In the MATCH study main adverse events were in line with previous trials, and cardiovascular events were uncommon in the studied populations [295]. The PLUS phase IV trial also reported adverse events similar to those seen in previous trials (hypertension, headache and nasopharyngitis being the most frequent) [296]. There were six episodes of retention recorded (1.7%) and overall, no clinically significant specific change was seen in Q_{max} and PVR. An open-label, randomised, 2-arm, 2-sequence study reported that the addition of mirabegron or tamsulosin to patients under tamsulosin or mirabegron monotherapy did not cause clinically relevant changes in cardiovascular safety or safety profiles [298].

Solifenacin and mirabegron were also compared in another RCT that has shown comparable efficacy but a better safety profile for mirabegron [299].

Practical considerations: Add-on therapy with mirabegron in patients with remaining symptoms under α1-blocker therapy has been evaluated only in short-term clinical trials. The short-term benefit remains uncertain with a low effect size in urinary frequency compared to placebo, and more studies with longer follow-up are required.

Summary of evidence	LE
Combination treatment with α1-blockers and mirabegron results in a slight decrease of number of voids and urgency episodes per day compared with α1-blockers alone.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and mirabegron.	1b

Recommendations	Strength rating
Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy.	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

Surgical treatment is one of the cornerstones of LUTS/BPO management. Based on its ubiquitous availability, as well as its efficacy, M-TURP has long been considered as the reference technique for the surgical management of LUTS/BPO. However, in recent years various techniques have been developed with the aim of providing a safe and effective alternative to M-TURP. Previously, the surgical section of the Guidelines was based on technology rather than surgical approach. As the clinical reality is primarily reflected by surgical approach and not necessarily by a specific technology, the chapter on surgical management has been restructured. It is now divided into the following five sections:

1. Resection;
2. Enucleation;
3. Vaporisation;
4. Alternative ablative techniques; and
5. Non-ablative techniques.

In addition, most of the studies are restricted by prostate size, which is also reflected in the present Guidelines. Notably, only a small fraction of RCTs are performed in patients with a prostate > 80 mL; therefore, high-level evidence for larger prostates are limited.

Based on Panel consensus, timeframes defining short-, mid- and long-term follow-up of patients submitted to surgical treatments are twelve, 36, and over 36 months, respectively. The durability of a technique is reflected by the re-operation rate during follow-up, the failure to wean patients off medication as well as the initiation of novel LUTS medication after surgery. However, for the majority of techniques only the re-operation rate is reported, and clinicians should inform patients that long-term surgical RCTs are often lacking. Some patients value sexual function and perceived higher safety over maximum efficacy and it is not therefore surprising that some patients consciously choose an alternative ablative or non-ablative technique despite the knowledge that it might not be their definitive treatment. In contrast, many urologists are critical about these procedures due to their inferior relief of BOO.

Recommendations on new devices or interventions will only be included in the Guidelines once supported by a minimum level of evidence. To clarify this the Panel have published their position on certainty of evidence (CoE) [300]. In summary, a device or technology is only included once supported by RCTs looking at both efficacy and safety, with adequate follow-up, and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [300]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include proof of concept, RCTs on efficacy and safety, as well as cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [300]. The panel assesses 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 addition, the Guidelines continues to include techniques under investigation. These are devices or technologies that have shown promising results in initial studies; however, they do not meet the aforementioned criteria yet to provide a CoE which allows the Panel to regard these devices or technologies as recommended alternatives. To account for evolving evidence, recommendations for some techniques under investigation have been made; however, these techniques remain under investigation until further studies provide the recommended CoE.

*5.3.1 **Resection of the prostate***

5.3.1.1 Monopolar and bipolar transurethral resection of the prostate

Mechanism of action: Transurethral resection of the prostate (TURP) is performed using two techniques: monopolar TURP (M-TURP) and bipolar TURP (B-TURP). Monopolar transurethral resection of the prostate removes tissue from the transition zone of the gland. Bipolar TURP addresses a major limitation of M-TURP by allowing performance in normal saline. Prostatic tissue removal is identical to M-TURP. 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). The various bipolar devices available differ in the way in which current flow is delivered [301, 302].

Efficacy: In a meta-analysis of twenty 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%) [303]. 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 [304]. 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 [102]. A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A SR analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [305]. 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%, respectively [306, 307].

Bipolar TURP is the most widely investigated alternative to M-TURP. Pooled results from 59 RCTs have been reported to date [308]. Early pooled results as well as at twelve months, concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL score and Q_{max}) [308, 309]. Subsequent meta-analyses supported these conclusions though trial quality was generally poor [303, 310-313]. The largest meta-analysis published to date, confirmed that B-TURP compared to M-TURP results in little to no difference in urological symptoms and bother (IPSS and QoL score) at twelve months [308]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [314-322]. A meta-analysis of RCTs comparing B-TURP vs. M-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [323].

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, and it was concluded that TURis was of equivalent efficacy to M-TURP [324].

Tolerability and safety: Peri-operative mortality and morbidity of M-TURP have decreased over time, but morbidity remains considerable (0.1% and 11.1%, respectively) [325]. 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 [306, 307].

The risk of TUR-syndrome decreased to < 1.1% [305, 326]. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% [325]. Short- to mid-term complications reported in an analysis of RCTs using M-TURP as a comparator were: 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%) [303]. Long-term complications of M-TURP comprise urinary incontinence (UI), urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [305].

Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable to M-TURP 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) [309]. Subsequent meta-analyses supported these conclusions [303, 310-313, 323]; however, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [309]. The largest meta-analysis published to date, concluded that B-TURP compared to M-TURP reduced TUR syndrome and blood transfusion events by twenty and 28 fewer events per 1000 participants, respectively [308]. The study also concluded that B-TURP may carry a similar risk of UI and may result in similar rates of re-TURP in the short-term (four fewer events and one more re-TURP per 1000 participants, respectively) compared to M-TURP [308]. 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 [313]. It was concluded that TURis is associated with improved peri-operative safety, eliminating the risk of TUR syndrome, reducing the risk of blood transfusion/clot retention and hospital stay. 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 between M-TURP and B-TURP in urethral stricture/BNC rates [314-322], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [321, 327]. 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 [321]. 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 at twelve months follow-up [327].

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 [328, 329]. 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) [329, 330]. Furthermore, the largest meta-analysis published to date, showed that erectile function measured by IIEF-5 appears to be similar at twelve months follow-up after B-TURP and M-TURP [308].

A comparative study [331] evaluated the safety of B-TURP in patients taking therapeutic oral anticoagulation (phenprocoumon) or anti-platelet drug therapy (acetylsalicylic acid or clopidogrel), without stopping or bridging the medication. Outcomes under acetylsalicylic acid were comparable to the unmedicated control group. Under oral anticoagulation therapy catheterisation (median 41-hours vs. 24-hours) and hospitalisation time was longer (median four days vs. three days), AUR rate was higher (18% vs. 6%), but blood transfusion rates did not differ to the control group. Under anti-platelet therapy blood transfusion (19% vs. 1%) and re-hospitalisation rates (19% vs. 3%) were higher.

Practical considerations: Monopolar-TURP is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (30-80 mL suitable for M-TURP). No studies on the optimal cut-off value exist, but the complication rates increase with prostate size [325]. The upper limit for M-TURP is suggested as 80 mL (based on Panel consensus, 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 [332].

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 [314-322]. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Summary of evidence	**LE**
Bipolar- or 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.	1a
Bipolar-TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable peri-operative safety profile.	1a

Recommendation	**Strength rating**
Offer bipolar- or monopolar-transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL.	Strong

5.3.1.2 Holmium laser resection of the prostate

With the advent of holmium laser enucleation of the prostate (section 5.3.2.3) and the fact that no relevant publications on holmium laser resection of the prostate (HoLRP) have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.1.3 Thulium:yttrium-aluminium-garnet laser (Tm:YAG) vaporesection of the prostate

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 [333]. Different applications such as vaporesection (ThuVARP) have been published [334].

Efficacy: Several meta-analyses with pooled data from both RCTs and non-RCTs have evaluated ThuVARP vs. M-TURP [335-337], and B-TURP [338-340]. The largest meta-analyses included nine RCTs and seven non-RCTs and reported no clinically relevant differences in efficacy (IPSS, QoL score and Q_{max}) between ThuVARP and M-TURP or B-TURP at twelve months [339]. A multicentre, RCT with 410 men reported that ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up [341]. The beneficial effect of TURP in terms of Q_{max} was strengthened in men aged < 70 years and in those diagnosed with LUTS rather than urinary retention. No differences in individual patient-reported urinary symptoms were seen between arms, with the exception of some evidence to indicate potential reduction in nocturia in the TURP arm. Data from one RCT with long-term follow-up showed no difference in efficacy and re-operation rates between ThuVARP and M-TURP (2.1% vs. 4.1%, respectively) [342]. 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 [343].

Tolerability and safety: In a number of meta-analyses longer operation times, shorter catheterisation/hospitalisation times and less blood loss without significant differences in transfusion rates or in any other short-term complication rates have been reported for ThuVARP compared to TURP [335-340]. A significantly higher transfusion rate was reported after M-TURP in two meta-analyses [337, 339]. However, overall RCT quality was relatively low with limited follow-up potentially accounting for under-reporting of late complications,

such as urethral stricture/BNC [339]. A multicentre RCT with 410 men, followed up for twelve months reported that ThuVARP and TURP show similar operation, catheterisation, and hospitalisation times between arms with no difference in the frequency or severity of surgical complications or in blood transfusions rate or haemoglobin change [341, 344]. Patients with urinary retention had similarly positive outcomes to those with LUTS [341, 344]. Data from three RCTs with mid- to long-term follow-up (18 to 48 months) showed no differences in late complication rates between ThuVARP and TURP (BNC: 0.0%-2.1% vs. 0.0%-4.1%; stricture: 0.0%-2.2% vs. 0.0%-2.2%, respectively) [342, 345, 346].

Haemoglobin drop was significantly higher in the bridging group in a retrospectively analysed case series of 103 patients who underwent ThuVARP and received either low molecular weight heparin bridging or continued antiplatelet/anticoagulant therapy [347].

Practical considerations: As a limited number of RCTs with mid- to long-term follow-up support the efficacy of ThuVARP, there is a need for ongoing investigation of the technique.

Summary of evidence	**LE**
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) has similar operation, catheterisation and hospitalisation times compared to TURP. ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at twelve months follow-up. ThuVARP and TURP show similar short-term safety. Mid- to long-term results on efficacy and safety compared to TURP are very limited.	1b

Recommendation	**Strength rating**
Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to TURP.	Weak

5.3.1.4 Transurethral incision of the prostate

Mechanism of action: Transurethral incision of the prostate (TUIP) involves incising the bladder outlet without tissue removal. Transurethral incision of the prostate is conventionally performed with Collins knife using monopolar electrocautery; however, alternative energy sources such as holmium laser may be used [348]. This technique may replace M-TURP in selected cases, especially in prostate sizes < 30 mL without a middle lobe.

Efficacy: An RCT comparing conventional TUIP vs. TUIP using holmium laser in prostates ≤ 30 mL with a follow-up of twelve months, found both procedures to be equally effective in relieving BOO with similarly low re-operation rates [348]. A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [349]. 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 meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after M-TURP (7.2%) [349].

Tolerability and safety: An RCT comparing conventional TUIP vs. TUIP using holmium laser reported both procedures to be safe with low complication rates; however, the operation time and retrograde ejaculation rate was significantly lower in the conventional TUIP arm [348]. No cases of TUR-syndrome have been recorded after TUIP. The risk of bleeding after TUIP is small [349].

Practical considerations: Transurethral incision of the prostate is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice between M-TURP and TUIP should be based primarily on prostate volume (< 30 mL TUIP) [349].

Summary of evidence	**LE**
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.	1a
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.	1a
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

Recommendation	**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

5.3.2 ***Enucleation of the prostate***

5.3.2.1 *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%. Efficacy is maintained for up to six years [350-355]. Data from an Austrian nationwide study of 1,286 men submitted to OP showed that 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 [9].

Two meta-analyses [356, 357] evaluated the overall efficacy of OP performed via a transvesical approach vs. two transurethral enucleation techniques for treating patients with large glands, namely bipolar transurethral enucleation of the prostate (B-TUEP) and holmium laser enucleation of the prostate (HoLEP). The larger study included nine RCTs involving 758 patients [357]. Five RCTs compared OP with B-TUEP [355, 358-361] and four RCTs compared OP with HoLEP [350, 351, 362, 363]. At three, six, twelve and 24-months follow-up there were no significant differences in Q_{max} [357]. Post-void residual, PSA, IPSS and QoL score showed no significant differences at one-, three-, six- and twelve-months follow-up [357]. Randomised controlled trials indicate that OP is as effective as HoLEP for improving micturition in large prostates [350, 351], with similar improvement regarding Q_{max}, IPSS score and re-operation rates after five years [350].

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [354]. Data from an Austrian nationwide study of 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days [307]. The estimated transfusion rate is about 7-14% [350, 353, 354, 356]. Long-term complications include transient UI (up to 10%), BNC and urethral stricture (about 6%) [350-352, 356, 364].

Two meta-analyses evaluated the overall safety of OP performed via a transvesical approach vs. B-TUEP and HoLEP [356, 357]. Operation time did not differ significantly between OP and B-TUEP but was significantly shorter for OP compared to HoLEP. Catheterisation and hospitalisation time were significantly longer for OP, which was also associated with more blood transfusions. There were no significant differences regarding other complications. There was no significant difference in IIEF-5 at three, six, twelve and 24-months follow-up.

