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 substantial economic burden. The present Guidelines offer practical evidence-based guidance on the assessment and treatment of men aged 40 years or older with various non-neurogenic benign forms of LUTS. The understanding of the LUT as a functional unit, and the multifactorial aetiology of associated symptoms, means that LUTS now constitute the main focus, rather than the former emphasis on Benign Prostatic Hyperplasia (BPH). It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - also taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

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

1.3   Available publications
A quick reference document (Pocket Guidelines) is available, both in print and in a number of versions for mobile 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 were first published in 2000. Standard procedure for EAU Guidelines includes an annual assessment of newly published literature in the field to guide future updates. The 2017 document presents a comprehensive update of the 2016 publication. The literature was assessed for all chapters.

2.   METHODS

2.1   Introduction
For the 2017 Management of Non-Neurogenic Male LUTS Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic Male LUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews with meta-analysis, randomised controlled trials (RCTs), and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between April 1st 2015 and May 31st 2016. A total of 1,622 unique records were identified, retrieved and screened for relevance. A detailed search strategy is available online: http://www.uroweb.org/guideline/ treatment-of-non-neurogenic-male-luts/supplementary-material.

References used in this text are assessed according to their level of evidence (LE) and Guidelines are given a grade of recommendation (GR), according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [1]. Additional methodology information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guidelines/. A list of all Associations endorsing the EAU Guidelines can also be viewed online at the above address.

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

2.3   Patients to whom the guidelines apply
Recommendations apply to men aged 40 years or older who seek professional help for LUTS in various

non-neurogenic and non-malignant conditions such as LUTS/Benign Prostatic Obstruction (BPO), detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with other contexts of LUT disease (e.g. concomitant neurological diseases, young age, prior LUT disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following sections. EAU Guidelines on Neuro-Urology, Urinary Incontinence, Urological Infections, Urolithiasis, or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3.   EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [2]. Lower urinary tract symptoms are prevalent, cause bother and impair QoL [3-6]. An increasing awareness of LUTS and storage symptoms in particular, is warranted to discuss management options that could increase QoL [7]. Lower urinary tract symptoms are strongly associated with ageing [3, 4], associated costs and burden are therefore likely to increase with future demographic changes [4, 8]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [9]. Most elderly men have at least one LUTS [4], however, symptoms are often mild or not very bothersome [6, 7, 10]. Lower urinary tract symptoms progress dynamically: for some individuals LUTS persist and progress over long time periods, and for others they remit [4]. LUTS have traditionally been related to bladder outlet obstruction (BOO), which is often caused by benign prostatic enlargement (BPE) resulting from the histologic condition of BPH [2, 5]. However, recent studies have shown that LUTS are often unrelated to the prostate [4, 11]. Bladder dysfunction may also cause LUTS, including detrusor overactivity/OAB, detrusor underactivity/underactive bladder, as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [11]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [12, 13]. In addition, many non-urological conditions also contribute to urinary symptoms, especially nocturia [4].

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 [2];
*   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 [2];
*   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 [2];
*   Benign prostatic obstruction is a form of BOO and may be diagnosed when the cause of outlet obstruction is known to be BPE [2]. In the Guidelines either the term BPO or BOO is used as reported by the original studies;
*   Benign prostatic hyperplasia is a term used (and reserved) for the typical histological pattern, which defines the disease;
*   Detrusor overactivity (DO) is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked [2];
*   Overactive bladder syndrome is characterised by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [14].

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 lower urinary tract symptoms (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 in these cases;
* 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 [15-17]. 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) [18, 19].

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

Recommendation	LE	GR
Take a complete medical history from men with LUTS.	4	A*

Upgraded based on Panel consensus.

4.2 Symptom score questionnaires

All published guidelines for male LUTS/BPH recommend using validated symptom score questionnaires [15, 17]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [20-26]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant, yet they are not disease-, or age-specific. A systematic review 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 [27].

4.2.1 The International Prostate Symptom Score (IPSS)

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one QoL question [21]. 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 ICS Male questionnaire. It is a widely used and validated patient completed questionnaire [22]. It contains 13 items, with subscales for nocturia and OAB, and is available in 17 languages.

4.2.3 Danish Prostate Symptom Score (DAN-PSS)

The DAN-PSS [25] is a symptom score used mainly in Denmark and Finland. The ICIQ-MLUTS and DAN-PSS measure the bother of each individual LUTS.

Recommendation	LE	GR
Use a validated symptom score questionnaire including quality of life assessment during the assessment of male LUTS and for re-evaluation during and/or after treatment.	3	B

4.3 Frequency volume charts and bladder diaries

The recording of volume and time of each void by the patient is referred to as a frequency volume chart (FVC). Inclusion of additional information such as fluid intake, use of pads, activities during recording, or symptom scores is termed a bladder diary [2]. Parameters that can be derived from the FVC and bladder diary include: daytime 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 [28, 29]. The FVC diary is particularly relevant in nocturia, where it underpins the categorisation of underlying mechanism(s) [30-32]. The use of FVCs may cause a 'bladder training effect', and influence the frequency of nocturnal voids [33].

The duration of the FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance [34]. A systematic review of the available literature recommended FVC should continue for three or more days [35].

Recommendations	LE	GR
Use a bladder diary to assess male LUTS with a prominent storage component or nocturia.	3	B
Tell the patient to complete a bladder diary for the duration of at least three days.	2b	B

4.4 Physical examination and digital-rectal examination

Physical examination to seek potential influences on LUTS, 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 [36]. 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 [37]. A model of visual aids

has been developed to help urologists estimate prostate volume more accurately [38]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < than 50 mL [39].

Recommendation	LE	GR
Perform a physical examination including digital rectal examination in the assessment of male LUTS.	3	B

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, including Guidelines on urinary tract cancers and urological infections [40-43].

Urinalysis is recommended in most Guidelines in the primary management of patients with LUTS [44, 45]. There is limited evidence, yet general expert consensus that the benefits outweigh the costs [46]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has recently been questioned [47].

Recommendation	LE	GR
Use urinalysis (by dipstick or urinary sediment) in the assessment of male LUTS.	3	A*

Upgraded based on Panel consensus.

4.6 Prostate-specific antigen (PSA)

4.6.1 PSA and the prediction of prostatic volume

Pooled analysis of placebo-controlled BPH trials showed that PSA has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76-0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70%, whilst maintaining a sensitivity between 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40 mL are PSA > 1.6 ng/mL, > 2.0 ng/mL, and > 2.3 ng/mL, for men with BPH in their 50s, 60s, and 70s, respectively [48].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [49]. 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 [50, 51].

4.6.2 PSA and the probability of PCa

The role of PSA in the diagnosis of PCa is presented by the EAU Guidelines on Prostate Cancer [52]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed.

4.6.3 PSA and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [53]. In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and maximum flow-rate (Q_{max}) [54]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression [55].

In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of acute urinary retention (AUR) and BPE-related surgery [56, 57]. 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 [58]. 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% [59]. Furthermore, in an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels [60].

Recommendations	LE	GR
Measure prostate-specific antigen (PSA) if a diagnosis of prostate cancer will change management.	1b	A
Measure PSA if it assists in the treatment and/or decision making process.	1b	A

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 [61]. Even though BPO may be responsible for these complications, there is no conclusive evidence on the mechanism [62].

One study reported that 11% of men with LUTS had renal insufficiency [61]. 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.* [63] reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels. Koch *et al.* [64] concluded that only those with an elevated creatinine level require investigational ultrasound (US) of the kidney.

In the Olmsted County community-dwelling men, there was a cross-sectional association between signs and symptoms of BPO (though not prostate volume) and chronic kidney disease (CKD) [65]. In 2,741 consecutive patients who presented with LUTS, decreased Q_{max}, a history of hypertension and/or diabetes were associated with CKD [66]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [67]. Patients with renal insufficiency are at an increased risk of developing post-operative complications [68].

Recommendation	LE	GR
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.	3	A*

Upgraded based on Panel consensus.

4.8 Post-void residual urine

Post-void residual (PVR) urine can be assessed by transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function (detrusor underactivity) [69, 70]. 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 predict BOO [71]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although a large PVR may indicate a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom progression [56, 57].

Monitoring of changes in PVR over time may allow for identification of patients at risk of acute urinary retention (AUR) [57]. This is of particular importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients on α1-blocker or WW [72]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established and this is a research priority.

Recommendation	LE	GR
Measure post-void residual in the assessment of male LUTS.	3	B

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 [73, 74], it is useful to repeat uroflowmetry measurements, especially if thevoided 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% [75]. 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 [76], detrusor underactivity or an under-filled bladder [77]. 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 [78] and correlating symptoms with objective findings.

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

4.10 Imaging

4.10.1 Upper urinary tract

Routine imaging of the upper urinary tract in men with LUTS is not recommended, as these men are not at increased risk for upper tract malignancy or other abnormalities when compared to the overall population [64, 79-81]. Several arguments support the use of renal US in preference to intravenous urography (IVU). Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, radiation dose and less side effects [79].

Recommendation	LE	GR
Perform ultrasound of the upper urinary tract in men with LUTS and a large post-void residual, or haematuria, or a history of urolithiasis.	3	B

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 US or TRUS [79].

4.10.2.1 Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. open prostatectomy, enucleation techniques, transurethral resection, 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 [81].

Transrectal US is superior to suprapubic (transabdominal) volume measurement [82, 83]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach.

Recommendations	LE	GR
Perform imaging of the prostate (either by transrectal or transabdominal ultrasound) when considering medical treatment for male LUTS, if it assists in the choice of the appropriate drug.	3	B
Perform imaging of the prostate (either by transrectal or transabdominal ultrasound) when considering surgical treatment.	3	B

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 urethral strictures where suspected.

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.

Shoukry *et al.* evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [84]. 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}.

Anikwe showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV), and the pre-operative Q_{max} value in 39 symptomatic men aged 53-83 years [85]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [86]. 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 [86].