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 and with appropriate patient consent, OP is a reasonable 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
Open prostatectomy shows similar short- and mid-term efficacy to B-TUEP and HoLEP for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1a
Open prostatectomy has a less favourable peri-operative safety profile compared to B-TUEP and HoLEP.	1a
The long-term functional results of OP are comparable to HoLEP.	1b

Recommendation	**Strength rating**
Offer open prostatectomy in the absence of bipolar transurethral enucleation of the prostate and holmium laser enucleation of the prostate to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	Strong

5.3.2.2 *Bipolar transurethral enucleation of the prostate)*

Mechanism of action: Following the principles of bipolar technology (section 5.3.1.1), the obstructive adenoma is enucleated endoscopically by the transurethral approach. Bipolar-transurethral enucleation of the prostate (B-TUEP) evolved from plasmakinetic (PK) B-TURP and was introduced by Gyrus ACMI. The technique, also referred to as PK enucleation of the prostate (PKEP), utilises a bipolar high-frequency generator and

a variety of detaching instruments, for this true bipolar system, including a point source in the form of a axipolar cystoscope electrode suitable for enucleation [365] or a resectoscope tip/resection loop [366, 367]. More recently, a novel form of B-TUEP has been described, bipolar plasma enucleation of the prostate (BPEP), stemming from B-TURP (TURis, Olympus Medical), that utilises a bipolar high frequency generator and a variety of detaching instruments including a mushroom- or button-like vapo-electrode [361, 368] and a Plasmasect enucleation electrode [369] for this quasi-bipolar system. Bipolar transurethral enucleation of the prostate is followed by either morcellation [361, 365] or resection [366-368, 370-372] of the enucleated adenoma.

Efficacy: One RCT evaluating PKEP vs. M-TURP in 204 patients with mean prostate volume < 80 mL reported a significant improvement in IPSS, QoL score, and Q_{max}, with urodynamically proven de-obstruction favouring PKEP at 36 months follow-up [367]. The RCT concluded that the mid-term clinical efficacy of PKEP was comparable to M-TURP [367]. One RCT evaluating PKEP vs. B-TURP in patients with prostate volume > 80 mL reported no clinically relevant differences in IPSS, QoL score, and Q_{max}, at six months follow up [373]. Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported not clinically relevant differences in IPSS, QoL score, Q_{max} and PVR at 24 months follow-up [374]. Two meta-analyses, reported similar efficacy at twelve months in terms of IPSS, QoL score and Q_{max} for B-TUEP (PKEP or BPEP) vs. B-TURP [375, 376]. Another meta-analysis evaluating B-TUEP vs. B-TURP, reported similar efficacy at 36 months in terms of IPSS, and Q_{max} [323]. Two RCTs evaluated the mid-term efficacy of PKEP vs. B-TURP at 36 months [366, 371] and one RCT evaluated long-term efficacy at 60 months [372]. Efficacy was significantly better for PKEP in patients with large prostates at 36, 48 and 60 months [366, 372]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Tolerability and safety: An RCT evaluating PKEP vs. M-TURP in patients with prostate volume < 80 mL and 36-month follow-up reported that PKEP is superior to M-TURP in terms of haemoglobin drop, irrigation, catheterisation, and hospitalisation time [367]. No significant differences between the arms were reported in operation time, blood transfusion rates, sexual function, or any other reported complications (TUR-syndrome, clot retention, incontinence, retrograde ejaculation, urethral structures/BNC) [367]. One RCT evaluating PKEP vs. B-TURP in patients' prostate volume > 80 mL and six months follow-up reported that PKEP is superior to B-TURP in terms of operation, irrigation, catheterisation, hospitalisation time and haemoglobin drop [373]. Significant differences were reported in blood transfusion, BNC and retrograde ejaculation rates favouring PKEP, but no differences in urethral stricture and ED rates were reported [373]. Another RCT evaluating BPEP vs. B-TURP in patients with prostate volume > 80 mL reported that BPEP had longer operative time but shorter irrigation, catheterisation, hospitalisation time and lower haemoglobin drop with no differences in blood transfusion, urethral stricture and UI rates at 24 months follow-up [374]. A meta-analysis evaluating PKEP vs. TURP reported that mid-term IIEF-5 scores were comparable [377]. Another meta-analysis reported less bleeding with B-TUEP compared to M-TURP but similar UI rates and AUR after catheter removal [323]. Two meta-analyses evaluating B-TUEP vs. B-TURP reported similar operation, catheterisation and hospitalisation times; lower acute urine retention rates; significantly reduced haemoglobin drop and blood transfusion rates; no difference in erectile function; and no difference in all other reported complication rates including urethral stricture/BNC rates for B-TUEP at 24 months follow-up [375, 376]. No difference in urethral stricture/BNC rates was reported at 60 months follow-up [372]. Comparative data on efficacy for B-TUEP vs. OP and the various forms of laser enucleation are presented in section 5.3.2.1 – 5.3.2.5, respectively.

Summary of evidence	**LE**
Bipolar transurethral (plasmakinetic) enucleation of the prostate shows favourable mid- to long-term efficacy compared to TURP.	1b
Bipolar transurethral (plasmakinetic) enucleation of the prostate has a favourable peri-operative safety profile and demonstrates similar mid- to long-term safety compared to TURP.	1b

Recommendation	**Strength rating**
Offer bipolar transurethral (plasmakinetic) enucleation of the prostate to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate.	Weak

5.3.2.3 Holmium laser enucleation 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 [378].

Efficacy: An initial meta-analysis reported no significant differences in short-term efficacy (Q_{max}) and re-intervention rates (4.3% vs. 8.8%) between HoLEP and M-TURP [379]; however, subsequent meta-analyses reported favourable short-term efficacy (Q_{max} and IPSS) for HoLEP [303, 336, 375, 380]. Another meta-analysis reported similar efficacy at 24 months in terms of IPSS, and Q_{max} [323]. Three meta-analyses evaluating HoLEP vs. B-TURP showed no significant differences in short-term efficacy (IPSS, QoL score and Q_{max}) [323, 375, 381]. One RCT comparing HoLEP with M-TURP in a small number of patients with mean prostate volume < 80 mL and a seven year follow-up found that the functional long-term results were comparable [382]. One RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 24 months [383]. Long-term (72 months) improvement in IPSS and Q_{max} was better for HoLEP, but there were no clinically relevant differences between the arms [384]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported no significant difference in IPSS, QoL score and Q_{max} at 36 months, however, the overall re-treatment rate was significantly lower following HoLEP with less patients restarting α-blockers and less re-operations [385]. Comparative efficacy data for HoLEP vs. OP is presented in section 5.3.2.1. One small RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported similar improvements in IPSS and Q_{max} as well as similar re-operation rates at twelve months follow-up [365]. An RCT comparing HoLEP vs. bipolar EEP reported no significant difference in IPSS, QoL score, PVR, and Q_{max} at one, three-, and twelve-months follow-up [386].

Tolerability and safety: Data from a large national database on peri-operative outcomes of 2,869 laser enucleation of the prostate and 37,577 TURP procedures supports that laser enucleation of the prostate is associated with longer operation times, shorter hospitalisation times, similar complication rates (including transfusions, and re-operations), but lower rates of infectious complications [387]. Several meta-analyses found that HoLEP has longer operation times, shorter catheterisation and hospitalisation times, reduced blood loss, fewer blood transfusions but no significant differences in urethral strictures (2.6% vs. 4.4%) and stress urinary incontinence (SUI) (1.5% vs. 1.5%) rates compared to M-TURP [336, 375, 379, 380, 388]. Another meta-analysis reported that HoLEP has shorter catheterisation times, lower haemoglobin drops, fewer blood transfusions, urethral strictures and UTIs but no significant differences in clot retention rates and AUR after catheter removal compared to M-TURP [323]. Three meta-analyses evaluated HoLEP vs. B-TURP [375, 381, 389]. One, reported longer operation times for HoLEP, but no significant differences in hospitalisation time or complication rates [375] whilst another reported no significant differences in operation and catheterisation times or short-term complication rates [381]. A SR reported that HoLEP has lower AUR rates after catheter removal but similar haemoglobin drop, UTI, urethral stricture, and UI rates [323]. A RCT comparing HoLEP with B-TURP in patients with prostate volume < 80 mL reported longer operation time, shorter catheterisation and hospitalisation times and a lower risk for haemorrhage for HoLEP with no significant differences in blood transfusion rates or other complication rates at 24 months [383]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80 mL reported shorter operation, catheterisation and hospitalisation times and lower blood transfusion rates for HoLEP but no differences in complication rates including UI and IIEF-5 score at 36 months [385]. Comparative data on safety of HoLEP vs. OP are presented in section 5.3.2.1. One small RCT evaluating HoLEP vs. PKEP in patients with mean prostate volume < 80 mL reported significantly shorter operation times for HoLEP, but similar catheterisation and hospitalisation times and complication rates at twelve months follow-up [365]. An RCT comparing HoLEP vs. bipolar B-TUEP demonstrated shorter operation and hospitalisation times and earlier catheter removal for HoLEP [386].

An RCT of pulse modulation in HoLEP (Virtual basket) demonstrated significantly less haemoglobin drop and reduced operation times when compared to conventional HoLEP [390].

Holmium laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications [391, 392]. 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 antiplatelet and anticoagulant therapy.

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP [393, 394]. 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 [395]. Attempts to maintain ejaculatory function with HoLEP have been reported to be successful in up to 46.2% of patients [396].

A meta-analysis of seven RCTs evaluating HoLEP vs. TURP reported that short- and mid-term IIEF-5 scores were comparable, whilst long-term scores were significantly better for HoLEP [397]. Two other meta-analyses detected no difference in mid-term retrograde ejaculation rates [398].

An RCT comparing HoLEP vs B-TUEP, reported shorter operation and hospitalisation times and earlier catheter removal for HoLEP [386].

Practical considerations: Holmium laser enucleation of the prostate requires experience and relevant endoscopic skills. The experience of the surgeon is the most important factor affecting the overall occurrence of complications [399, 400]. Mentorship programmes are advised to improve surgical performance from both an institutional and personal learning curve perspective [401-403].

Summary of evidence	LE
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar mid- to long-term efficacy when compared to TURP.	1b
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates similar short-term safety when compared to TURP.	1a
Laser enucleation of the prostate using Ho:YAG laser (HoLEP) demonstrates longer operation times, but a more favourable peri-operative profile when compared to TURP.	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

5.3.2.4 Thulium:yttrium-aluminium-garnet laser (Tm:YAG) enucleation of the prostate

Mechanism of action: The Tm:YAG laser has been described in section 5.3.1.3. Enucleation using the Tm:YAG laser includes ThuVEP (vapoenucleation i.e. excising technique) and ThuLEP (blunt enucleation).

Efficacy: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported no clinically relevant differences in short-term efficacy (Q_{max}, IPSS and QoL score) [323, 375]. An RCT with five years follow-up comparing ThuLEP with B-TURP found no difference between the two procedures for Q_{max}, IPSS, PVR, and QoL [404]. A meta-analysis [405] evaluating ThuLEP vs. HoLEP showed no clinically relevant differences in IPSS, QoL score and Q_{max} at twelve months in accordance with one RCT showing similar results at eighteen months [406]. Furthermore, ThuLEP and PKEP were compared in one RCT with twelve months follow-up the outcome of which showed no difference with regard to efficacy [407]. There are mainly prospective case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [408-411]. A cohort study with median follow-up of 36.5 months reported improved Q_{max} (19.1 vs. 7.75 mL/s), PVR (31.9 vs. 150 mL), IPSS (4.5 vs. 24), and QoL scores (1 vs. 5), with a PSA reduction of 86.5% [412].

Tolerability and safety: Two meta-analyses evaluating ThuLEP vs. M-TURP and B-TURP reported a longer operation time and shorter catheterisation time for ThuLEP compared to M-TURP and a shorter hospitalisation time for ThuLEP compared to B-TURP [323, 375]. Lower blood transfusion rates compared to M-TURP, lower clot retention rates compared to B-TURP, and no difference in the other complication rates were also reported for ThuLEP [323, 375]. An RCT comparing ThuLEP with B-TURP reported a significant difference in IIEF-5 score favouring ThuLEP at twelve months [413]. A meta-analysis evaluating ThuLEP vs. HoLEP showed significantly lower haemoglobin drop for ThuLEP [405]. Transient UI was more common for HoLEP. Intra-operatively ThuLEP showed shorter operation times when compared to HoLEP [375] and a multicenter RCT demonstrated lower haemoglobin loss for ThuLEP compared to HoLEP [390].

Another meta-analysis [414] evaluating ThuLEP vs. HoLEP showed a significant difference is enucleation time favouring ThuLEP, but no significant differences in operation, catheterisation and hospitalisation times and short-term complication rates. These results were in accordance with one RCT showing similar results, including no urethral and bladder neck strictures, at eighteen months [406]. ThuLEP and PKEP were compared in one RCT with twelve months follow-up [407]. No significant difference in complication rates was detected, but haemoglobin level decrease and catheterisation time was significantly lower for ThuLEP.

In comparative studies ThuVEP shows high intra-operative safety [415], also in case series of patients with large prostates [408] and anticoagulation or bleeding disorders [409, 410]. In a cohort study on ThuVEP, UTIs occurred in two patients, urethral stricture and BNC developed in one patient each, respectively and one patient was treated for recurrent adenoma of the prostate [412]. 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 [416]. 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% [410]. Two studies addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [417, 418].

Practical considerations: ThuLEP seems to offer similar efficacy and safety when compared to TURP, bipolar enucleation and HoLEP; whereas, ThuVEP is not supported by RCTs. Based on the limited number of RCTs there is a need for ongoing investigation of these techniques.

Summary of evidence	LE
Enucleation of the prostate using the Tm:YAG laser demonstrates similar efficacy when compared to M-TURP/bipolar transurethral (plasmakinetic) enucleation, HoLEP and B-TURP in the short-, mid-, and long-term, respectively.	1b
Enucleation of the prostate using the Tm:YAG laser (ThuLEP) demonstrates similar safety compared to TURP/bipolar transurethral (plasmakinetic) enucleation, and HoLEP in the short- and mid-term, respectively.	1b
Vapoenucleation of the prostate using a Tm:YAG laser (ThuVEP) seems to be safe in patients with large prostates and those receiving anticoagulant or antiplatelet therapy.	2b

Recommendations	Strength rating
Offer enucleation of the prostate using the Tm:YAG laser (ThuLEP, ThuVEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate, holmium laser enucleation or bipolar transurethral (plasmakinetic) enucleation.	Weak
Offer Tm:YAG laser enucleation of the prostate to patients receiving anticoagulant or antiplatelet therapy.	Weak

5.3.2.5 Diode laser enucleation of the prostate (DiLEP)

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: One small RCT comparing 1,318 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL reported no significant differences in IPSS, QoL score, Q_{max} and PVR at six months follow-up [419]. Another RCT comparing 1,470 nm DiLEP with B-TURP in 157 patients with mean prostate volume < 80 mL also reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up [420]. In addition, three RCTs comparing 980 nm DiLEP with PKEP in patients with mean prostate volume < 80 mL [421, 422] and > 80 mL [423] reported no significant differences in IPSS, QoL score, Q_{max} and PVR at twelve months follow-up. An RCT of DilEP (980 nm) vs. HoLEP detected no significant difference in Q_{max}, PVR, IPSS, and QoL at three, six and twelve months follow-up [424].

Tolerability and safety: One small RCT comparing 1,318 nm DiLEP with B-TURP in patients with mean prostate volume < 80 mL and six months follow-up reported a significantly longer operation time for DiLEP, but shorter catheterisation and hospitalisation times, as well as less blood loss (without differences in blood transfusion rates) [419]. No differences in complication rates were reported between the two arms [419]. Another RCT comparing 1,470 nm DiLEP with B-TURP in 157 patients with prostate volume < 80 mL and twelve months follow-up reported significantly shorter operation, catheterisation, and hospitalisation times with less blood loss (without differences in blood transfusion rates) for DiLEP, with no differences in complication rates between the two arms [420]. Three RCTs comparing 980 nm DiLEP with PKEP in patients with prostate volume < 80 mL [421, 422] and > 80 mL [423] and twelve months follow-up reported conflicting peri-operative outcomes: operation time (no difference between arms [421], significanly shorter for DiLEP [422] or sgnificanly longer for DiLEP [423]); catheterisation time (no difference between the two arms [421], significanly shorter for DiLEP [422, 423]); hospitalisation time (no difference between arms [421, 422], significanly shorter for DiLEP [423]); blood loss (no difference in haemoglobin drop between arms [421], significantly lower haemoglobin drop for DiLEP [422, 423]). All trials reported no differences in blood transfusion rates and complication rates [421-423]. An RCT of DiLEP (980 nm) vs. HoLEP with twelve months follow-up demonstrated no significant difference in peri-operative outcomes including operation and hospitalisation times, resected tissue weight and catheter duration with the DiLEP group also showing lower haemoglobin drop [424].

Practical considerations: Diode laser enucleation seems to offer similar efficacy and safety when compared to either B-TURP or bipolar transurethral (plasmakinetic) enucleation. Based on the limited number of mainly low-quality RCTs, and controversial data on the retreatment rate, results for DiLEP should be evaluated in further higher quality RCTs.

Summary of evidence	LE
Laser enucleation of the prostate using the 1,318 nm or 1,470 laser showed comparable short-term efficacy and safety to B-TURP. Peri-operative parameters like blood loss, catheterisation time and hospital stay are in favour of diode enucleation.	1b
Laser enucleation of the prostate using the 980 nm laser showed comparable short-term efficacy and safety to bipolar transurethral (plasmakinetic) enucleation.	1b

Recommendation	Strength rating
Offer 120-W 980 nm, 1,318 nm or 1,470 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable alternative to bipolar transurethral (plasmakinetic) enucleation or bipolar transurethral resection of the prostate.	Weak

5.3.2.6 Enucleation techniques under investigation

5.3.2.6.1 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 [425], while the first RASP was reported in 2008 [426]. Both LSP and RASP are performed using different personalised techniques, based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP.

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, and the mean improvement in IPSS was 17.2 [427]. There were no differences in improvements in Q_{max} and IPSS [427]. A meta-analysis comparing MISP vs. OP reported no significant differences with regard to functional and symptom parameters between the two techniques [428]. A multicentre RCT with median follow-up of 26 months did not demonstrate any significantly different functional or peri-operative results between LSP, RASP and HoLEP [429].

Two recent retrospective series on RASP were not included in the meta-analysis which confirm these findings [430, 431]. The largest retrospective series reports 1,330 consecutive cases including 487 RASP (36.6%) and 843 LSP (63.4%) cases. The authors confirm that both techniques can be safely and effectively done in selected centres [430].

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. OP for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OP demonstrated a significant shorter average length of hospital stay, but longer mean operative time. The robotic approach was also associated with a lower estimated blood loss. 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 [432]. In a multicentre RCT comparing LSP, RASP and HoLEP LSP demonstrated significantly longer catheterisation times than RASP and HoLEP, whilst RASP and LSP showed longer hospitalisation times and lower rates of *de novo* bladder storage symptoms [429]. A meta-analysis comping MISP vs. OP demonstrated shorter hospital stay, irrigation time, as well as blood loss and transfusion rates for MISP [428]. A SR and meta-analysis reported the mean duration of operation was 141 minutes and the mean intra-operative blood loss was 284 mL. 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. There were no differences in peri-operative complications between both procedures [427].

Practical considerations: Minimal invasive simple prostatectomy seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [427]. 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

5.3.2.6.2 532 nm ('Greenlight') laser enucleation 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 today 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.

Two approaches for KTP/LBO laser-based enucleation technique exist [433]. GreenLEP is an anatomical enucleation technique following the principle of blunt dissection of the adenoma with the sheath and laser energy for incision as described for ThuLEP [434]. *En bloc* GreenLEP preparation has been popularised with the same approach. A variation of the most commonly applied GreenLEP technique, with tissue morcellation, is the *in-situ* vaporisation of apically enucleated tissue, also referred to as anatomic vaporisation-incision technique [434, 435]. To date, no RCTs evaluating enucleation using the KTP/LBO laser have been carried out [436].

*5.3.3 **Vaporisation of the prostate***

5.3.3.1 Bipolar transurethral vaporisation of the prostate

Mechanism of action: Bipolar transurethral vaporisation of the prostate (B-TUVP) was introduced in the late 1990s ("PK" B-TUVP). The technique was derived from PK B-TURP and utilised a bipolar electrode and a high-frequency generator to create a plasma effect able to vaporise prostatic tissue [437]. 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 [438]. A distinct difference between B-TUVP and its ancestor (monopolar TUVP), is that B-TUVP displays thinner (< 2 mm) coagulation zones [439], compared to the disproportionate extent of those created by the former (up to 10 mm) [440], potentially resulting in mostly irritative side-effects and SUI [439, 441, 442].

Efficacy: Bipolar-TUVP has been evaluated as a TURP alternative for treating moderate-to-severe LUTS in thirteen RCTs, including a total of 1,244 men with a prostate size of < 80 mL [317, 443-454]. Early RCTs evaluated the PK B-TUVP system [443-447]; however, during the last decade, only the "plasma" B-TUVP system with the "mushroom- or button-like" electrode (Olympus, Medical) has been evaluated [317, 448-454]. Results have been pooled in three meta-analyses [303, 455, 456], and a narrative synthesis has been produced in two SRs [303, 457]. The follow-up in most RCTs is twelve months [443-446, 448-450, 452, 454]. The longest follow-up is 36 months in a small RCT (n = 40) and eighteen months in a subsequent RCT (n = 340); evaluating PK [447] and plasma B-TUVP [317], respectively.

Early pooled results concluded that no significant differences exist in short-term efficacy (IPSS, QoL score, Q_{max} and PVR) between PK B-TUVP and TURP [303]. However, the promising initial efficacy profile of the former may be compromised by inferior clinical outcomes (IPSS and Q_{max}) at mid-term. Larger RCTs with longer follow-up are necessary to draw definite conclusions [303, 447]. A SR of seven RCTs comparing PK and plasma B-TUVP with TURP concluded that functional outcomes of B-TUVP and TURP do not differ [457]. The poor quality of the included RCTs and the fact that most data was derived from a single institution was highlighted [457]. A similar SR of eight RCTs comparing both B-TUVP techniques with TURP concluded that: not enough consistent data suitable for a meta-analysis exists; that the main functional results are contradictory; and that heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions [303]. A meta-analysis comparing B-TUVP with TURP reported similar efficacy at twelve-month follow-up in terms of IPSS, and Q_{max} [323]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP vs. TURP, concluded that both techniques result in a similar improvement of LUTS [456].

Tolerability and safety: Early pooled results concluded that no statistically significant differences exist for intra-operative and short-term complications between PK B-TUVP and TURP, but peri-operative complications are significantly fewer after B-TUVP [303]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [303]. Mid-term safety results (urethral stricture, ED, and retrograde ejaculation) have also been reported to be similar [447], but larger RCTs with longer follow-up are necessary to draw definite conclusions [303, 447]. A SR of seven RCTs comparing PK and plasma B-TUVP 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) [457]. A similar SR of eight RCTs comparing both B-TUVP techniques with TURP 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 [303]. A meta-analysis reported that B-TUVP has

shorter and similar catheterisation time compared to M-TURP and B-TURP, respectively; lower haemoglobin drop compared to either TURP technique; significantly fewer clot retentions/blood transfusions compared to M-TURP but not B-TURP; and no difference in other complication rates compared to either TURP technique [323]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP vs. TURP, concluded that no significant differences exist between the techniques in overall complication and transfusion rates [456]. However, a statistically significant difference was detected in major complication rates (Clavien 3, 4); including urethral stricture, severe bleeding necessitating re-operation and UI) and in the duration of catheterisation favouring plasma B-TUVP.

Practical considerations: Bipolar-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 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**
Bipolar-TUVP and TURP have similar short-term efficacy.	1a
Plasmakinetic B-TUVP has a favourable peri-operative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1a
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1a

Recommendation	**Strength rating**
Offer bipolar transurethral vaporisation of the prostate as an alternative to transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with a prostate volume of 30-80 mL.	Weak

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 have been described in section 5.3.2.6.2.

Efficacy: 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 [458]. 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 [459-461]. 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 six-, twelve-, and 24-month follow-up when compared to TURP [462]. A meta-analysis of two RCTs reported similar efficacy of 120-W PVP, compared to M-TURP at 36-months follow-up [323].

The only available RCT for the 180-W laser reported non-inferiority to TURP in terms of IPSS, Q_{max}, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. Efficacy outcomes were similar to TURP with stable results at 24 months follow-up [463].

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 [464]. Comparable improvements in IPSS, QoL, Q_{max}, or urodynamic parameters were reported from two RCTs with a maximum follow-up of 24 months [460, 465]. A SR and meta-analysis of eleven RCTs comparing M-TURP with the 80-W KTP or 120-W HPS system found no significant difference with respect to IPSS and Q_{max} improvement [466].

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 [467].

One RCT compared B-TUVP with PVP with the 180-W XPS Laser. Comparable improvement in IPSS and Q_{max} were reported at 24 months follow-up [468].

Tolerability and safety: A meta-analysis of 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 [303]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, UTI, meatal stenosis, urethral stricture, or bladder neck stenosis [303]. 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 UTI [462]. A SR and meta-analysis of eleven RCTs comparing M-TURP with the 80-W KTP or 120-W HPS system found that PVP was superior to M-TURP with regard to transfusion

rate, clot retention, catheterisation and hospitalisation time. A meta-analysis confirmed that PVP was superior to both M-TURP/B-TURP with regard to catheterisation and to M-TURP but not to B-TURP with regard to transfusion rate and clot retention [323].

180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications. Re-operation free survival during a 24 month follow-up was comparable between the TURP-arm and the 180-W XPS laser-arm [463]. In an RCT comparing the 120-W HPS laser with TURP, with a follow-up of 36 months, the re-operation rate was significantly higher after PVP (11% vs. 1.8%; p = 0.04) [464].

Based mostly on case series, the 80-,120- and 180-W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [469-472]; 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%) [472]. 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 [473]. 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 [474]. 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 [475].

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 [476-478].

A meta-analysis of five RCTs comparing collectively all three “Greenlight” lasers with TURP detected no difference in retrograde ejaculation rates [398]. 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 [479]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [480, 481]. However, IIEF-5 scores were significantly decreased at six-, twelve-, and 24- months in patients with pre-operative IIEF-5 greater than nineteen [482].

No significant difference with respect to peri- and post-operative complications was reported in an RCT comparing B-TUVP and PVP with the 180-W XPS Laser. Redo TURP for recurrent adenoma was required in 9.8% (B-TUVP) and 1.7% (PVP) of the patients during 24-months follow-up, respectively [468].