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

4.12 Urodynamics

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

4.12.1 Diagnosing bladder outlet obstruction

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

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [87, 88]. In men with LUTS attributed to BPE, DO was present in 61% and independently associated with BOO grade and ageing [87].

The prevalence of DUA in men with LUTS is 11-40% [89, 90]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [91, 92]. There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with PFS with respect to the outcome of treatment but one such study is ongoing in the UK.

A Cochrane meta-analysis was done to determine whether performing invasive urodynamic investigation reduces the number of men with continuing symptoms of voiding dysfunction. Two trials with 350 patients were included. Invasive urodynamic testing changed clinical decision making, patients who underwent urodynamics were less likely to undergo surgery; however, no evidence was found to demonstrate whether this led to reduced symptoms of voiding dysfunction after treatment [93].

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 may reflect the lack of evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 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 [94].

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.

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

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

4.13.1 Prostatic configuration/intravesical prostatic protrusion (IPP)

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [95]. 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 [95].

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

Intravesical prostatic protrusion correlates well with BPO (presence and severity) on urodynamic testing, with a PPV of 94% and a NPV of 79% [96]. 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} [97]. Furthermore, IPP also appears to successfully predict the outcome of a trial without catheter (TWOC) after AUR [98, 99]. However, no information with regard to intra- or inter-observer variability and learning curve is yet available. Therefore, 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 is 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 [100].

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 [101]. 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 [71]. 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 [102].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Q_{ave} of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. One study could not demonstrate any difference in BWT between patients with normal urodynamics, BOO or DO. However, the study did not use a specific bladder filling volume for measuring BWT [103]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [104]. 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 [105, 106]. Severe LUTS and a high UEBW (> 35 g) are risk factors for prostate/BPH surgery in men on α-blockers [107].

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 [108] and interobserver agreement [109]. A nomogram has also been derived [110] whilst a method in which flow is not interrupted is also under investigation [111].

The data generated with the external condom method [112] correlates with invasive PFS in a high proportion of patients [113]. Resistive index [114] and prostatic urethral angle [115] 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 by a systematic review performed by the Panel [116].

A total of 42 studies were included in this review, this summary print version is supplemented by a detailed online version (http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/). The majority were prospective cohort studies, and the diagnostic accuracy of the following non-invasive tests were assessed: penile cuff test; uroflowmetry; detrusor/bladder wall thickness; bladder weight; external condom catheter method; IPP; doppler US; prostate volume/height; near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the different urodynamic definitions of BOO used across different studies and the small number of studies for each test. It was found that specificity, sensitivity, PPV and NPV of the non-invasive tests were highly variable. Therefore, even though

several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive urodynamics remains the modality of choice.

Recommendation	LE	GR
None of the non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS can currently be recommended as an alternative to pressure-flow studies.	1a	B

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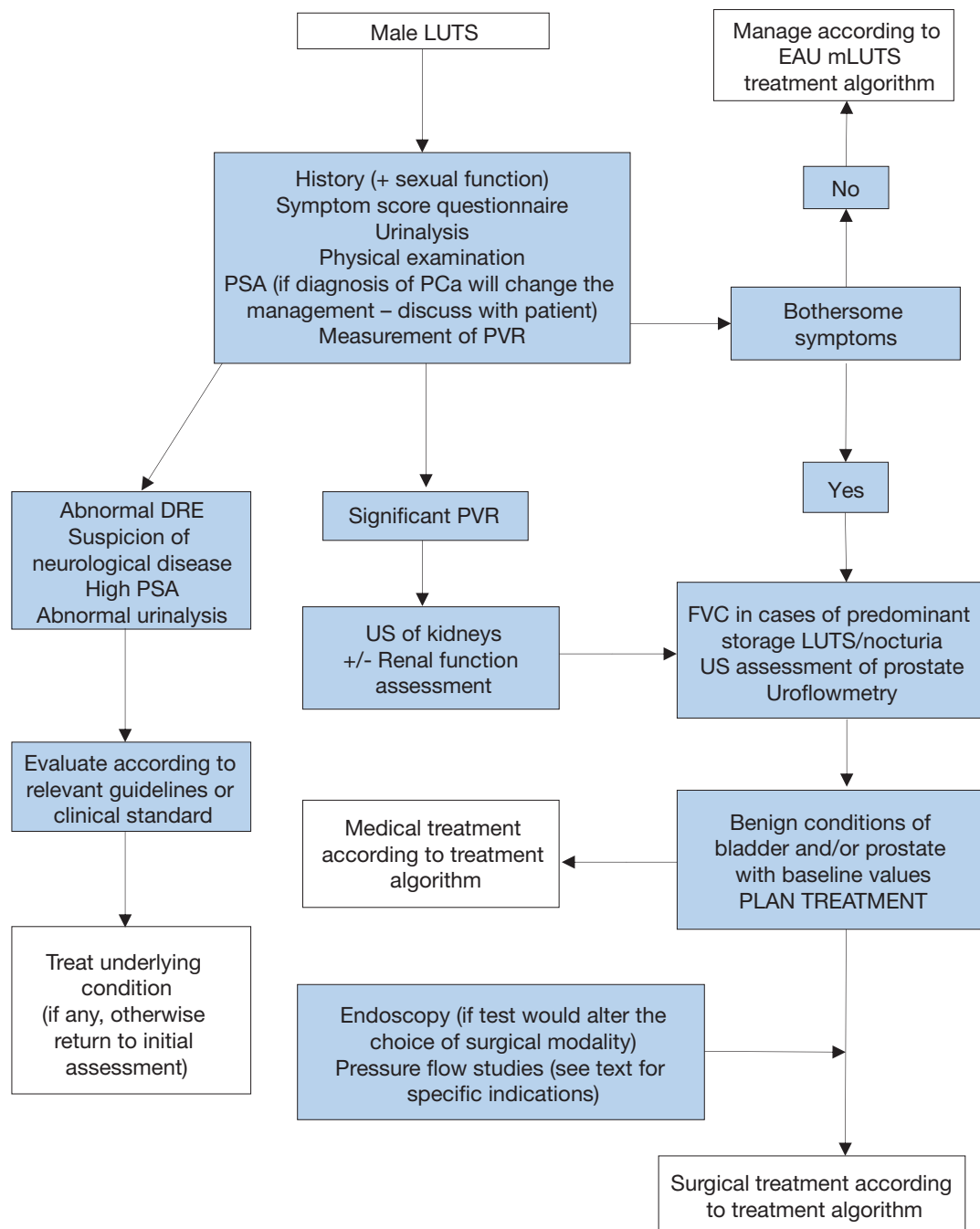
DRE = digital-rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms;
PCa = prostate cancer; PSA = prostate specific antigen; PVR = post-void residual; US = ultrasound.

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) [117, 118], whilst others can remain stable for years [119]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [120].

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 [121, 122]. Increasing symptom bother and PVR volumes are the strongest predictors of clinical failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

5.1.2 Behavioural and dietary modifications

It is customary for this type of management to include the following components:
- education (about the patient's condition);
- reassurance (that cancer is not a cause of the urinary symptoms);
- periodic monitoring;
- lifestyle advice [119, 120, 123, 124] such as:
  - reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public);
  - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and irritant effect, thereby increasing fluid output and enhancing frequency, urgency and nocturia;
  - use of relaxed and double-voiding techniques;
  - urethral milking to prevent post-micturition dribble;
  - distraction techniques such as penile squeeze, breathing exercises, perineal pressure, and mental tricks to take the mind off the bladder and toilet, to help control storage symptoms;
  - bladder retraining that encourages men to hold on when they have sensory urgency to increase their bladder capacity and the time between voids;
  - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply especially to diuretics);
  - providing necessary assistance when there is impairment of dexterity, mobility, or mental state;
  - treatment of constipation.

There now exists evidence (LE: 1b) that self-management as part of WW reduces both symptoms and progression [123, 124] (online supplementary Table S.12). Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only for up to a year [123].

5.1.3 Practical considerations

The components of self-management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [125]. Further research in this area is required.

Recommendations	LE	GR
Offer men with mild/moderate symptoms, minimally bothered by their symptoms, watchful waiting.	1b	A
Offer men with LUTS lifestyle advice prior to or concurrent with treatment.	1b	A

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 [126]. However, α1-blockers have little effect on urodynamically determined bladder outlet resistance [127], and treatment-associated improvement of LUTS correlates poorly with obstruction [128]. Thus, other mechanisms of action may be relevant.

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

α1-blockers currently available are: alfuzosin hydrochloride (alfuzosin); doxazosin mesylate (doxazosin); silodosin; tamsulosin hydrochloride (tamsulosin); terazosin hydrochloride (terazosin). α1-blockers exist in different formulations (online supplementary Table S.13). Although different formulations result in different pharmacokinetic and tolerability profiles, the overall clinical impact of the different formulations is modest.

Efficacy: Indirect comparisons and limited direct comparisons between α1-blockers demonstrate that all α1-blockers have a similar efficacy in appropriate doses [129]. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [130].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25% (online supplementary Table S.14). However, considerable improvements also occurred in the corresponding placebo arms [55, 130]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [55, 130].

α1-blockers can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less then one year, but α1-blockers do seem to be more efficacious in patients with smaller prostates (< 40 mL) in longer-term studies [56, 131-134]. α1-blocker efficacy is similar across age groups [130]. α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [132-134]. Nevertheless, 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 for alfuzosin and tamsulosin [135]. Patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α1-blocker-induced vasodilatation [136]. In contrast, the frequency of hypotension with the α1A- selective blocker silodosin is comparable with placebo [137]. In a large retrospective cohort analysis of men aged $\geq$ 66 years treated with α 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 [138].

An adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [139]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [140]. 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 systematic review concluded that α1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation [141]. 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 [142]. 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 often considered the first line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events. 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.