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.

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 evidence available 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 Vaporisation techniques under investigation

5.3.3.3.1 Diode laser vaporisation of the prostate

Mechanism of action: For prostate surgery, diode lasers with a wavelength of 980 nm are marketed for vaporisation; however, only a few have been evaluated in clinical trials [333].

Efficacy: Two RCTs for 120-W 980 nm diode laser vaporisation vs. M-TURP are available [483, 484]. The first RCT with 24-month follow-up reported equal symptomatic and clinical parameters at one and six months. However, at twelve- and 24-months the results were significantly in favour of TURP, repeat TURP was more frequent in the diode laser group [483]. The second RCT reported equivocal results for both interventions at three-month follow-up [484].

Tolerability and safety: Published studies on 980 nm diode laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [485, 486]. In a number of studies, a high rate of post-operative dysuria was reported [483, 485-487]. A meta-analysis comparing diode laser vaporisation vs. M-TURP reported shorter catheterisation time and lower transfusion rates for diode laser vaporisation [323]. In an RCT reflecting on peri-operative and post-operative complications no significant differences were demonstrated for clot retention, AUR after catheter removal, UUI and UTI [483]. 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 [483].

Fibre modifications can potentially reduce surgical time [488]. Early publications on diode vaporisation reported high re-operation rates (8-33%) and persisting SUI (9.1%) [483, 485-487].

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

Summary of evidence	**LE**
Laser vaporisation of the prostate using the 120-W 980 nm diode 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. Evidence is limited by the number and quality of the available studies.	1b
In a number of studies severe post-operative complications such as severe storage symptoms, and persisting incontinence occurred with laser vaporisation of the prostate using the 120-W 980 nm diode laser.	3
Laser vaporisation using the 120-W 980 nm diode laser seems to be safe with regard to haemostasis in patients receiving anticoagulant therapy.	3

5.3.4 ***Alternative ablative techniques***

5.3.4.1 Aquablation – image guided robotic waterjet ablation: AquaBeam

Mechanism of action: 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; therefore, it is truly a robotic operation. After completion of ablation haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [489].

Efficacy: In a double-blind, multicentre, prospective RCT 181 patients were randomised to TURP or Aquablation [490, 491]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes), but resection time was significantly lower for Aquablation (4 vs. 27 minutes). 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. Larger prostates (50-80 mL) demonstrated a more pronounced benefit. At one year follow-up, mean IPSS reduction was 15.1 with a mean percent reduction in IPSS score of 67% for both groups. Ninety three percent and 86.7% of patients had improvements of at least five points from baseline, respectively. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was

reported between the groups. One TURP subject (1.5%) and three Aquablation subjects (2.6%) underwent re-TURP within one year of the study procedure [492].

At two years, improvements in IPSS and flow rate were maintained in both groups [493]. Surgical retreatment rates after twelve months for Aquablation were 1.7% and 0% for TURP. Over three years, mean IPSS improvements were 14.4 and 13.9 points in the Aquablation and TURP groups, respectively. Similarly, three-year improvements in Q_{max} were 11.6 and 8.2 cc/sec. There were no surgical retreatments for BPH beyond twenty months, for either Aquablation or TURP [494]. Over three years, surgical retreatments were 4.3% and 1.5% respectively. A limitation of RCTs is whether they are generalisable; however, a cohort study reported similar results in their first 118 consecutive patients [495].

A subgroup analysis of the WATER study [490] reported that in men with larger more complex prostates, Aquablation was associated with both superior symptom improvement and a better safety profile with less post-operative anejaculation [496].

In a cohort study of 101 men (WATER II) 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 [497]. At twelve months, significant improvements were seen in Q_{max} (increase of 12.5 cc/sec) and PVR (drop of 171 cc) in those with PVR > 100 at baseline). No patient underwent a repeat procedure for BPH symptoms [498]. In a comparison of the WATER (RCT: prostates 30-80 cc) and WATER II (cohort study; > 80 cc) at two years, the improvements were maintained in both IPSS and flow rates. At two years, the surgical retreatment rate was 4% in WATER and 2% in WATER II [499].

Another RCT comparing Aquablation with TURP performed urodynamic studies on 66 patients at six months follow-up and reported significant changes in pdetQ_{max} (reductions of 35 and 34 cm H_20, respectively) and large improvements in BOO index in both groups [500].

Tolerability and safety: An RCT has shown that fewer men in the Aquablation group had a persistent Clavien-Dindo grade 1 or 2 or higher adverse event compared to TURP (26% vs. 42%) at three months following treatment. 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 [492]. Maintenance of antegrade ejaculation was slightly lower in WATER II 81% compared to 90% in the smaller prostates of WATER I [501].

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%) [497]. In WATER II there was a 2% incontinence rate at twelve months, and ten patients did require a transfusion post-operatively while five required take-back fulgurations [498].

In a SR of seven patient groups involving 446 patients treated by aquablation, although there was a significant haemoglobin drop (2.06 g/dL), it did not translate into increased transfusion rates. Aquablation achieves overall lower rates of adverse events. In the first three months of the WATER RCT Clavien Dindo 2-5 events occurred in 19% for aquablation and 29% for TURP (NS). Between three and twelve months they occurred in 5.3% and 10.7% respectively and there was no statistically significant difference again between the one- and two-year follow-up [502].

Practical considerations: During mid-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 a prostate volume of 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*

5.3.4.2 Prostatic artery embolisation

Mechanism of action: Prostatic artery embolisation (PAE) 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 and contrast enhanced MR angiography can help identify prostatic arteries and prevent off-target embolisation particularly in patients with challenging anatomical configurations [503, 504].

Efficacy: Superior efficacy of PAE compared with a sham procedure was found in a six-month randomised, single-blind, sham-controlled trial in 80 patients with severe LUTS, refractory to medical treatment. The decrease in IPSS was significant at six months, 5.03 +/- 8.13 in the sham group and 17.1 +/- 7.25 in the PAE group [505].

In two earlier RCTs conducted for direct comparison of PAE with TURP [506, 507], 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.

An RCT comparing PAE with TURP in 99 patients 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 significant de-obstructive effectiveness according to pressure flow studies (56% vs. 93% shift towards less obstructive category) [503]. An RCT of 60 patients randomised into three equal arms of M-TURP, B-TURP, and PAE followed up at six months concluded that improvement in IPSS score, and Q_{max}, but not in PVR were statistically significantly better for M-TURP and B-TURP vs. PAE [508]. A two-year follow up of this RCT showed no significant difference in IPSS improvement (9.21 points for PAE and 12.09 points for TURP) but TURP was superior for flow rate, prostate volume and PVR improvement. Twenty one percent of patients who initially had PAE underwent TURP within two years. There were less complications for PAE [509].

A SR and meta-analysis including the three above mentioned RCTs and two non-RCTs comparative studies (n = 708 patients), showed that TURP achieved a significantly higher mean post-operative difference for IPSS and IPSS-QoL, 3.80 and 0.73 points, respectively compared to PAE [510]. All of the functional outcomes assessed were significantly superior after TURP: 3.62 mL/s for Q_{max}, 11.51 mL for prostate volume, 11.86 mL for PVR, and 1.02 ng/mL for PSA [510]. A meta-analysis of four RCTs concluded that TURP is associated with significantly higher improvements in Q_{max} [511]. The mean differences in IPSS, QoL score and PVR were not significantly different between TURP and PAE [511].

A recent SR and Meta-analysis including six studies with 598 patients showed that TURP resulted in significantly greater improvement in Q_{max}, prostate volume, and PSA compared to PAE [511]. However, there was no significant difference between PAE and TURP in IPSS improvement, IPSS QoL, IIEF and PVR. PAE was associated with significantly fewer adverse events (39.0% vs. 77.7%) and shorter hospitalisation times (mean difference = -1.94 days), but longer procedural times (mean difference = 51.43 min) [511].

Another SR and meta-analysis of ten RCTs (one vs. sham, five vs. TURP and four exploring variations in PAE technique) confirmed that PAE is non-inferior to TURP in improving patient reported outcome measures (PROMs), though TURP is superior to PAE for most objective outcomes [512].

In a single centre retrospective analysis of 75 PAE patients over a three-year period, PAE was shown to be a safe, effective, and durable treatment option for non-index patients with urinary retention (87% catheter free) or gross haematuria (resolved 87.5%) [513].

Tolerability and safety: In a SR of comparative studies PAE resulted in significantly more adverse events than TURP/OP (41.6% vs. 30.4%). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%) [514].

Another RCT however, reported significantly fewer adverse events occurred after PAE than after TURP (36 vs. 70 events). For secondary outcomes, PAE showed favourable results in terms of blood loss [503]. A RCT of 60 patients randomised into three equal arms of M-TURP, B-TURP, and PAE followed up at six months concluded that operative time was significantly longer for PAE (89 min for PAE vs. 59 min and 68 min for M-TURP and B-TURP) [508]. Catheter was removed on the third and fifth day in the TURP and PAE arms, respectively. No significant haemoglobin drop was detected (no need for blood transfusions) among arms. One patient developed TUR syndrome in the M-TURP arm; two patients from the PAE group developed AUR after catheter removal and four patients from the PAE group developed postembolisation syndrome [508].

A subsequent SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the post-operative complication rate between TURP and PAE [515]. A SR of 708 patients reported fewer side effects than established surgical procedures [510]. A meta-analysis of four RCTs concluded that PAE was associated with significantly shorter hospitalisation time, longer procedural time, fewer total side effects but similar rates of severe side effects [511]. The mean differences in IIEF-5 score were not significantly different between TURP and PAE [511]. Another meta-analysis of two RCTs detected no difference in retrograde ejaculation rates [398]. Post-operative erectile function measured by IIEF-5 was in favour of PAE with mean difference in change of 2.56 points. In another updated meta-analysis PAE was associated with lower sexual dysfunction than TURP (OR 0.24) [516].

Concerns still exist about non-target embolisation, reported in earlier studies [517]; however, more recent studies report less incidents [510, 518].

A SR of 22 studies reporting radiation exposure during PAE, with a twenty-fold range of exposures, estimated that the median risk for a 66-year-old patient of a cancer related death was 0.117%, equivalent to a reduced life expectancy of 5.4 days. Radiation exposure therefore should be part of the counselling for patients considered for PAE. These data suggest there is potential for significant radiation reduction in some centres using appropriate protocols [519].

For secondary outcomes, procedural time was shorter for TURP, but in PAE patients, bladder catheter indwelling time, and duration of hospital stay were significantly shorter [462].

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 [520]. There are data suggesting that larger prostates have a higher chance of a superior outcome with PAE in post hoc analysis of RCTs, but larger trials are required to clarify the most suitable patients for PAE [497, 521].

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 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*

5.3.4.3 Alternative ablative techniques under investigation

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

Mechanism of action: 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 the liquid phase 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 RCT, 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment [522]. 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. Further validated objective outcome measures such as BPH impact index (BPHII), Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and ICS Male Item Short Form Survey for male incontinence demonstrated improvement 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 [523, 524]. Surgical retreatment rate was 4.4% over four years [524]. A Cochrane review found no studies comparing convective radiofrequency water vapour thermal therapy to any other active treatment form, such as TURP [525].

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 [522].

Practical considerations: There are two SRs of the Rezum cohort studies. One concludes that Rezum provides improvement in BPH symptoms that exceeds established minimal clinically important difference thresholds, preserves sexual function, and is associated with low surgical retreatment rates over four years. Therefore, suggesting that it may be a valuable addition to the urological armamentarium to treat LUTS in men with BPH [526]. The other, a Cochrane review reported that the certainty of evidence ranged from moderate to very low, with study limitations and imprecision being the most common reasons for down-grading of the evidence [525]. 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.

*5.3.5 **Non-ablative techniques***

5.3.5.1 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 leaving 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%) [527-532]. Prostatic urethral lift was initially evaluated vs. sham in a multicentre study with one [529] three [533] and five [534] years follow-up of the treated cohort. 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 was 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, 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 with 40% in the TURP patients. 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 [535]. 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 [536]. 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 [532]. Sexual function was preserved with a small improvement estimated at twelve months.

A retrospective observational study of 1,413 consecutive patients from North America and Australia split patients into those still voiding (Group A) and those in retention (Group B). The results from Group A were comparable to the results from the clinical trials and of the 165 patients in Group B, 69% were catheter free after five days, 83% after one month and 89% by study end [537].

A Cochrane review of the sham RCT and the RCT against TURP concluded that PUL appears less effective than TURP in improving urological symptoms in both the short- and long term, while QoL outcomes may be similar. The effect on erectile function appears similar but ejaculatory function may be better with PUL [538].

A SR of surgical re-interventions of eleven studies (2,016 patients), among which TURP/laser (51.0%), repeat PUL (32.7%) and device explant (19.6%) were most common, revealed an annual rate of surgical re-intervention of 6.0% per year (95% CI: 3.0-8.9) [539].

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%) [529, 532-534]. 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 [527-531]. A SR and meta-analysis found that sexual function remained stable or improved slightly during the 24-month follow-up period [512].

Practical considerations: There are only limited data on treating patients with an obstructed/protruding middle lobe [540]. It appears that they can be effectively treated with a variation in the standard technique, but further data are needed [540]. 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

5.3.5.2 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 [541]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data suggests apoptosis-induced atrophy of the prostate with both drugs [541].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [542, 543]. A SR and meta-analysis showed no differences in efficacy compared with placebo and concluded that there is no evidence of clinical benefit in medical practice [544]. The positive results from Phase II-studies have not been confirmed in Phase III-trials for PRX302 [545, 546]. 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 [547].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [541]. A SR and meta-analysis showed low incident rates of procedure-related adverse

events [544]. 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 [547].

Practical considerations: Although experimental evidence for compounds such as PRX302 were promising for their transition to clinical use positive results from Phase II-studies have not been confirmed in Phase III-trials. Nevertheless, an RCT evaluating transperineal intraprostatic BoNT-A injection vs. TURP concluded that IPSS significantly decreased in all patients, with a non-significant difference between the arms and that the BoNT-A injection significantly maintained erectile function compared to TURP at twelve months [548]. More high-quality evidence against reference techniques is needed.

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

5.3.5.3 Non-ablative techniques under investigation

5.3.5.3.1 (i)TIND

Mechanism of action: 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 [549]. The change from baseline in IPSS, QoL score and Q_{max} was significant at every follow-up time point [550].

In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. Mean Q_{max} at one month increased from 7.3 to 11.2 (5.7) ml/s and was 14.7 ml/s at twelve months. The IPSS decreased from 22.5 to 11.7 after one month and to 8.8 at twelve months. In parallel, the mean IPSS QoL score drop reached 1.6 by the end of the study. During the twelve-month period, two patients required medical therapy, two patients required TURP, and ten patients were lost to follow-up [551].

In a multicenter RCT, 175 men were randomised 2:1 between iTIND and sham procedures. Patients were assessed at baseline, 45 days, three, and twelve months postoperatively. Unblinding occurred at three months. A total of 78.6% of patients in the iTIND arm showed a reduction of ≥ 3 points in IPSS, vs. 60% of patients in the control arm at three months. At twelve months, compared to baseline, the iTIND group reported a mean 9.25 decrease in IPSS, a 3.52mL/s increase in peak urinary flow rate and a 1.9-point reduction in QoL. There was a comparable loss of follow-up from baseline groups to three months of 29% of patients in the iTIND arm, and 30% of patients in the sham arm [552].

Tolerability and safety: The device have been reported as 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.

Using the second-generation device none of the 61 sexually active patients who completed the twelve-month follow-up period reported sexual or ejaculatory dysfunction compared to baseline[551].

In the RCT against sham study adverse events were typically mild and transient, most were Clavien-Dindo grade 1 or 2 with 38.1% in the iTIND arm and 17.5% in the control arm. No new ejaculatory or erectile dysfunction occurred [552].

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

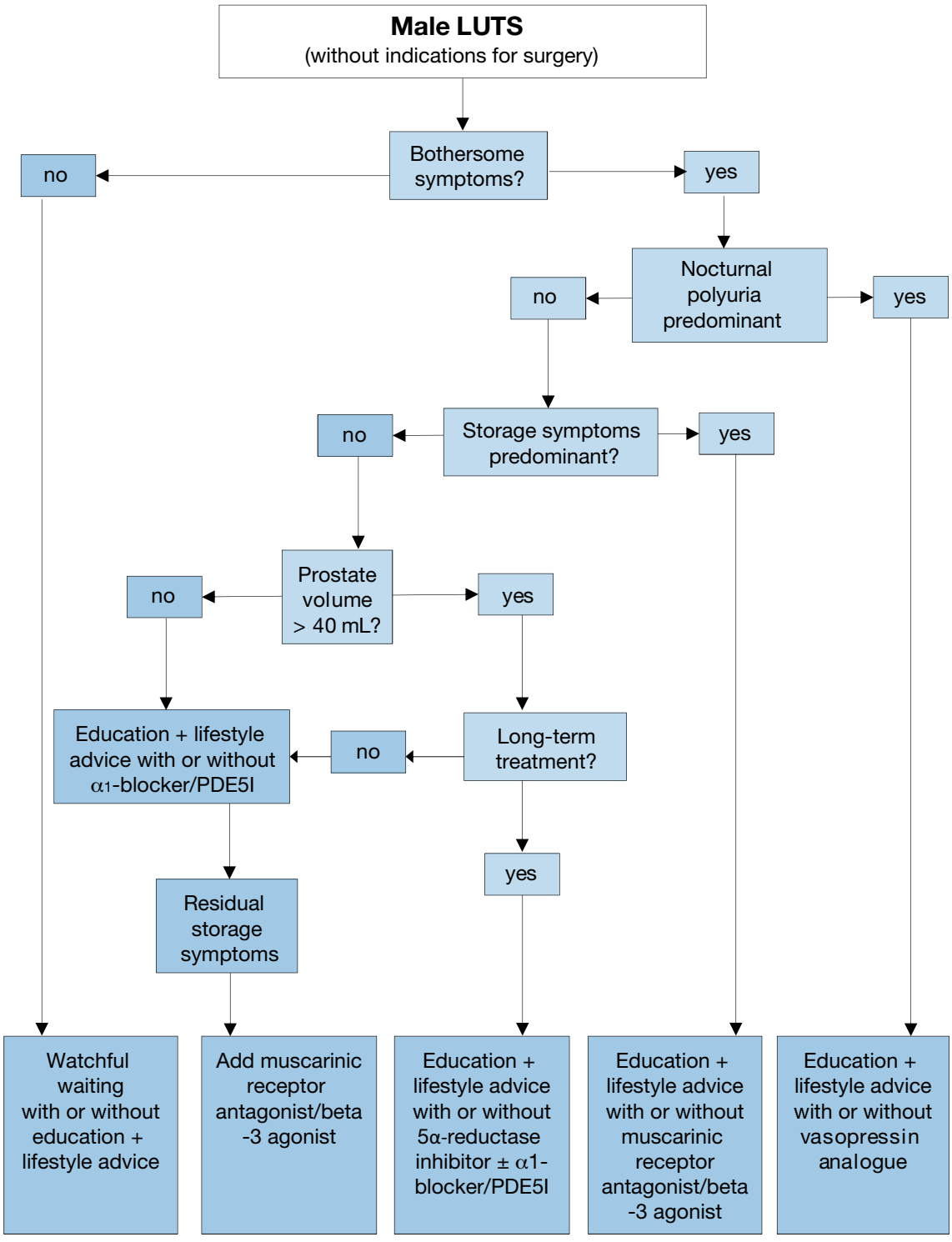
5.4 Patient selection

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).

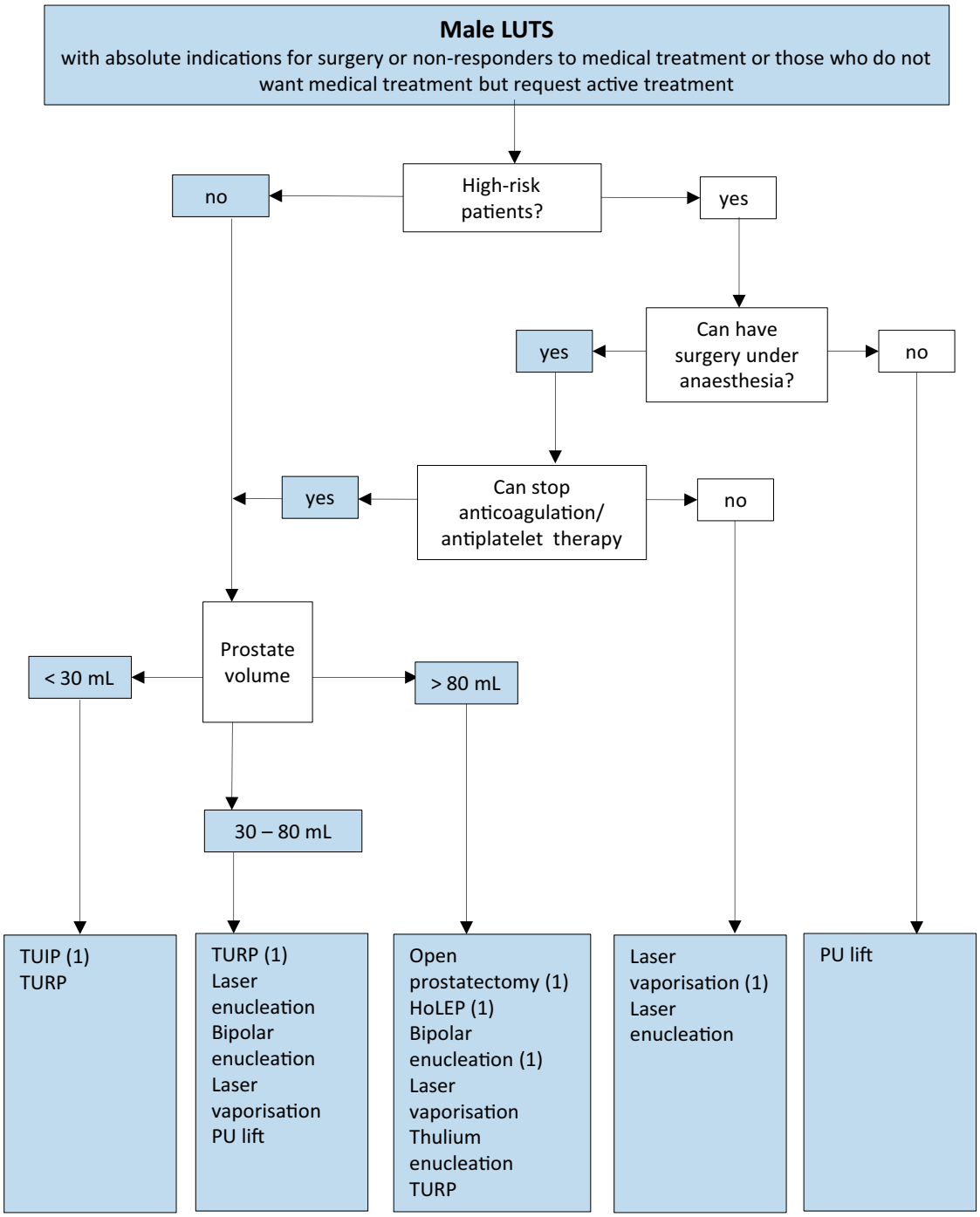
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients' 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, 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; PU = prostatic urethral; TUIP = transurethral incision of the prostate; TURP = transurethral resection of the prostate.

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 [553].

Nocturia has been defined as the complaint of waking at night to void [6]. The ICS Standardisation Steering Committee has introduced the concept of *main sleep period*, defined as "the period from the time of

falling asleep to the time of intending to rise for the next "day" [554].

Nocturia 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 sub optimally 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 [555]:

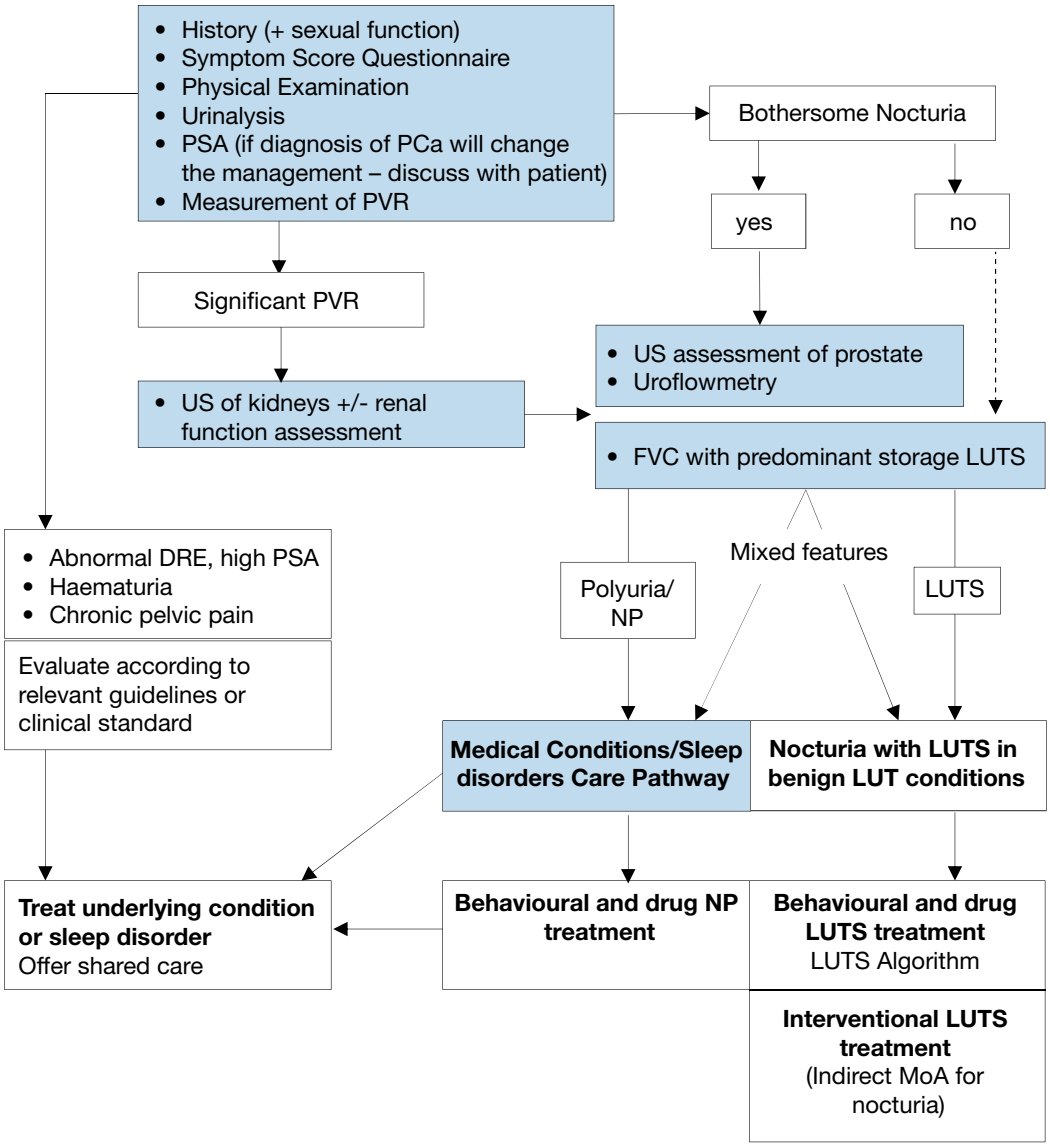
1. bladder storage problems;
2. 24-hour polyuria (> 40 mL/kg urine output over a 24-hour period);
3. nocturnal polyuria (NP; defined as excessive production of urine during the individual's main sleep period, i.e. nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [6]);
4. sleep disorders;
5. mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on the 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, 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 • Increased exercise • Leg elevation • Weight loss 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

ISC = intermittent self catherisation

*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 [556], 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 [557].