Recommendations	LE	GR
Offer α1-blockers to men with moderate-to-severe LUTS.	1a	A
Counsel patients about the treatment related side effects associated with selective versus non-selective α-blockers.	1a	A

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, a nuclear-bound steroid enzyme [143]. Two isoforms of this enzyme exist:

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

Two 5α-reductase inhibitors (5-ARIs) are available for clinical use: dutasteride and finasteride (online supplementary Table S.15). Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5-ARI). 5-ARIs act by inducing apoptosis of prostate epithelial cells [144] 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 [145]. Mean prostate volume reduction and PSA decrease may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy: Clinical effects relative to placebo are seen after a minimum treatment duration of at least six to twelve 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 (online supplementary Table S.16) [56, 133, 134, 146-152]. A indirect comparison and one direct comparative trial (twelve months duration) indicate that dutasteride and finasteride are equally effective in the treatment of LUTS [145, 153]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40 mL [154]. 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 at baseline [155, 156]. A long-term trial with dutasteride in symptomatic men with prostate volumes > 30 mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as, or even more effectively than, the α1-blocker tamsulosin [133, 152, 157]. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5-ARIs, but not α1-blockers, reduce the long-term (> one year) risk of AUR or need for surgery [56, 150, 158]. In the PLESS study, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55% at four years, compared with placebo [150]. In the MTOPS study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) [56]. A pooled analysis of randomised trials with two-year follow-up data, reported that treatment with finasteride significantly decreased the occurrence of AUR by 57%, and surgical intervention by 34%, in moderately symptomatic LUTS [159]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [160, 161].

Finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation [162].

Tolerability and safety: The most relevant adverse effects of 5-ARIs are related to sexual function, and include reduced libido, erectile dysfunction (ED) and less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume [56, 134, 145]. The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients.

Data from two trials on PCa chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARIs arms [163, 164]. Although no causal relationship with high-grade PCa has been proven, men taking 5-ARIs should be followed-up regularly using serial PSA testing and any confirmed PSA increase should be evaluated accordingly. There is a long-standing debate regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [165]. In a five year population-based study performed in Taiwan, Hsieh *et al.* could not identify an association between the use of 5-ARIs and increased cardiovascular side effects, in elderly men (> 65 years) [165].

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). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and the need for surgery. Due to the slow onset of action, they are suitable only for long-term treatment (years). Their effect on the serum PSA concentration needs to be considered in relation to PCa screening.

Recommendations	LE	GR
Use 5α-reductase inhibitors in men who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL).	1b	A
Counsel patients about the delayed symptom improvement with 5α-reductase inhibitors.	1a	A

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, epithelial cells of the salivary glands, or the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. M2 are more numerous, but the M3 subtype is functionally more important in bladder contractions in healthy humans [166, 167]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [168, 169].

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms (online supplementary Table S.17): darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [170, 171].

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 [172]. 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 [173]. 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% [174].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested (online supplementary Table S.18) [175-180]. 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 [176, 178, 181]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores, and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks [177, 180].

In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety Study, men who received tolterodine monotherapy saw improvement only in urgency incontinence, but not urgency, IPSS (total or storage subscore), or the overall percentage of patients reporting treatment benefit compared with placebo [179].

A further analysis showed that men with PSA levels of < 1.3 ng/mL (smaller prostates) might benefit more from antimuscarinic drugs [182]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [180, 183]. In a small RCT without placebo, propiverine improved frequency and urgency episodes [183]. In an open-label study, tolterodine decreased 24-hour micturition, nocturia and American Urological Association Symptom Index scores [180].

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

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8 mg showed higher PVRs (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) [179]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8 mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4 mg (both 0.8%).

These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Theoretically antimuscarinics might decrease bladder strength, and hence might be associated with PVR urine or urinary retention. A twelve week safety study on men with mild to moderate BOO showed that tolterodine increased the PVR (49 mL vs. 16 mL) but not acute urinary retention (3% in both arms) [184]. 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 [184].

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

Recommendations	LE	GR
Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B
Prescribe antimuscarinics with caution in men with a post-void residual volume > 150 mL.	4	C

5.2.4 Phosphodiesterase 5 inhibitors

Mechanism of action: Phosphodiesterase 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDEs might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate, or bladder [185]. Moreover, chronic treatment with PDE5Is seems to increase blood perfusion and oxygenation in the LUT [186]. Finally, PDE5Is could reduce chronic inflammation in the prostate and bladder [187]. The exact mechanism of PDE5Is on LUTS remains unclear.

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

Efficacy: Several RCTs have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS, and improve QoL (online supplementary Table S.19). However, Q_{max} did not significantly differ from placebo in most trials. In a meta-analysis, PDE5Is were found to improve IPSS and IIEF score, but not Q_{max} [188].

Tadalafil 5 mg reduces IPSS by 22-37% (online supplementary Table S.19), and improvement may be seen within a week of initiation of treatment [189]. A three point or greater total IPSS improvement was observed in 59.8% of tadalafil treated men within one week and in 79.3% within four weeks [190]. The maximum trial (open label) duration was 52 weeks [191]. 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 [192]. In a recent post hoc analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/ comorbidities except for patients receiving more than one antihypertensive medication. The use of diuretics may contribute to patients' perception of a negated efficacy [193]. Among sexually active men > 45 years with comorbid LUTS/BPH and ED, tadalafil improved both conditions [194].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%, p < 0.001) vs. indirect (7.5%, p = 0.32) treatment effects via IIEF-EF improvement [195]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [196].

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 [188]. The effects of tadalafil 5 mg combined with finasteride 5 mg were assessed in a 26-week placebo-controlled RCT. The combination of tadalafil and finasteride provided an early improvement in urinary symptoms (p < 0.022 after 4, 12 and 26 weeks), with a significant improvement of storage and voiding symptoms and QoL. Combination therapy was well tolerated and improved erectile function [197]. 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 [188]. Discontinuation rate due to adverse effects for tadalafil was 2.0% [198] and did not differ by age, LUTS severity, testosterone levels, or prostate volume in the pooled data analyses [192].

PDE5Is are contraindicated in patients using nitrates, the potassium channel opener nicorandil, or the α1-blockers doxazosin and terazosin. They are also contraindicated in patients who have unstable angina pectoris, have had a recent myocardial infarction (< three months) or stroke (< six months), myocardial insufficiency (New York Heart Association stage > 2), hypotension, poorly controlled blood pressure, significant hepatic or renal insufficiency, or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is.

Practical considerations: To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without ED. The meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [188]. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one year follow-up [191], therefore conclusions about its efficacy or tolerability greater than one year are not possible. There is limited information on reduction of prostate size and no data on disease progression.

Recommendation	LE	GR
Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction.	1a	A

5.2.5 Plant extracts - phytotherapy

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). The most widely used plants are Cucurbita pepo (pumpkin seeds), Hypoxis rooperi (South African star grass), Pygeum africanum (bark of the African plum tree), Secale cereale (rye pollen), Serenoa repens (syn. Sabal serrulata; saw palmetto) and Urtica dioica (roots of the stinging nettle).

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids, and lectins [199]. *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 [199-201]. These effects have not been confirmed *in vivo*, 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 [202]. In addition, batches from the same producer may contain different concentrations of active ingredients [203]. A review of recent extraction techniques and their impact on the composition/biological activity of Serenoa repens based available 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 [204]. Thus the pharmacokinetic properties can vary significantly.

Online supplementary Table S.20 presents the trials with the highest LE for each plant extract. In general, no phytotherapeutic agent has been shown to reduce prostate size, and no trial has proven a reduction of BOO or a decrease in disease progression.

A cochrane meta-analyses suggest that men treated with Pygeum africanum were twice as likely to report symptom improvement whilst men treated with Secale cereale were twice as likely to benefit from therapy compared to placebo and that Serenoa repens was not superior to placebo, finasteride, or tamsulosin for IPSS (similar levels of IPSS improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence) [205-207].

Recently, short-term studies on the combination of plant extracts with tamsulosin have been published with promising results [208, 209]. Combination treatment with Serenoa Repens (SeR), lycopene (Ly), selenium (Se) and tamsulosin was more effective than single therapies (SeR-Ly-Se or tamsulosin) in improving IPSS and increasing Q_{max} in patients with LUTS at twelve months. The combination treatment of Serenoa repens and tamsulosin was shown to be more effective than tamsulosin monotherapy in reducing storage symptoms but changes in IPSS, voiding subscore, QoL, Q_{max}, PVR, PSA, and prostate volume showed no significant differences between the two groups.

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

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

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

5.2.6 *Beta-3 agonist*

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

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 [210-214]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency incontinence, and urgency and also patient perception of treatment benefit. These studies had a predominantly female study population.

Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [215], 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 [216].

Tolerability and safety: The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [210-213]. 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. 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 [210]. 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 [217]. The overall change in PVR with mirabegron is small [217].

Practical considerations: Long-term studies on the efficacy and safety of mirabegron in men of any age with LUTS are not yet available. Studies on the use of mirabegron in combination with other pharmacotherapeutic agents for male LUTS are pending. However, pharmacokinetic interaction upon add-on of mirabegron or tamsulosin to existing tamsulosin or mirabegron therapy does not cause clinically relevant changes in safety profiles [218]. One small study has looked at change in symptom scores in men receiving mirabegron with tamsulosin 0.2 mg daily [219]. A phase four study, with a small proportion of male subjects, reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [220].

Recommendation	LE	GR
Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms.	1b	B

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 (online supplementary Table S.21). 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 [147, 148, 221]. 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 [56].

Long-term data (four years) from MTOPS, and Combination of Avodart and Tamsulosin (CombAT) studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α-blocker alone in reducing the risk of AUR or need for surgery [56, 133, 134].

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 [134]. Thus the differences in MTOPS may reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial [222, 223]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [222], 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 [223]. LUTS 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 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) [56]. In addition, finasteride (alone or in combination), but not doxazosin, significantly reduced both the risks of AUR and the need for BPH related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71%, and symptom deterioration by 41% compared with tamsulosin, after four years [224]. 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 1.8 points (p < 0.001) [225]. 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 [226].

More recently, a combination of the 5-ARI, finasteride, and tadalafil 5 mg was tested in a large scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in the chapter on PDE5Is [197].

Tolerability and safety: Adverse events for both drug classes have been reported with combination treatment [56, 133, 134]. 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.

Practical considerations: Compared with α1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max}, and is superior in prevention of disease progression. However, combination therapy is also associated with a higher rate of adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than twelve months) is intended and patients should be informed about this. Discontinuation of the α1-blocker after six months might be considered in men with moderate LUTS.

Recommendation	LE	GR
Use combination treatment of an α1-blocker and 5α-reductase inhibitor in men with moderate-to-severe LUTS and risk of disease progression (e.g. prostate volume > 40 mL).	1b	A

5.2.7.2   α1-blockers + muscarinic receptor antagonists

Mechanism of action: Combination treatment consists of an α1-blocker together with an antimuscarinic aiming to antagonise both α1-adrenoceptors and muscarinic receptors. The possible combinations have not all been tested in clinical trials yet.

Efficacy: Several RCTs and prospective studies investigated combination therapy, lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α1-blocker [179, 180, 224, 227-233] (online supplementary Table S.22). One trial used the α1-blocker naftopidil (not registered in most European countries) with and without antimuscarinics [234]. 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 [235].

Combination treatment is more efficacious in reducing urgency, UUI, voiding frequency, nocturia, or IPSS compared with α1-blockers or placebo alone, and improves QoL [179, 236]. Symptom improvement is higher regardless of PSA concentration, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3 ng/mL [182].

Persistent LUTS during α1-blocker treatment can be reduced by the additional use of an antimuscarinic, [180, 224, 227, 233, 237, 238]. Two systematic reviews of the efficacy and safety of antimuscarinics in men suggested that combination treatment provides significant benefit [239, 240]. Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [241]. Long term use of combination therapy has been reported in patients receiving treatment for up to a year, showing symptomatic response is maintained, with a low incidence of AUR [242]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150 mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health related quality of life (HRQoL) compared with placebo and α1-blocker monotherapy [243].

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 xerostomia. Some side-effects (e.g. xerostomia or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low [239, 240]. Antimuscarinics do not cause evident deterioration in maximum flow rate used in conjunction with an α1-blocker in men with OAB symptoms [236, 244].

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 [245]. The combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo [245].

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.

Recommendations	LE	GR
Use combination treatment of an 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.	1b	B
Prescribe combination treatment with caution in men with a post-void residual volume > 150 mL.	2b	B

5.3   Surgical treatment

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

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

Efficacy: In a recent analysis of 20 contemporary RCTs with a maximum follow-up of five years, TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL score (-69%), and PVR (-77%) [246]. 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 [247]. 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 [92].

Online supplementary Table S.24 presents RCTs comparing TUIP with TURP [248-255]. A meta-analysis of short- and long-term data from ten RCTs found similar LUTS improvements and lower but insignificant improvements in Q_{max} for TUIP [250]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30 mL and three < 60 mL.

A second prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. A review analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of sixteen months [256]. In a large-scale study of 20,671 men, the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at one, five, and eight years follow-up, respectively, and the respective incidence of re-TURP was 2.9%, 5.8% and 7.4% [257]. A meta-analysis of six trials showed that re-operation was more common after TUIP (18.4%) than after TURP (7.2%) [250].

Tolerability and safety: Peri-operative mortality and morbidity have decreased over time, but the latter remains considerable (0.1% and 11.1%, respectively) [258]. The possibility of increased long-term mortality compared to open surgery [259] has not been verified [260-262]. Data from 20,671 TURPs and 2,452 open prostatectomies (OP) showed that short- and long-term procedural mortality was similar (0.7% vs. 0.9% at 90 days, 2.8% vs. 2.7% at one year, 12.7% vs. 11.8% at five years, 20% vs. 20.9% at eight years) and that the eight year myocardial infarction rates were identical (4.8% vs. 4.9%) [257].

The risk of TUR-syndrome decreased to < 1.1% [256, 263]. No case has been recorded after TUIP. Data from 10,654 TURPs reported bleeding requiring transfusion in 2.9% [258]. The risk after TUIP is negligible. Similar results for TURP complications were reported by an analysis of contemporary RCTs using TURP as a comparator: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%), and UTI 4.1% (0-22%) [246]. Long-term complications comprise urinary incontinence (1.8% after TUIP vs. 2.2% after TURP), urinary retention and UTIs, bladder neck contracture (BNC) (4.7% after TURP), urethral stricture (3.8% after TURP vs. 4.1% after TUIP), retrograde ejaculation (65.4% after TURP vs. 18.2% after TUIP), and ED (6.5% after TURP) [256].

Practical considerations: TURP and TUIP are effective treatments for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (< 30 mL and 30-80 mL suitable for TUIP and TURP, respectively). No studies on the optimal cut-off value exist but the complication rates increase with prostate size [258]. The upper limit for TURP is suggested as 80 mL (based on Panel expert opinion, under the assumption that this limit depends on the surgeon's experience, resection speed, and choice of resectoscope size).

5.3.1.1 Modifications of TURP: bipolar TURP

Mechanism of action: Bipolar TURP (B-TURP) addresses a major limitation of monopolar TURP (M-TURP) by allowing performance in normal saline. Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally; energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ("true" bipolar systems) or the sheath ("quasi" bipolar systems). Prostatic tissue removal is identical to M-TURP; however, B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue. Energy from the loop is transmitted to the saline solution, resulting in excitation of sodium ions to form plasma; molecules are then easily cleaved under relatively low voltage enabling resection. During coagulation, heat dissipates within vessel walls, creating a sealing coagulum and collagen shrinkage. The various bipolar devices available differ in the way in which current flow is delivered [264, 265].

Efficacy: Bipolar TURP is the most widely and thoroughly investigated alternative to M-TURP. Results from > 40 RCTs [266] have been reported, of which around half have been pooled in RCT-based meta-analyses [246, 267-270]. Early pooled results concluded that no clinically relevant differences exist in short-term (up to twelve months) efficacy (IPSS, QoL score and Q_{max}) [268]. Subsequent meta-analyses supported these conclusions [246, 267, 269, 270], though trial quality was generally poor. Data from RCTs with a follow-up of 12-60 months show no differences in efficacy parameters (online supplementary Table S.25) [271-277].

A meta-analysis has been recently conducted to specifically evaluate the quasi-bipolar Transurethral Resection in Saline (TURis, Olympus Medical) system vs. M-TURP, (http://www.nice.org.uk/guidance/mtg23/

resources/the-turis-system-for-transurethral-resection-of-the-prostate-64371933166021). Ten unique RCTs (1,870 patients) were included. It was concluded that TURis was of equivalent efficacy to M-TURP.

Tolerability and safety: Early pooled results concluded that no differences exist in short-term (up to twelve months) urethral stricture/BNC rates, but B-TURP is preferable due to a more favourable peri-operative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; shorter irrigation, catheterisation, and possibly hospitalisation times) [268]. Subsequent meta-analyses supported these conclusions [246, 267, 269, 270]. However, trial quality was relatively poor and limited follow-up might cause under-reporting of late complications, such as urethral stricture/BNC [268]. Data from individual RCTs with a follow-up of 12-60 months showed no differences in urethral stricture/BNC rates [270] (online supplementary Table S.25). However, in a recent RCT, a significantly higher stricture (urethral stricture + BNC) rate was detected for the first time in the B-TURP arm [278]. In this trial, 136 patients were randomised 1:1 to B-TURP (TURis) or M-TURP arm and followed up for 36 months. The primary endpoint was safety, including long-term complications such as strictures (urethral stricture + BNC). A significant difference in stricture rates favouring M-TURP was detected (6.6% vs. 19.0%). When patients were stratified according to prostate volume, no difference was detected in stricture rates between the arms in those with a prostate volume of up to 70 mL (TURis 3/40 [7.5%] vs. M-TURP: 3/39 [7.7%]; P = 1.00). However, in patients with prostate volume > 70 mL, a significantly higher stricture rate was seen in those submitted to TURis (9/23 [39.1] vs. 1/22 [4.6%]; P = 0.01). Furthermore, in another RCT, a significantly higher BNC (but not urethral stricture) rate was detected for the first time in the B-TURP arm [279]. In this trial 137 patients were randomised 1:1 to B-TURP (performed with a "true" bipolar system [Gyrus PK SuperPulse, Olympus Medical]) or M-TURP arm and followed up to twelve months [279]. A significant difference in BNC rates favouring M-TURP was detected (0.0% vs. 8.5%; P=0.02), reinforcing a previously expressed potential association of BNC formation with the extremely focused electrical activity of a "true" bipolar system at the prostate level and thus, in close proximity to the bladder neck [276].

A RCT using the erectile function domain of the IIEF (IIEF-ED) showed that M-TURP and B-TURP have a similar effect on erectile function [280]. A comparative evaluation 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) [281].

A meta-analysis (http://www.nice.org.uk/guidance/mtg23/resources/the-turis-system-fortransurethral-resection-of-the-prostate-64371933166021) has shown that TURis reduces the risk of TUR-syndrome and the need for blood transfusion compared to M-TURP. It is plausible that TURis reduces length of hospital stay and re-admissions after surgery, although the evidence on these outcomes is limited.

Practical considerations: B-TURP offers an attractive alternative to M-TURP in patients with moderate-to-severe LUTS secondary to BPO, with similar efficacy but lower peri-operative morbidity [268]. The duration of improvements with B-TURP were documented in a number of RCTs with a follow-up of greater than twelve months. Mid-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP. The choice of B-TURP should be based on equipment availability, surgeon's experience, and patient's preference.

Recommendations	LE	GR
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe.	1a	A
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.	1a	A

5.3.2 Open prostatectomy

Mechanism of action: Open prostatectomy is the oldest surgical treatment for moderate-to-severe LUTS secondary to BPO. Obstructive adenomas are enucleated using the index finger, approaching from within the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands (> 80-100 mL).