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 [553]. 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%) [553]. 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 [553].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [558, 559]. 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 to -0.1]; men = -0.4 [95% CI: -0.6 to -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 [560].

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 [561]. 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 apnoea, 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 [562], antimuscarinics [563-565], 5-ARIs [566] and PDE5Is [567]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [553]. 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 [553]. Benefits with combination therapies were not consistently observed.

5.5.3.3 Other medications

Agents to promote sleep [568], diuretics [569], non-steroidal anti-inflammatory agents (NSAIDs) [570] and phytotherapy [571] were reported as being associated with response or QoL improvement [553]. 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
Alpha 1-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

5.6 Management of male urinary incontinence

The aim of the following section is to provide evidence-based recommendations for the management of male urinary incontinence.

5.6.1 Epidemiology and Pathophysiology

Urinary incontinence is defined as an unintentional loss of urine and is reported to have a prevalence of 11% in men aged 60 to 64 years old to 31% in men ≥ 85 years and to affect up to 32% of men with LUTS [572-574]. Urinary incontinence can be further classified into three types: stress urinary incontinence (SUI); urgency urinary incontinence (UUI); and mixed urinary incontinence (MUI). Overflow urinary incontinence, post-micturition dribble, nocturnal enuresis, and total incontinence are specific forms of UI that are outside the current scope of this guideline. An overview of the epidemiology and pathophysiology of male UI is given in Table 4.

Table 4: Epidemiology and pathophysiology overview of male UI [574-578].

Type	Definition	Causes and associated factors	Pathophysiology	Clinical presentation
Stress UI: prevalence < 10%	Urine loss during movement or efforts or in general during increased abdominal pressure.	• Benign Prostatic Obstruction surgery • Neurogenic condition • Pelvic surgery • Radical prostatectomy • Urethral surgery	Sphincter deficiency	**Symptoms:** UI during physical activity, exercises, e.g. during coughing, sneezing,no leakage during sleep, no nocturnal enuresis **Voiding diary/Pad test:** with activity **Cough stress test:** leakage can coincide with coughing
Urgency UI: prevalence 40-80%	Urine loss concomitant or immediately following an urgency episode.	• Ageing process • Anorectal dysfunction/GI disorders • Behavioural factors (fluid intake and caffeine consumption) • Chronic BPO • Idiopathic • Intrinsic bladder diseases (cystitis, fibrosis, interstitial cystitis) • Metabolic syndrome • Neurogenic conditions • UTIs	• Detrusor overactivity (neurogenic or not) • Urothelial stimulation • Increased afferent signalling • Others (pelvic organ cross talk, bladder wall ischemia etc.)	**Symptoms:** urgency, usually associated with, increased frequency and nocturia **Voiding diary:** urgency, frequency and nocturia
Mixed UI: prevalence 10-30%	Any combination of SUI and UUI.	Causes of both SIU and UUI	Combination of SUI and UUI	**Symptoms:** UI equally as often with physical activity as with a sense of urgency **Voiding diary:** varies **Cough stress test:** may show leakage with coughing

BPO = benign prostatic obstruction; GI = gastrointestinal; SUI = stress urinary incontinence; UI = urinary incontinence; UTI = urinary tract infection; UUI = urgency urinary incontinence

*5.6.2 **Diagnostic Evaluation***

Medical history and physical examination of males with UI is the same as for male LUTS and should allow UI to be categorised into SUI, UUI or MUI and to identify other types of UI (overflow UI, nocturnal enuresis), or those who need rapid referral to an appropriate specialist (e.g., pelvic diseases, neurological conditions).

Specific validated questionnaires can help to quantify UI severity; however, a detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of this guideline. For more information on available questionnaires see the 6th ICI review on patient reported outcomes assessment [579].

Voiding diaries are a standardised method of measuring symptom severity, including frequency and extent of UI episodes, voided volume and 24-hour or nocturnal total urine volume [43].

Pad tests can be used to quantify severity of UI and to monitor patient's response to treatment although the usefulness of these tests in predicting outcome of treatment is uncertain. Despite this, early post-operative testing with pad tests may predict future continence in men after prostatectomy [580, 581].

Urodynamic testing (multichannel cystometry, video-urodynamics) and specific tests of urethral function (urethral pressure profilometry, Valsalva leak point pressure, retrograde urethral resistance) should be considered on an individual basis, such as in cases when invasive treatment is considered. A Cochrane review showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery, while there is limited evidence that it should be used for the assessment of post prostatectomy UI [579].

Post-void residual volume measurement can be applied with caution to men with non-neurogenic UI, as the prevalence, severity, and clinical application of PVR in men with UI is uncertain.

Imaging (US, MRI, CT scan) can improve the understanding of the anatomical and functional abnormalities that may cause UI and thus help its management [582].

Urinalysis: Reagent strip ('dipstick') urinalysis may indicate UTI, proteinuria, haematuria, or glycosuria, requiring further tests as recommended according to other EAU Guidelines, e.g., Guidelines on urinary tract cancers and urological infections [48-51].

Summary of evidence	**LE**
Validated specific symptom score questionnaires and voiding diaries assist in the screening for and categorisation of UI.	3
Pad test can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.	3
There is limited evidence that urodynamics and PVR affect treatment choice in men with uncomplicated UI .	3

Recommendation	**Strength rating**
Take a complete medical history including symptoms and comorbidities, medications, and a focused physical examination in the evaluation of men with urinary incontinence (UI).	Strong
Use a validated symptom score questionnaire, bladder diary and pad-test to assess UI.	Strong
Measure post-void residual in the assessment of UI.	Strong
Perform urodynamics for UI when considering invasive treatment.	Weak

*5.6.3 **Conservative treatment***

5.6.3.1 Simple clinical interventions

5.6.3.1.1 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity and diet. Modification of these factors may improve UI, but most of the evidence for these interventions come from studies with predominately female study populations. However, as many of these interventions are now generalised public health measures their recommendation is in line with general medical practice [583-585].

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated [583, 586]. A cross-sectional population survey found no statistical association between caffeine intake and UI [587]. Conversely, an RCT showed that reduction of caffeine intake, associated with behavioural therapy, resulted in reduced urgency but not UI compared to behavioural therapy alone [588].

5.6.3.1.2 Treatment of comorbidities

Urinary incontinence, especially in the elderly, has been associated with multiple comorbid conditions [589]. It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. Interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidities or ageing on UI. Although changing drug regimens for underlying diseases may be considered as a possible early intervention, there is limited evidence of benefit [590]. There is also a risk that stopping or altering medication may result in greater harm than benefit.

5.6.3.1.3 Constipation

One RCT, with a majority female population, found that a multimodal intervention in elderly patients, involving assisted toileting, fluid intake, etc., reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [591]. However, there is no evidence to show whether treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

5.6.3.1.4 Containment

Containment includes the use of absorbent pads, urinary catheters, external collection devices and penile clamps. A SR of six RCTs comparing different types of pads found that pads filled with super absorbent material were better than standard pads [592]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [593].

A Cochrane review compared different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [594]. A SR of non-randomised studies found no differences in UTI outcome or Upper Urinary Tract (UUT) changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [595]. For people using intermittent catheterisation, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [596].

An RCT in 56 men with post-prostatectomy incontinence (PPI) compared sheath drainage system, body-worn urinal, penile clamp, and absorbent pads. It was found that the three devices and absorbent pads have different strengths and limitations that make them more (or less) suitable for particular activities. Most men prefer to use a combination of devices and pads to meet their lifestyle needs. Hinge-type penile clamp was good for short vigorous activities as it was the most secure, least likely to leak and most discreet, although almost all men described it as uncomfortable or painful [597].

Summary of evidence	**LE**
There is limited evidence that lifestyle interventions e.g., weight reduction, smoking cessation or diet modification improves UI in males.	3
There is limited evidence that improving comorbidities or changing drug regimens for underlying disease improves UI in males.	3
Pads and/or penile sheaths are palliative options for management of UI.	1b

Recommendation	**Strength rating**
Offer lifestyle advice that may improve urinary incontinence (UI) to patients; however, patients should be informed that the evidence for these interventions is lacking.	Weak
Review any medication associated with the development or worsening of UI.	Weak
Use pads and/or penile sheaths as a palliative option for the management of UI.	Weak

5.6.3.2 Behavioural and Physical therapies

Behavioural and physical therapies encompass all treatments which require a form of self-motivated personal retraining by the patient and include techniques which are used to augment this effect. Usually in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education, and possibly cognitive therapy. Further details for behavioural treatments are outlined in section 5.1.2 of these guidelines.

5.6.3.2.1 Prompted or timed voiding

With prompted voiding, carers rather than the patient, initiate the decision to void. Two SRs confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [598, 599]. Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding, including two RCTs, found inconsistent improvement in continence compared with standard care in cognitively impaired adults [600].

5.6.3.2.2 Bladder training

Bladder training goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes, and restore patient

confidence in controlling bladder function. The ideal form or intensity of a bladder training program for UI is unclear. It is also unclear whether bladder training can prevent the development of UI. The addition of bladder training to anticholinergic therapy did not improve UI compared to antimuscarinics alone, but it did improve frequency and nocturia [601]. In seven RCTs, BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI [601].

5.6.3.2.3 Pelvic floor muscle training

A 2015 Cochrane review concluded that there was no overall benefit at twelve months post-surgery for men who received post-operative pelvic floor muscle training (PFMT) for the treatment of PPI and that the benefits of conservative treatment of PPI remain uncertain [602]. However, a subsequent SR and meta-analysis showed that PFMT either alone or in combination with biofeedback and/or electrical stimulation was effective for treating PPI, significantly reducing the time to continence recovery [603]. A further meta-analysis demonstrated that the addition of guided programs using biofeedback and/or pelvic floor muscle electric stimulation (PFES) significantly improved continence recovery rates at one- and three-month intervals post-surgery compared to PFMT alone [604].

Two subsequent SRs in patients who underwent robotic-assisted radical prostatectomy demonstrated that the addition of PFMT to the post-operative management plan shorten the time to continence recovery [605, 606].

Two RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [607, 608]. One RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy, and who had had no previous therapy [609].

One RCT compared PFMT to no treatment in men undergoing TURP. There was no demonstrable difference in the incidence of post-operative incontinence up to twelve months [610]. On the other hand, an RCT in men who underwent HoLEP, demonstrated that PFMT when started pre-operatively promoted early recovery of continence [611].

Other RCTs demonstrated that like PFMT, increased pelvic floor muscle strength and quicker return to continence may be achieved with the Pilates method [612], the oscillating rod [613], a combination of biofeedback with electrostimulation [614] and whole body vibration training [615]. Furthermore, quicker return to continence and improved QoL may be achieved, even with extended and continuing nursing care [616].

5.6.3.2.4 Electrical stimulation

The majority of evidence on electrical stimulation refers to women with SUI and many are of generally low quality, with a variety of stimulation parameters, treatment regimens and outcome parameters [610].

An RCT of 70 PPI men receiving surface or intra-anal electrostimulation reported a significant reduction in UI in terms of grams of urine loss and a significant improvement in QoL from baseline, but no statistically significant difference between treatment arms [617].

A Cochrane review of six RCTs on electrical stimulation in men with UI concluded that there was some evidence that electrical stimulation enhanced the effect of PFMT in the short-term but not after six months. Electrical stimulation was also more effective than sham stimulation at six, but not twelve months; however, there were more adverse effects including pain and discomfort with electrical stimulation [618].

Electromagnetic stimulation has been promoted as a treatment for UI, but only weak evidence of the short- and long-term effects has been reported in SRs [619, 620].

5.6.3.2.5 Posterior tibial nerve stimulation

Posterior tibial nerve stimulation (PTNS) has been studied as a treatment of UI, especially UUI. Electrical stimulation of the posterior tibial nerve delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done either percutaneously using a fine, 34-G, needle, inserted just above the medial aspect of the ankle (P-PTNS) or transcutaneously using surface electrodes (T-PTNS). Percutaneous PTNS treatment cycles typically consist of twelve weekly treatments of 30 minutes and T-PTNS treatment cycles typically consists of self-administered, twenty-minute daily sessions, after adequate education.