Efficacy: A few RCTs showed that holmium laser enucleation of the prostate (HoLEP), photoselective vaporisation of the prostate (PVP) and more recently, enucleation of the prostate using bipolar circuitry lead to similar outcomes compared to OP in men with large glands at a significantly lower complication rate [282-289]. 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% [282-284, 290, 291]. Efficacy is maintained for up to six years [292].

Two RCT-based meta-analysis evaluated the overall efficacy of endoscopic enucleation of the

prostate (EEP) vs. OP for treating patients with large glands [293, 294]. The larger study included RCTs involving 758 patients. Five RCTs compared OP with HoLEP [282, 283, 287] and four RCTs compared OP with EEP using bipolar circuitry [272-274, 278]. Open prostatectomy was performed via a transvesical approach in all RCTs. At 3-, 6-, 12- and 24-month follow-up, there were no significant differences in Q_{max} between EEP and OP. Post-void residual, PSA, IPSS and QoL score also showed no significant difference at 1-, 3-, 6- and 12-months. Furthermore, IIEF also showed no significant difference at 3-, 6- and 12- months. It was concluded that EEP appears to be an effective minimally invasive option for treating large prostates.

Tolerability and safety: Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [291]. The estimated transfusion rate is about 7-14% [282, 290, 291, 293]. Long-term complications include transient urinary incontinence (up to 10%), BNC and urethral stricture (about 6%) [282-284, 293, 295].

Two recent RCT-based meta-analysis evaluated the overall safety of EEP vs. OP for treating patients with large glands [293, 294]. Operation time was significantly longer for EEP, due to a significantly longer operation time needed for HoLEP (no difference was detected between OP and EEP using bipolar circuitry). Catheterisation and hospitalisation time was significantly shorter with EEP whilst IIEF-5 showed no significant difference between OP and EEP at twelve months [283, 286, 294]. Endoscopic enucleation of the prostate was also associated with fewer blood transfusions but there were no significant differences regarding other complications. It was concluded that EEP appears to be a minimally invasive option for treating large prostates.

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

Recommendation	LE	GR
Offer endoscopic enucleation of the prostate or open prostatectomy to treat moderate-to-severe LUTS in men with prostate size > 80 mL.	1a	A

5.3.3 Transurethral microwave therapy (TUMT)

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

Efficacy: A systematic review and meta-analysis assessed therapeutic efficacy in different devices/software, including Prostatron (Prostasoft 2.0 and 2.5) and ProstaLund Feedback (online supplementary Table S.27) [281]. Symptom score after TUMT decreased by 65% in twelve months, compared to 77% after TURP. Transurethral resection of the prostate also achieved greater improvement in Q_{max} (119% vs. 70%) [296].

In one pooled analysis of three studies (two RCTs and one cohort study), with a twelve month follow-up, responder rate was 85.3% for ProstaLund Feedback TUMT (PLFT) and 85.9% for TURP [297]. The IPSS showed a subjective, non-inferior improvement with PLFT [297]. However, although both PLFT and TURP improved Q_{max} significantly, PLFT was inferior.

Previously, urinary retention was considered a contraindication for TUMT. Nowadays, LE:2b studies have reported a 77-93% short-term success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously [298-301]. In one study with longer follow-up, cumulative retreatment risk at five years was estimated to be 42% for those without retention and 59% for those with retention at the baseline [302].

An RCT-based systematic review [296] (though the trials had different follow-up periods) found that TUMT patients (7.54/100 person-years) were more likely than TURP patients (1.05/100 person-years) to require retreatment for symptoms.

In a multicentre RCT with a five year follow-up, no significant differences were found in Q_{max} and IPSS between TUMT (PLFT; the Core-Therm device) and TURP. Additional treatment was needed in 10% after TUMT and in 4.3% after TURP. However, one must be cautious when interpreting these data because there was substantial loss to follow-up; less than half of the patients were analysed at four to five years. In addition, patients who remained in the study were likely to represent the best data (responders).

Tolerability and safety: Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency, and require pain medication for therapy. Pooled morbidity data comparing TUMT and TURP have been published [296, 297, 303]. In the Cochrane review of RCTs, catheterisation time, dysuria/urgency

and urinary retention rates were significantly smaller with TURP. On the other hand, hospitalisation time, haematuria, clot retention, transfusion, TUR-syndrome, sexual dysfunction and retreatment rates for urethral stricture/BNC were significantly smaller for TUMT [296].

Practical considerations: Endoscopy prior to TUMT is essential to identify the presence of a prostate middle lobe or an insufficient length of the prostatic urethra. Due to the low peri- and post-operative morbidity and lack of need for anaesthesia, TUMT is a true outpatient procedure and an option for (elderly) patients with comorbidities or greater anaesthesia risks [304].

Recommendations	LE	GR
Transurethral microwave therapy achieves symptom improvement comparable with, transurethral resection of the prostate (TURP) but transurethral microwave therapy is associated with decreased morbidity and lower flow improvements.	1a	A
Durability is in favour of TURP which has lower retreatment rates compared to transurethral microwave therapy.	1a	A

5.3.4 Transurethral needle ablation of the prostate

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

Efficacy: A meta-analysis of two RCTs, two non-randomised comparative and ten single-arm studies showed that TUNA™ achieved a 50% decrease in IPSS and a 70% improvement in Q_{max} at one year [305]. These findings are supported by a more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) [306]. Transurethral needle ablation of the prostate significantly improved IPSS and Q_{max}, but compared to TURP these improvements were significantly lower at twelve months. Mean differences in TURP vs. TUNA™ were 4.7 for IPSS and 5.9 mL/s for Q_{max} [306].

Clinical studies on the impact of TUNA™ on BPO [307, 308] showed a significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max}. However, one out of six patients were still obstructed at one year [307].

The overall retreatment rate after TUNA™ was 19% based on an analysis of seventeen non-comparative studies (median follow-up unreported; only three out of seventeen studies had follow-up exceeding two years [306]); a rate considerably higher than that seen with TURP.

Tolerability and safety: Transient urinary retention and storage LUTS are common for weeks post-operatively [309, 310]. Generally, TUNA™ is associated with fewer adverse events compared to TURP, including mild haematuria, UTIs, strictures, incontinence, ED, and ejaculation disorders [305].

Practical considerations: Transurethral needle ablation of the prostate can be performed as a day-case procedure under local anaesthesia or sedation [309]. However, TUNA™ is not suitable for prostates > 75 mL or isolated bladder neck obstruction. In addition, TUNA™ cannot effectively treat prostatic middle lobes. There are also concerns about the durability of the effects achieved by TUNA™.

Recommendations	LE	GR
Transurethral needle ablation is a minimally invasive alternative with decreased morbidity compared to transurethral resection of the prostate (TURP) but with less efficacy	1a	A
Durability is in favour of TURP with lower retreatment rates compared to transurethral needle ablation.	1a	A

5.3.5 Laser treatments of the prostate

5.3.5.1 Holmium laser enucleation and holmium laser resection of the prostate

Mechanism of action: The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 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 [311]. Holmium laser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) result in BPO relief and, secondarily, in LUTS reduction.

Efficacy: In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at six or twelve months post-operatively (online supplementary Table S.29) [312]. One RCT comparing TURP with HoLRP with a minimum follow-up of four years showed no difference in urodynamics after 48 months [313]. Three meta-analyses covering trials on HoLEP vs. TURP found that symptom improvement was comparable or superior with HoLEP (online supplementary Table S.29) [314-316]. One RCT comparing photoselective vaporisation of the prostate (PVP) and HoLEP in patients with prostates > 60 mL showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP [317]. Another RCT on HoLAP and 80-W PVP showed comparable functional improvement within a median follow-up of 71 months [318].

RCTs indicate that HoLEP is as effective as OP for improving micturition in large prostates [282, 283], with similar re-operation rates after five years (5% vs. 6.7%, respectively) [282]. One RCT comparing HoLEP with TURP in a small number of patients with a seven year follow-up found that the functional long term results of HoLEP were comparable with TURP [319]. A retrospective study of HoLEP with the longest follow-up of up to ten years (mean 62 months) reported durable functional results with low re-operation rates [320].

Tolerability and safety: Dysuria is the most common post-operative complication [311, 314]. Compared to TURP, HoLRP has shorter catheterisation and hospitalisation times [312, 321]. Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP [313]. Three meta-analyses found that HoLEP has shorter catheterisation time and hospital stay, reduced blood loss, and fewer blood transfusions, but a longer operation time compared with TURP [314-316]. In a meta-analysis, no significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs. 4.4%), stress urinary incontinence (1.5% vs. 1.5%), and re-intervention (4.3% vs. 8.8%) [300]. HoLEP is superior to OP for blood loss, catheterisation and hospitalisation time [282, 283].

HoLEP has been safely performed in patients using anticoagulant medications [322, 323]. In a study of 83 patients, blood transfusion was required in seven patients (8%) [324]. A retrospective study compared the safety results of HoLEP in 39 patients who were on anticoagulant therapy at the time of their surgery, and 37 controls [323]. No transfusions were required and bleeding complication rates were not significantly different [323]. Short-term studies showed that patients with urinary retention could be treated with HoLEP [325, 326].

The impact on erectile function and retrograde ejaculation is comparable between HoLEP and TURP/OP [283, 327]. Erectile function did not decrease from baseline in either group; three quarters of sexually active patients had retrograde ejaculation after HoLEP.

Practical considerations: Holmium laser operations are surgical procedures that require experience and relevant endoscopic skills. The experience of the surgeon was the most important factor affecting the overall occurrence of complications [322, 328].