A female-predominant sham controlled RCT, assessed effectiveness of PTNS in OAB population. There were 22.8% and 20% males in the treatment and sham arms, respectively [621]. Overactive bladder symptoms improved significantly in 54.5% of patients in the PTNS arm compared to 20.9% in the sham arm. A non-inferiority RCT comparing T-PTNS compared to P-PTNS, reported significant improvements in daytime frequency, urgency and UUI episodes without significant difference between treatment arms after twelve weeks of therapy [622]. A SR on T-PTNS in idiopathic and neurogenic female-predominant (males < 10%) population, reported significant improvement in OAB symptoms in 48-93% of patients and cure of UUI episodes in 25-45% [623].

For PTNS, mild pain and discomfort at the puncture site is the most common adverse event [624]. Small haematomas, swelling, leg tingling and vasovagal reaction to needle placement have also been reported [621]. Treatment adherence is generally high at 89.7% [622]. Contra-indications include a cardiac pacemaker and skin disease at the site of stimulation.

There is some evidence that PTNS may benefit male patients with OAB, but due to too insufficient data, no recommendation on PTNS in males can be made at this time. However, considering the safety of this therapy, it can be offered to male patients as an alternative option prior to more invasive treatments.

Summary of evidence	LE
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
The combination of bladder training with antimuscarinic drugs does not result in greater improvement of UI but may improve frequency and nocturia.	1b
There is conflicting evidence on whether the addition of bladder training, electrostimulation or biofeedback increases the effectiveness of PFMT alone.	1b
Pre-operative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b
Electrical stimulation may add benefit to PFMT up to six months.	2
Electrical stimulation may improve UI compared to sham up to six months.	2
There is limited evidence for the effectiveness of PTNS in male population.	2
There is no evidence that PTNS cures UUI in male population.	2

Recommendations	Strength rating
Implement prompted voiding for patients with urinary incontinence (UI) where appropriate.	Strong
Offer bladder training as a complementary treatment for UI.	Weak
Offer pelvic floor muscle training alone or in combination with biofeedback and/or electrostimulation to men undergoing radical prostatectomy to speed recovery from UI.	Weak

*5.6.4 **Pharmacological management***

5.6.4.1 Drugs for urgency urinary incontinence

Muscarinic receptor antagonists [625-628] and beta-3 agonist [295-297, 629-632] are currently the first-line pharmacological treatments for UUI. The mechanism of action, efficacy, and safety and tolerability profiles of both classes of drugs are discussed in detail in sections 5.2.3 and 5.2.4, respectively.

5.6.4.2 Drugs for stress urinary incontinence

A SR of eight studies evaluating the efficacy of duloxetine in postprostatectomy SUI reported that duloxetine resulted in a mean dry rate of 58% (25–89%), mean improvement in pad number of 61% (12–100%), and mean improvement in one-hour pad weight of 68% (53–90%), at short-term follow-up (mean one to nine months) [633]. However, mean adverse event rates were high, and treatment was discontinued in 38% of cases. The overall certainty of the evidence was low due to study heterogeneity and methodological limitations. Further RCTs with long-term follow-up are required.

Summary of evidence	LE
Antimuscarinic monotherapy can significantly improve urgency, UUI, and increased daytime frequency.	1b
Mirabegron is superior to placebo and as efficacious as antimuscarinics for improvement of UUI.	1b
Duloxetine led to a short-term improvement in postprostatectomy SUI symptoms and QoL improvement; however, a significant proportion of men discontinued treatment.	1b

Recommendations	Strength rating
Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment.	Strong
Offer duloxetine to men with stress urinary incontinence.	Weak
Inform patients about the possible adverse events of duloxetine and that its use is off label for this indication in Europe.	Strong

5.6.5 *Surgical treatment for stress urinary incontinence*

5.6.5.1 *Bulking agents in men*

Mechanism of Action: Urethral bulking agents work by adding bulk and improving the coaptation of a damaged sphincter zone. They represent a treatment option in men with either small volume leak or those unfit for more invasive treatment options [634].

Efficacy: A Cochrane review on surgical treatment of PPI identified only one RCT that fulfilled the inclusion criteria. This trial randomised 45 men to Macroplastique injection or artificial urinary sphincter (AUS) implantation and compared their outcomes at 48 months [634]. Significant improvement was reported in both groups for men with minimal incontinence, but in men with total incontinence there was a significant difference in continence rates favouring AUS implantation (72% vs. 23%) [635]. A SR of eight studies (n=142) in men using Macroplastique, Opsys, Durasphere and Urolastic, showed short-term improvement, and reported dry rates between 0-83% [634]. A propensity score-matched analysis of 104 men with PPI, compared submucosal injection of Macroplastique to transobturator male sling (TiLOOP male) [636]. At twelve months follow-up, the reported failure free rates were 15.4% and 76.9%, the daily use of 0-1 pads was 21.2% and 67.3% and the satisfaction rate was 3.8% and 71.2%, respectively. Several small cohort studies of several different bulking agents have not shown any benefit.

A narrative review including data from 25 articles, reports a success rate with all bulking procedures of 54.3%, with 37.5% of symptoms improvement and almost 30% of dryness [637].

In a SR and meta-analysis, three studies addressed bulking agents. Two of them, involving a total of 384 participants, showed a pooled short-term cure rate of 26.1% and a single study on 68 subjects reported a 10.3% long term cure rate. Short- and long-term reoperation rates were not described [638].

Tolerability and safety: Bulking agent associated dysuria and haematuria are frequently reported to be transient and self-resolving [634]. The risk of urinary retention requiring, clean intermittent self-catheterisation (CISC) or long-term catheter use is minimal [639]. However, they may provoke allergic reactions [640] and carry a potential risk for migration [641] to proximal and distal lymph nodes [642]. Overall, post procedural urinary retention rates range between 3-17%, with rare need for temporary catheterization, while post-operatory urinary tract infections ranged from 6-7% [637].

Practical considerations: Bulking agents have shown low cure rates but remain an option for men unfit for more invasive treatment options.

Summary of evidence	**LE**
There is very limited evidence that bulking agents are effective for the treatment of PPI.	2

Recommendation	**Strength rating**
Do not offer bulking agents to men with postprostatectomy incontinence.	Weak

5.6.5.2 *Male Slings*

Male slings have been introduced to treat mild-to-moderate PPI. However, the definitions of mild and moderate UI are unclear. The majority of studies define cure as ‘no pad use’ or ‘one security pad per 24-hours’. Some authors used more strict criteria such as ‘urine loss of less than 2 g per 24-hour pad test’ [643].

5.6.5.2.1 Non-adjustable slings

Mechanism of Action: Non-adjustable male slings are positioned under the urethra and fixed by a retropubic or transobturator approach. The tension is adjusted during the surgery, and it cannot be re-adjusted post-operatively. Synthetic slings restore continence in males either by urethral compression and/or by repositioning the bulb of urethra [644, 645].

Efficacy: A SR and meta-analysis involving 33 prospective cohorts and one RCT comparing sling to AUS, reported that both options are effective in improving UI and QoL [646]. Following sling insertion, the overall cure rate was 60% (95% CI: 0.51-0.67) and 56% (95% CI: 0.44-0.68) for slings and AUS, respectively. The 24-hour pad use was -3.33 (95% CI: -4.33 to -2.34) and -3.75 (95% CI: -4.56 to -2.93) for slings and AUS, respectively. Similar findings were reported by a network meta-analysis that showed comparable efficacy between slings and AUS [647].

The MASTER Trial, a non-inferiority RCT comparing the outcomes of continence surgery in men with bothersome urodynamic SUI, using a very strict definition of UI after prostate surgery, reported that at twelve-

months incontinence rates were 87% for male sling vs. 84.2% for AUS (95% CI: -11.6-4.6, P_{NI}=0.003]), confirming non-inferiority [648]. The subgroup analysis suggested that male sling is inferior to AUS for men with greater incontinence at baseline (pad weight > 250g); however, the difference did not reach statistical significance.

For the re-positioning sling (AdVance™ and AdVanceXP©), a mean subjective cure rate of 49% (8.6 - 73.7%) after mean follow-up of three years has been reported for 136 patients [649]. A prospective multicentre cohort study, with 60-month follow-up, in men with AdVanceXP© demonstrated a constant continence outcome over time with a 57.6% cure rate, 25.4% improvement rate and 16.9% failure rate. These findings were verified in an additional study which reported cure rates of 66.7% and 71.7%, improvement rates of 26.5% and 24.4% and failures rates of 6.9% and 13.3% at 24- and 48-months, respectively [650]. A retrospective comparative study showed that both options are safe and effective in the treatment of male SUI [651].

With the transobturator compressive I-Stop TOMS male sling, 38% of men were dry at twelve months, but this reduced to 23% and 15% after four and five years, respectively [652].

Tolerability and safety: A SR and meta-analysis of 1,170 men with SUI and male sling, reported that the predictors of failure are prior radiation, severity of incontinence and previous surgeries [653]. Pelvic radiotherapy has also been reported in other studies as a negative prognostic factor [654]. A comparison among radiated vs. non-radiated men who had AdVanceXP reported a greater degree of post-operative improvement in the non-radiated group (49.6% vs. 22.2%) as well as greater satisfaction rates (95% vs. 64%) [655]. The most common complication with male slings is pain and local superficial wound infection [656]. Chronic pain has been observed in 1.3% of men who had non-adjustable slings [656]. Post-operative transient voiding dysfunction occurred in 4.3-10.3%, mostly as *de novo* urgency or urinary retention, while erosions and chronic pain were uncommon (0-0.4%), as was explantation [649, 650, 657-659].

Practical considerations: Fixed male slings are considered safe and improve continence, but their efficacy is limited in men with severe incontinence or previous radiotherapy.

5.6.5.2.2 Adjustable slings in males

Mechanism of Action: Adjustable slings in males are those for which the tension of the sling can be adjusted post-operatively. Three main systems have been used in men: the Remeex® system [660], the Argus® system [661] and the ATOMS® system [662].

Efficacy: There is one small RCT for adjustable slings in males [663]. Most studies consist of prospective or retrospective case series, with variable follow-up and different definitions of success [660, 662-666]. A SR reported objective cure rates varying between 17-92% after adjustable sling implantation [656].

For the Remeex® system, only two studies, with conflicting findings, have been published. One study followed nineteen patients for nearly seven years and reported 70% success, with no explants, infections, or erosions [660]. The second study followed fourteen patients for 25 months. Only 36% of patients were satisfied and multiple re-adjustments were needed. Mechanical failure was reported in 21% [664].

Data on the Argus® system has been reported for 404 men, but only few series have reported on more than 40 patients, with the longest follow-up being 35-months. Success rates varied between 17-93%, with a mean of 73.0% reporting subjective cure [665, 666]. A head-to-head comparison between the two Argus systems reported similar efficacy outcomes at 44 months, but Argus T was associated with a higher inguinal pain and explantation rate [667]. A small study of 22 men with PPI randomised to AdVance or Argus T reported superior 24-hour pad test results and of patient satisfaction levels for Argus T at eighteen-months follow-up [663].

A SR of the ATOMS system reported the pooled evidence from 1,393 patients with a 67% dryness, 90% improvement after adjustment and 16.4% complication rate [662]. The expulsion rate was 5.75%. Another SR and meta-analysis with 3,059 patients reported that ATOMS was superior to ProACT in mean dryness rate (68% vs. 55%), overall improvement (91% vs. 80%), satisfaction rate (87% vs. 56%), mean number of filing adjustments (2.4 vs. 3.5) and post-operative pad use per day (1.1 vs. 2.1) [668].

Tolerability and Safety: The most frequent complications in adjustable male slings are pain, erosions, and infections [656]. Pain at the implant site was usually only temporary, but chronic pain has been reported in 1.5% of men [665, 666]. The number of implants requiring re-adjustment is reported between 8-38.6% [666, 669, 670]. Explantation rates range from 10-15.8% and erosion rate is estimated around 10% [653]. The most

common reasons for explantation are device infection (4.1-8%), erosions (4-12%), and urethral perforations (2.7-16%). A SR reported a device explantation rate of 5% vs. 25% and a major complication rate of 4.2% vs. 10.4% for ATOMS and ProACT, respectively [668].

Practical considerations: There is no evidence that adjustability offers additional benefit as RCTs are lacking; therefore, no recommendation can be made at this time. Explantation rate seems superior to fixed male sling based on external comparisons.

5.6.5.2.3 Autologous slings

The strategy of intra-operative placement of an autologous vas deferens sling below the vesico-urethral anastomosis during robotic-assisted radical prostatectomy (RARP) has been explored with the intention to improve early return of continence. Two RCTs [671, 672] showed an advantage of sling vs. no sling at one-month follow-up, and another study [673] showed an advantage of a 6-branch vs. a 2-branch sling at one month follow-up. However, a larger RCT (n=195), showed that continence rate and near-continence rate were similar between groups at six months with 66% vs. 65% and 86% vs. 88%, respectively [674].

Summary of evidence	**LE**
There is limited short-, medium- and long-term evidence that fixed transobturator male slings cure or improve PPI in patients with mild-to-moderate incontinence.	1b
Men with severe incontinence, previous radiotherapy or transurethral surgery may have less benefit from fixed transobturator male slings.	2
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is no evidence that adjustability offers additional benefit over other types of slings.	3
There is no evidence that intra-operative placement of an autologous sling during RARP improves return of continence at six months.	1b

Recommendations	**Strength rating**
Offer non-adjustable transobturator slings to men with mild-to-moderate* post-prostatectomy incontinence.	Weak
Inform men that severe incontinence, prior pelvic radiotherapy or transurethral surgery may worsen the outcome of non-adjustable male sling surgery.	Weak

** The terms "mild" and "moderate" PPI remain undefined.*

5.6.5.3 Compression devices in males

5.6.5.3.1 Artificial urinary sphincter

Mechanism of action: The AUS is the standard treatment for moderate-to-severe male SUI. The AMS 800 three component system with inflatable cuff, control pump and pressure regulating balloon is the device with the longest follow-up and the greatest level of evidence [675]. The ZSI 375 is a two-component device, inflatable cuff, and control pump, allowing an easier implantation process [676]. Other AUS devices have been launched e.g., the Victo and Br-SL-AS 904 systems, but robust evidence regarding their efficacy and safety is pending [677].