5.3.5.2   532 nm ('Greenlight') laser vaporisation of prostate
Mechanism of action: The Kalium-Titanyl-Phosphate (KTP) and the lithium triborate (LBO) lasers work at a wavelength of 532 nm. Laser energy is absorbed by haemoglobin, but not by water. Vaporisation leads to immediate removal of prostatic tissue, relief of BPO, and reduction of LUTS. In 2016 the standard Greenlight procedure was 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. These three "Greenlight" laser systems differ not only in maximum power output, but more significantly in fibre design and the associated energy tissue interaction of each.

Efficacy: A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 (online supplementary Table S.29) [329]. 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 [330-332]. With the 180-W (XPS) laser efficacy is comparable to TURP in terms of IPSS, Q_{max}, PVR volume, prostate volume reduction, PSA decrease and QoL questionnaires. The XPS laser prostatectomy is superior to TURP in terms of catheterisation time, length of hospital stay and time to stable health status.

The longest RCT using the 80-W KTP laser has a follow-up of only twelve months [330]. A case series showed durable functional outcomes with the 80-W KTP laser, with an overall retreatment rate of 8.9% at five years [333]. Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months reported a retreatment rate of 14.8% [334]. At twelve months self-reported urinary incontinence was 2.9% with XPS and 3.0% with TURP. Surgical re-intervention was comparably low after twelve months for both XPS and TURP.

Significant improvements in voiding parameters at a follow-up of twelve months were demonstrated urodynamically [335]. 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 [336]. The re-operation rate was

higher after PVP (11% vs. 1.8%; p = 0.04) [336]. Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months [331, 337].

A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement for the 180-W laser and the former Greenlight laser systems [338].

Tolerability and safety: A meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but shorter catheterisation time and length of hospital stay after PVP [329]. Blood transfusions and clot retention were less with PVP. No difference was noted in post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis [329]. According to the Goliath Study, 180-W Greenlight laser prostatectomy is non-inferior to TURP in terms of peri-operative complications, including post-operative dysuria rate (XPS 19.1%;TURP 21.8%). Post-operative Clavien III re-interventions are more likely within the first 30 days after TURP compared to XPS (3.8% vs. 9.8%; p = 0.04), but comparable after twelve months follow-up. There are more severe bleeding complications within 30 days after TURP and more mild bleeding complications after XPS laser prostatectomy over twelve months, leading to a comparable overall incidence between both techniques.

The Greenlight laser appears to be safe in high-risk patients under anticoagulation treatment [339-343]. In one study, anticoagulant patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [342]. Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomised trials [343-345].

The impact of Greenlight laser on sexual function and abnormal ejaculation was similar to that of TURP after twelve months [346]. In addition, no difference was reported between OP/TURP and Greenlight PVP for erectile function [347, 348], IIEF-5 scores are maintained after treatment. However, in patients with pre-operative IIEF-5 > 19, the post-operative IIEF-5 scores were significantly decreased at 6, 12, and 24 months [349].

Practical considerations: The 180-W XPS laser should be regarded as the reference for Greenlight laser prostatectomy. However, many former studies were done with the out-dated 80-W and 120-W lasers therefore, results need to be interpreted accordingly. Long-term results from the Goliath Study (180-W XPS vs. TURP) are pending. The intermediate two year follow-up data showed efficacy and safety outcomes similar to TURP [350].

5.3.5.3   Diode laser vaporisation of the prostate
Mechanism of action: For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318, and 1,470 nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [351].

Efficacy: Case series, and two comparative studies of vaporisation using a 980 nm diode laser or a 120-W HPS laser, are available [352-358]. Quality of life, IPSS, Q_{max}, and PVR improved significantly in all studies compared to baseline and were similar for both laser, at six and twelve months [352, 353].

One RCT with a twelve month follow-up compared the 980 nm diode laser with bipolar enucleation and found equal clinical outcome [359]. One small RCT with a six month follow-up comparing laser enucleation using a 1,318 nm diode laser with B-TURP reported similar efficacy (online supplementary Table S.29) [360]. This data is further supported by one RCT, comparing 980 nm diode laser vaporisation vs. TURP within a two year follow-up [361]. Redo TURP was more frequent in the diode laser group (online supplementary Table S.29) [359].

Tolerability and safety: Published studies on 980 nm laser vaporisation indicate high haemostatic potential, although anticoagulants or platelet aggregation inhibitors were taken in 24% and 52% of patients, respectively [352, 353]. Post-operatively, a high rate of dysuria was reported [352-354, 361]. Fibre modifications led to a significant reduction in surgical time [355]. Furthermore, the literature on diode vaporisation reports high re-operation rates (8-33%) and persisting stress urinary incontinence (9.1%) [352-354, 361]. In contrast, the two RCTs on diode laser enucleation showed that blood loss, hospitalisation and catheterisation time were in favour of diode laser enucleation, with equivalent clinical outcome for either bipolar enucleation [359] or TURP [360] during follow-up.

Practical considerations: Diode laser vaporisation leads to immediate improvement of LUTS due to BPO and provides good haemostatic properties. Diode laser enucleation seems to offer similar efficacy and safety when compared to either TURP or bipolar enucleation. Based on the limited number, mainly low quality RCTs and controversial data on the retreatment rate, results for diode laser vaporisation should be evaluated in further higher quality RCTs.

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

Mechanism of action: In the Tm:YAG laser, a wavelength between 1,940 and 2,013 nm is emitted in continuous wave mode. The laser is primarily used in front-fire applications [351, 362]. Different applications, ranging from vaporisation (ThuVaP), vaporesection (ThuVaRP), and enucleation (ThuVEP/ThuLEP: similar enucleating techniques) are published.

Efficacy: One RCT with a four year follow-up comparing ThuVARP to M-TURP, showed comparable efficacy and favourable re-operation rates in the ThuVaRP group [363] (online supplementary Table S.29). One RCT and one non-RCT compared ThuVaRP with M-TURP [364, 365], while two RCTs comparing ThuVaRP and B-TURP were published recently [366, 367]. In summary, studies show comparable improvement of symptoms and voiding parameters. There are only a few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment [368-371]. ThuLEP and HoLEP were compared in one RCT with eighteen months follow-up with comparable outcomes in both arms (online supplementary Table S.29) [356]. Furthermore, ThuLEP and bipolar enucleation were compared in one RCT with twelve months follow-up. The outcome showed no difference with regard to efficacy whilst the decrease in hemoglobin level and catheter time were significantly lower for ThulEP [372].

Tolerability and safety: Thulium laser prostatectomy shows high intra-operative safety in RCTs [363, 364], as well as in case series in patients with large prostates [368] and anticoagulation or bleeding disorders [369, 373]. Catheterisation time, hospital stay, and blood loss were shorter compared to TURP [364-366]. The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and the re-operation rate was 0-7.1% during follow-up [364, 365, 374]. Urethral stricture after ThuVEP occurred in 1.6%, and the overall retreatment rate was 3.4% (mean follow-up 16.5 months) [375]. No urethral and bladder neck strictures after ThuLEP were reported during the eighteen months follow-up [376]. Recently, a study focused on post-operative complications after ThuVEP (vapoenucleation) reported adverse events in 31% of cases, with 6.6% complications greater then Clavien grade II [377]. 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% [373]. Two studies (one case control, one RCT vs. TURP) addressed the impact of ThuVEP on sexual function, demonstrating no effect on erectile function with increased prevalence of retrograde ejaculation post-operatively [378, 379].

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. Urethral stricture and bladder neck contracture accounted for 2.6 % and 1.6 % of patients, respectively. Persistent stress incontinence was found in 0.1 % whilst, re-operation due to BPH recurrence was required in 1.2 % patients [380].

In two RCTs on ThuLEP versus TURP, one RCT on ThuLEP versus bipolar enucleation and one RCT on ThuLEP versus HoLEP, ThuLEP appeared to be equivalent with regard to clinical efficacy and superior with regard to intra-operative haemostasis. The same was demonstrated for ThuVEP vs. TURP in one RCT [381].

Practical considerations: The limited number of RCTs and only a few studies with long-term follow-up (up to 48 months) support the efficacy of thulium laser prostatectomy therefore, there is a need for ongoing confirmation.

Recommendations	LE	GR
Holmium laser enucleation and 532-nm laser vaporisation of the prostate are alternatives to transurethral resection of the prostate (TURP) in men with moderate-to-severe LUTS leading to immediate, objective, and subjective improvements comparable with TURP.	1a	A
The short-term and mid-term functional results of 532-nm laser vaporisation of the prostate are comparable with TURP.	1b	A
The long-term functional results of holmium laser enucleation are comparable with TURP or open prostatectomy.	1b	A
Thulium enucleation may be an alternative to TURP and holmium laser enucleation in men with moderate-to-severe LUTS leading to immediate and mid-term objective and subjective improvements.	1b	A
Diode laser operations lead to short-term objective and subjective improvement.	1b	B
Tm:YAG vaporesection is an alternative to TURP for small- and medium-size prostates.	1b	A
With regard to intra-operative safety and haemostatic properties, diode and thulium lasers appear to be safe.	3	C
With regard to intra-operative safety, 532-nm laser vaporisation is superior to TURP.	1b	A
532-nm laser vaporisation should be considered in patients receiving anticoagulant medication or with a high cardiovascular risk.	3	B

5.3.6 Prostatic stents

Mechanism of action: The use of an endoprosthesis to preserve luminal patency is a well-established concept. Prostatic stents were primarily designed as an alternative to an indwelling catheter but have also been assessed as a primary treatment option in patients without significant comorbidities [382, 383].

A prostatic stent requires a functioning detrusor [384]. Permanent stents are biocompatible, allowing for epithelialisation. Temporary stents do not epithelialise and may be either biostable or biodegradable. Temporary stents can provide short-term relief from BPO in patients temporarily unfit for surgery, or after minimally invasive treatment [384].

Efficacy: Several small case studies on a range of stents of different designs and materials provide low level evidence for their use. Online supplementary Table S.30 describes the most important studies [382, 383, 385-388]. There was a substantial loss to follow-up in all studies. There are no studies comparing stents with sham or other treatment modalities, and only one RCT compared two versions of a prostatic stent for BPO [389].