Efficacy A meta-analysis of 33 cohort studies and one RCT, reported significant improvement after AUS implantation in overall cure rates (56%) and reductions in pad used per 24-hours (-3.75) [646]. Several observational studies reported on functional outcomes after AMS 800. Social continence rates (0-1 pads used daily) ranged from 55-76.8% [678-680]. A 77.2% continence rate and 89.5% subjective satisfaction rate have been reported after median follow-up of > 15 years in 57 men who had undergone AUS placement [681]. A prospective cohort study of 40 patients with a mean follow-up of 53 months, showed that from all urodynamic parameters only low bladder compliance had a negative impact on outcome [682]. However, another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [683]. Some recent multicenter studies have confirmed older statements that surgeon's experience and higher surgical volume is associated with better outcomes and a lower revision rate after AUS implantation [684, 685].

The data regarding ZSI 375 is limited. A retrospective, non-randomised trial across several centres in Europe, reported an 84.4% success rate (19.3% dry rate and 65.1% improved 0-1 pads per day) after 43 months [676]. A 72% success rate was reported at seven years follow-up for 45 patients who underwent placement of the ZSI 375 device in France [686].

Tolerability and safety: Artificial urinary sphincter complications include device infection/erosion (8.5%), mechanical failure (6.2%) and urethral atrophy (7.9%) [687]. In multivariate analysis, radiation therapy was

independently associated with risk of urethral atrophy, as were older age and a longer time interval between prostate cancer treatment and AUS surgery [680]. Urethral erosion is associated with previous irradiation and penoscrotal approach [688]. The reported revision rates at three years for any reason were 10-29.1% [678, 688-690]. The risk of urethral erosion after ZSI 375 AUS is 8.2-13.3% and risk of mechanical failure is 2.2-2.5% [676].

Practical Considerations: Artificial urinary sphincter is efficacious and improves the QoL of men with PPI. To minimise complications, it is advised to refer patients to specialised centres experienced in AUS implementation. Men considering insertion of an AUS should be fully informed that the success of the intervention relies on their ability to operate the pump. Treating physicians should keep in mind that operating the AUS may become difficult in men who develop cognitive impairment or lose manual dexterity. Artificial urinary sphincter has a limited lifespan and 'maintenance' re-operations are common in the long-term. These re-interventions should not be classified as complications [675].

5.6.5.3.2 Non-circumferential compression device (ProACT®)

Mechanism of action: The ProACT® system consists of two devices. Each device includes the balloon, the bi-lumen tubing, and the volume-adjustment port. The devices are introduced by a trocar via two small perineal incisions and are placed under fluoroscopic guidance on each side of the bladder neck, close to the vesico-urethral anastomotic site. The balloons can be filled, and their volume can be adjusted post-operatively using a hypodermic needle injected through the intra-scrotal port.

Efficacy: A SR and meta-analysis of nineteen studies including 1,264 patients reported a 60.2% dry rate, significant reduction in number of pads used per day (-3.1) and greatly improved QoL scores for ProACT® [691]: however, the level of heterogeneity among the included studies was high. A comparison between ATOMS and ProACT®, showed that the former is associated with higher improvement and satisfaction rates and fewer complications [668]. A quasi-randomised trial comparing ProACT® with bone-anchored male slings found that both resulted in similar improvements in SUI (68% vs. 65%, respectively) [692]. A questionnaire study showed that 50% of patients were still significantly bothered by persistent incontinence following ProACT® [693]. A subgroup analysis of radiotherapy patients reported worst outcomes as compared to patients not receiving radiotherapy (46% vs. 68% success rate) as well as a higher percentage of urethral erosion for ProACT® [694].

Tolerability and safety: The most common intra-operative complication during ProACT® implantation is perforation of the bladder and/or urethra. A meta-analysis estimated a perforation rate of 5.3% [691]. The estimated overall revision rate is 22.2%, and the main causes are erosion (3.8%), device leaking (4.1%) and migration (6.5%) [691]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [692, 693, 695-697].

Practical Considerations: ProACT® has a satisfactory rate of success and seems to be a reasonable alternative for the treatment of male UI; however, it is associated with high complication rates.

Summary of evidence	**LE**
Primary AUS implantation is effective for cure of SUI in men.	1b
There are conflicting data on whether previous pelvic radiotherapy affects the outcome of AUS implantation.	3
The non-circumferential compression device (ProACT®) is effective for treatment of PPI SUI; however, it is associated with a high failure and complication rate leading to frequent explantation particularly after pelvic radiation therapy.	2b
The rate of explantation of the AUS due to infection or erosion remains high (up to 24% in some series).	3

Recommendations	**Strength rating**
Offer artificial urinary sphincter (AUS) to men with moderate-to-severe stress urinary incontinence.	Strong
Implantation of AUS or ProACT® for men should only be offered in expert centres.	Weak
Warn men receiving AUS or ProACT® that, although cure can be achieved there is a high risk of complications, mechanical failure, and the need for explantation.	Strong
Do not offer non-circumferential compression device (ProACT®) to men who have had pelvic radiotherapy.	Weak

5.6.6 ***Surgical treatment for urgency urinary incontinence***

5.6.6.1 *Bladder wall injection of botulinum Toxin A*

Mechanism of action: The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [541]. Onabotulinum toxin A (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory non-neurogenic UUI in adults [698, 699].

Efficacy: An RCT of OAB-wet patients whose symptoms were not adequately managed with anticholinergics and who receive either bladder wall injections of onabotA (100 U) or saline reported a 50% reduction in UUI episodes/day whilst the number of micturitions/day reduced by more than two in patients receiving onabotA [700]. A total of 22.9% of the patients in the onabotA arm were fully dry vs. 6.5% in the saline arm.

A SR and meta-analysis comparing the efficacy of onabotA, mirabegron and anticholinergics in adults with idiopathic OAB reported that patients who received onabotA (100U) achieved greater reduction in UI episodes, surgery, micturition frequency and the highest odds of achieving dryness as well as > 50% reduction from baseline UI episodes per day [701].

A randomised, placebo-controlled pilot study, assessing the effect of onabotA for the treatment of refractory OAB symptoms after prostatectomy reported significantly improved QoL and ICIQ scores and improvements in daily frequency in patients receiving onabotA compared to placebo [702]. A retrospective trial assessed onabotA efficacy in 65 non-obstructed men with refractory OAB and reported significant improvement in UDI-6 score (-4.2) and IIQ-7 (-6.0) scores, compared to baseline [703].

In a retrospective, single-centre cohort study onabotA treatment for OAB in 120 patients lead to lower CISC rates in male patients after prior de-obstructive surgery than in surgery-naïve patients (28.6% CISC in the group without prior surgery, 7.5% in the TURP subgroup, and 4.2% in the radical prostatectomy subgroup) [704].

A phase IIIb trial randomised solifenacin-naive patients (10% males) with refractory OAB to onabotA, solifenacin or placebo, and showed that patients receiving onabotA had significantly greater changes in UI episodes (-3.19) compared to solifenacin (-2.6) and placebo (-1.33) [705].

A network meta-analysis (male population range 9.8-40.2%) which compared onabotA to mirabegron demonstrated that onabotA was associated with improved outcomes in frequency episodes per day (-0.43 [-1.22-0.37]) and in UI episodes per day (-0.46 [-1.46-0.53]) [706].

Tolerability and safety: Urinary retention and UTIs are the two most common adverse events after onabotA injection. Other reported adverse events include haematuria, dysuria and post-treatment pain [707]. Compared to mirabegron, onabotA is associated with higher risk for UTI and treatment emergent adverse events [706]. A retrospective analysis compared the use of CISC after onabotA injection, among men who had previous prostatectomy vs. those without prior surgery [704]. A 7.5% catheterisation rate after TURP, 4.2% rate after radical prostatectomy and 28.6% rate in men without prior prostate surgery was reported.

Practical Considerations: BoNT-A injections is a recommended treatment option for men with refractory UUI. Despite the lack of a universally accepted injection protocol, gender specific studies and absence of studies in BPO patients, BoNT-A seems superior to medical therapy. It is associated with a higher UTIs and urinary retention risk, coupled with the need for repeated injections. A dedicated series in male population, focused on treatment persistence, has shown a high discontinuation rate [708]. Patients treated for OAB with onabotA treatment that have not undergone prior de-obstruction are more likely to develop retention and subsequent CISC.

Summary of evidence	**LE**
A single treatment session of onabotA (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and QoL.	1b
There is no evidence that repeated injections of onabotA have reduced efficacy, but discontinuation rates are high.	3
There is an increased risk of retention and UTI with onabotA injections.	2

Recommendations	Strength rating
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy.	Weak
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterisation (ensure that they are willing and able to do so).	Strong

5.6.6.2 Sacral nerve stimulation (neuromodulation)

Mechanism of action: Sacral nerve stimulation (SNS) delivers low amplitude electrical impulses to the sacral nerve roots via an electrode implanted adjacent to the third sacral nerve root and connected to an attached pulse generator implanted in the buttock. It works by modulating neural activity thus stabilising bladder electrical activity through an unknown mechanism. It is a two-stage process: in the first stage, a tined lead electrode is placed percutaneously near the S3 root and linked to an external stimulator to assess the response. If symptoms reduced more than 50%, patients are candidates for the second stage which is the full implant.

Efficacy: Several trials assess the clinical effectiveness of SNS. All RCTs suffer from the limitation that patients and assessors cannot be blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. In addition, the percentage of male population in these trials is around 10%. A meta-analysis compared the effectiveness of SNS to onabotA and reported no significant difference in successfully treated cases at six-month follow-up (RR 0.93; 95% CI: 0.63-1.39) [709].

Tolerability and safety: Main complications after SNS are pain at the implant site (13-42%), lead migration (4.0-21%), leg or back pain (3.0-18%) and wound infection (5.7-6.7%). Surgical revision is required in 29-33% of patients due to device malfunction, battery or device replacement or lead migration [710].

Practical Considerations: SNS represents an alternative to onabotA in patients with refractory OAB, as it has shown good success rates and an acceptable safety profile.

Summary of evidence	LE
Sacral nerve stimulation is effective after failed conservative treatment for OAB/UUI, but no sham controls have been used.	2a

Recommendation	Strength rating
Offer sacral nerve stimulation to patients who have urgency urinary incontinence refractory to medical therapy and are willing to undergo surgical treatment.	Weak

5.6.6.3 Cystoplasty/urinary diversion

Mechanism of action: Augmentation cystoplasty involves the interposition of a detubularised segment of bowel into the bivalved bladder wall, aiming to increase bladder capacity and reduce OAB related symptoms. Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation.

Efficacy: There are no RCTs comparing bladder augmentation to other treatments for patients with refractory OAB/UUI. In a large study with three years follow-up augmentation cystoplasty resulted in a post-operative continence rate of 93% in idiopathic detrusor overactivity patients, 78% in neurogenic overactivity and up to 90% when an artificial urinary sphincter was implanted, respectively [711]. The largest case series of bladder augmentation in an idiopathic population included only women [712]. At an average follow up of 75.4 months only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. A small prospective mixed gender trial reported high patient satisfaction rates with augmentation cystoplasty vs. onabotA therapy [713]. A small study comparing ileal with colonic conduits concluded that there were no differences in the relative risks of UUT infection and uretero-intestinal stenosis [714]. However, there are no studies that have specifically examined these techniques in the treatment of intractable OAB/UUI [714]. Therefore, careful consideration on which operation is undertaken will depend on thorough pre-operative counselling, access to stoma/continence nurses as well as patient factors to allow for fully informed patient choice.

Tolerability and safety: Cystoplasty and urinary diversion are major urologic operations. The early post-operative complications include infection, bowel obstruction, bleeding, and cardiorespiratory complications.

Long-term complications include metabolic disturbances (hyperchloraemic metabolic acidosis), change in bowel habits, increased mucus production, stone formation, bladder perforation and rarely bladder cancer [715]. Following augmentation cystoplasty or diversion, the majority of patients will depend on self-catheterisation for bladder emptying. Patients with urinary conduit will depend on lifelong urine bags.

Practical Considerations: Augmentation cystoplasty and urinary diversion represent realistic treatment options for men with refractory OAB. However, both options involve a major operation, with a non-negligible long-term complication rate and a lifelong reliance on catheterisation or urine bags.

Summary of evidence	**LE**
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic OAB.	3
The need to perform CISC following augmentation cystoplasty is high.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term complications.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3

Recommendations	**Strength rating**
Offer augmentation cystoplasty to patients with overactive bladder (OAB)/urgency urinary incontinence (UUI) who have failed all other treatment options and are able and willing to perform self-catheterisation.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of complications; the risk of having to perform clean intermittent self-catheterisation and the need for life-long surveillance.	Strong
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of OAB/UUI, who will accept a stoma.	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

After prostate surgery, patients 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 of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: http://uroweb.org/guideline. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative and travel and meeting expenses. No honoraria or other reimbursements have been provided.

9. CITATION INFORMATION

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