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series (990 patients), with differing follow-ups [390]. These studies reported relevant symptom improvement and Q_{max} increase [390]. The pooled data from studies with patients who were catheter dependent showed that 84% of patients (148/176) regained the ability to void spontaneously after UroLume treatment [390, 391].

The data on non-epithelialising prostatic stents was summarised in a systematic review on the efficacy of Memokath, a self-expanding metallic prostatic stent [392]. Overall, IPSS was reduced by 11-19 points and Q_{max} increased by 3-11 mL/s [392].

Tolerability and safety: In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation [384]. The most immediate and common adverse events include perineal pain or bladder storage symptoms.

Practical considerations: Due to common side effects and a high migration rate, prostatic stents have a limited role in the treatment of moderate-to-severe LUTS. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment [384].

Recommendation	LE	GR
Offer prostatic stents as an alternative to catheterisation in men unfit for surgery.	3	C

5.3.7 Prostatic urethral lift

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

Efficacy: The available studies on PUL are presented in online supplementary Table S.31 [393-398]. In general, PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%). There is only one RCT comparing PUL with sham [393]. The primary endpoint was meet at three months with a 50% reduction in AUA-SI from 22.1 to 11.0 points and remained stable up to twelve months. Change for AUA-SI was 88% greater for the treatment group than sham control. Also Q_{max} increased significantly from 8.1 to 12.4 mL/s relative to baseline at three months and this result could still be 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 nor relative to sham control.

An RCT of 80 patients, conducted in nine European countries, comparing PUL to TURP was published in 2015. At twelve months, IPSS improvement was -11.4 for PUL and -15.4 for TURP. There was no retrograde ejaculation among PUL patients, while 40% of TURP patients lost the ability to ejaculate. Surgical recovery was measured using a validated instrument and confirmed that recovery from PUL is more rapid and more extensive in the first three to six months [399]. However, TURP resulted in much greater improvements in Q_{max} (+13.7 ± 10.4 mL/s) after twelve months compared to PUL. (4.0 ± 4.8 mL/s).

In a recent meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS (-7.2 to -8.7 points), Q_{max} (3.8 to 4.0 mL/s), and QoL (-2.2 to -2.4 points) [398]. Sexual function was preserved with a small improvement estimated at twelve months.

A multi-centre, randomised and blinded trial of PUL in men with bothersome LUTS due to BPH showed that at three years, average improvements from baseline were significant for total IPSS (41.1%), QoL (48.8%), Q_{max} (53.1%) and individual IPSS symptoms. Symptomatic improvement was independent of prostate size. There were no *de novo*, sustained ejaculatory or erectile dysfunction events and all sexual function assessments showed average stability or improvement after PUL [400].

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%). 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 [393-397].

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

Recommendation	LE	GR
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe. Inform patients that long-term effects have not been evaluated.	1a	B

5.3.8 *Novel interventions*
5.3.8.1 *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), NX-1207 and PRX302. The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons via cleavage of synaptosome-associated protein 25 (SNAP-25). However, BoNT-A also appears to act at various other levels by modulating the neurotransmissions of sympathetic, parasympathetic and sensory nerve terminals in the prostate, leading to a reduction in growth and apoptosis of the prostate [401]. The detailed mechanisms of action for the injectables NX-1207 and PRX302 are not completely understood, but experimental data associates apoptosis-induced atrophy of the prostate with both drugs [401].

Efficacy: Results from clinical trials have shown only modest clinical benefits, that do not seem to be superior to placebo, for BoNT-A [402, 403] (see online supplementary Table S.32). A recent systematic review and meta-analysis showed no differences in efficacy compared with placebo, and concluded that there is no evidence of clinical benefits in medical practice [404]. With regard to NX-1207 and PRX302, the positive results from Phase II-studies have not be confirmed in Phase III-trials thus far [405, 406].

Safety: Studies including safety assessments have reported only a few mild and self-limiting adverse events for all injectable drugs [401]. Furthermore, a recent systematic review and meta-analysis showed low incident rates of procedure-related adverse events [404].

Practical considerations: Although experimental evidence for compounds such as NX-1207, PRX302 and BoNT-A was promising for their transition to clinical use, randomised, controlled studies of all three of these injectable agents have not been able to reveal any significant clinical benefits.

Recommendation	LE	GR
Do not offer Botulinum toxin injection treatment to patients with male LUTS.	1a	B

5.3.8.2 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 [407], while the first RASP was reported in 2008 [408]. Both LSP and RASP are performed using different personalised techniques, developed based on the transcapsular (Millin) or transvesical (Freyer) techniques of OP. An extraperitoneal approach is mostly used for LSP, while a transperitoneal approach is mostly used for RASP.

Efficacy: A recent systematic review and meta-analysis showed that in 27 observational studies including 764 patients, the mean increase in Q_{max} was 14.3 mL/s (95% CI 13.1-15.6), and the mean improvement in IPSS was 17.2 (95% CI 15.2-19.2). Mean duration of operation was 141 min (95% CI 124-159), and the mean intra-operative blood loss was 284 mL (95% CI 243-325). One hundred and four patients (13.6%) developed a surgical complication. In comparative studies to OP, length of hospital stay (WMD -1.6 days, p = 0.02), length of catheter use (WMD -1.3 days, p = 0.04) and estimated blood loss (WMD -187 mL, p = 0.015) were significantly lower in the MISP group, while the duration of operation was longer than in OP (WMD 37.8 min, p < 0.0001). There were no differences in improvements in Q_{max}, IPSS and peri-operative complications between both procedures (see online supplementary Table S.33).

Two recent retrospective series on RASP are now available which were not included in the meta-analysis which confirm these findings [409, 410]. The largest retrospective series reports 1,330 consecutive cases including 487 robotic (36.6%) and 843 laparoscopic (63.4%) simple prostatectomy cases. The authors confirm that both techniques can be safely and effectively done in selected centres [409]. Technical variations also include an intrafasical (IF) approach. Comparing laproscopic, robotic and robotic IF simple prostatectomy, the IF-RSP technique is safe and effective, with results at one year follow-up for continence, IPSS and Sexual Health Inventory for Men scores similar to those for the LSP and RSP techniques [411].

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 hematuria requiring irrigation, UTI and AUR; in the LSP series, the most common complications were UTI, ileus and AUR.

Practical considerations: Data on MISP are increasing from selected centres. MISP seems comparable to OP in terms of efficacy and safety, providing similar improvements in Q_{max} and IPSS [412]. 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.

Evidence Statement	LE
Minimal invasive simple prostatectomy seems to be feasible in men with prostate sizes > 80 mL needing surgical treatment; however, RCTs are needed.	2a

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. Online supplementary Table S.34 provides differential information about speed of onset and influence on basic parameters of conservative, medical or surgical treatment options.

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.
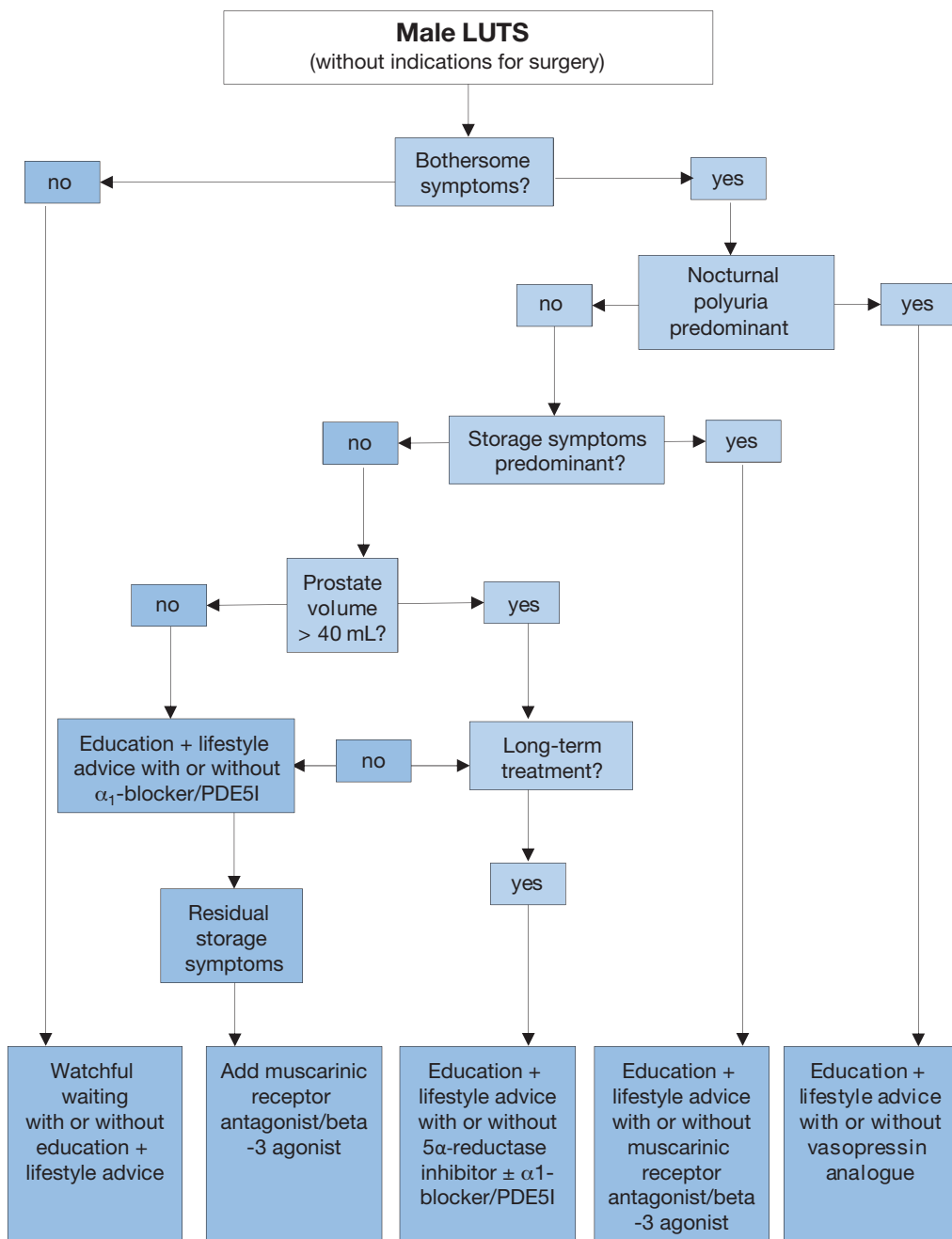
LUTS = lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitors.
Notice: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

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

Male LUTS
with absolute indications for surgery or non-responders to medical treatment or those who do not want medical treatment but request active treatment

High-risk patients? → low / high

Can have surgery under anaesthesia? → yes / no

Can stop anticoagulation/antiplatelet therapy → yes / no

Prostate volume → < 30 mL / 30 – 80 mL / > 80 mL

< 30 mL
TUIP (1)
TURP

30 – 80 mL
TURP (1)
Laser enucleation
Bipolar enucleation
Laser vaporisation
PU lift
TUMT
TUNA

> 80 mL
Open prostatectomy (1)
HoLEP (1)
Bipolar enucleation (1)
Laser vaporisation
Thulium enucleation
TURP

Laser vaporisation (1)
Laser enucleation

TUMT
TUNA
PU lift
Stent

(1) Current standard/first choice. The alternative treatments are presented in alphabetical order.
Notice: Readers are strongly recommended to read the full text that highlights the current position of each treatment in detail.

Laser vaporisation includes GreenLight, thulium, and diode lasers vaporisation;
Laser enucleation includes holmium and thulium laser enucleation.
HoLEP = holmium laser enucleation; TUIP = transurethral incision of the prostate; TUMT = transurethral microwave therapy; TUNA = transurethral needle ablation; TURP = transurethral resection of the prostate.

5.5   Management of Nocturia in men with lower urinary tract symptoms

The following section reports a systematic review 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. This summary

print version is supplemented by a detailed online version (http://uroweb.org/guideline/ treatment-of-non-neurogenic-maleluts/).

Nocturia is defined as the complaint of waking at night to void [2]. It reflects the relationship between the amount of urine produced while asleep, and the ability of the bladder to store the urine received. Nocturia can occur as part of lower urinary tract dysfunction (LUTD), such as OAB and chronic pelvic pain syndrome. Nocturia can also occur in association with other forms of LUTD, such as BOO, but here it is debated whether the link is one of causation or simply the co-existence of two common conditions. Crucially, nocturia may have behavioural, sleep disturbance (primary or secondary) or systemic causes unrelated to LUTD (Table 1). 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 1: 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.

Figure 5. Evaluation of Nocturia in non-neurogenic Male LUTS.
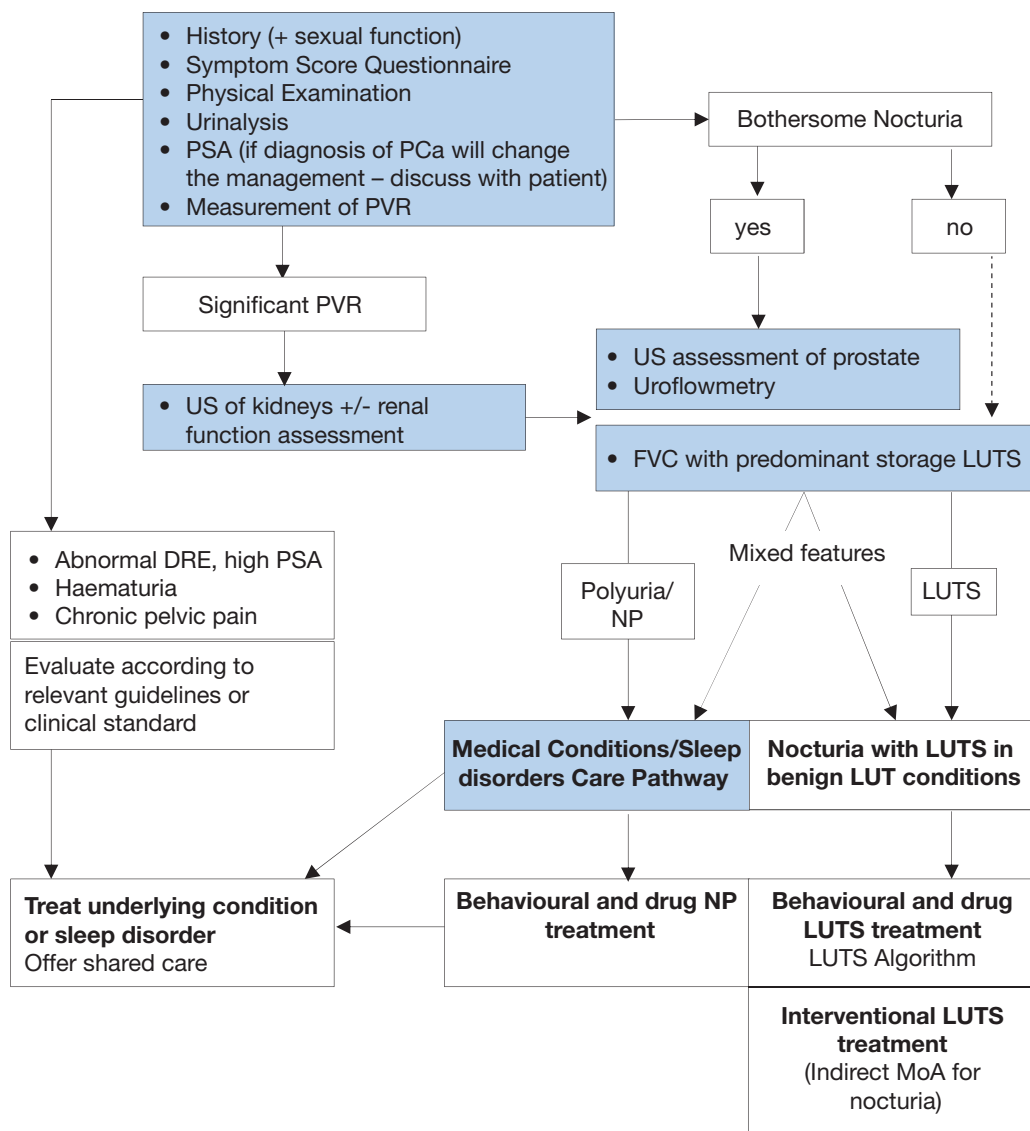
Assessment must establish whether the patient has polyuria, LUTS, sleep disorder or a combination. Therapy may be driven by the bother it causes, but non-bothersome nocturia may warrant assessment of a frequency volume chart (indicated by the dotted line) depending on history and clinical examination 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.

5.5.2 *Medical conditions and sleep disorders Shared Care Pathway*
Causative categories for nocturia comprise [413]:
1. Bladder storage problems;
2. 24-hour (global) polyuria (> 40 mL/kg urine output over a 24-hour period);
3. Nocturnal polyuria (NP; nocturnal output exceeding 20% of 24-hour urine output in the young, or 33% of urine output in people > 65 [2]);
4. Sleep disorders;
5. Mixed aetiology.

Potentially relevant systemic conditions are those which impair physiological fluid balance, including influences on: levels of free water, salt, other solutes and plasma oncotic pressure; endocrine regulation e.g. by antidiuretic hormone (ADH), 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 (Figure 6). They should not proceed along any LUTD management pathway unless a causative link with LUTD is justifiably suspected, and systemic or sleep abnormalities have been considered.

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

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

Figure 6: 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	**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
Interventional therapy • Therapy of refractory storage LUTS • Therapy of refractory voiding LUTS		

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 [414], with specific doses, titrated dosing, differing formulations, and options for route of administration. Antidiuretic therapy using desmopressin, with dose titration to achieve clinical response, is more effective than placebo in terms of reduced nocturnal voiding frequency and other outcome measures. Three studies evaluating titrated-dose desmopressin in which men were included, reported seven serious adverse events in 530 patients, with one death. There were seventeen cases of hyponatraemia and seven of hypertension. Headache was reported in 53 and nausea in fifteen.

Practical considerations

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

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. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia. Applicable medications include; selective α1-adrenergic antagonists [415], antimuscarinics [416-418], 5α-reductase inhibitors [419] and PDE5Is [420].

5.5.3.3   Other medications
Diuretics, agents to promote sleep [421], diuretics [422], non-steroidal anti-inflammatory agents (NSAIDs) [423] and phytotherapy [424]. 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.

Recommendations	LE	GR
Treatment should aim to address underlying causative factors, which may be behavioural, systemic condition(s), sleep disorders, lower urinary tract dysfunction, or a combination of factors.	4	A*
Discuss lifestyle changes to reduce nocturnal urine volume and episodes of nocturia, and improve sleep quality.	3	A*
Desmopressin may be prescribed to decrease nocturia due to nocturnal polyuria in men under the age of 65. Screening for hyponatremia must be undertaken at baseline, during dose titration and during treatment.	1a	A
α1-adrenergic antagonists may be offered to men with nocturia associated with LUTS.	1b	B
Antimuscarinic drugs may be offered to men with nocturia associated with overactive bladder.	1b	B
5α-reductase inhibitors may be offered to men with nocturia who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL).	1b	C
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	1b	B
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	C
Agents to promote sleep may be used to aid return to sleep in men with nocturia.	2	C

Upgraded based on Panel consensus.

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. FVC or bladder diaries should be used to assess response to treatment for predominant storage symptoms or nocturnal polyuria.

Patients receiving 5-ARIs should be reviewed after 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 as well as after one month, and if serum sodium concentration has remained normal, every three

months subsequently. The following tests are recommended at follow-up visits: serum-sodium concentration and frequency volume chart. The follow-up sequence should be restarted after dose escalation.

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

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

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

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8.   CONFLICT OF INTEREST

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