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

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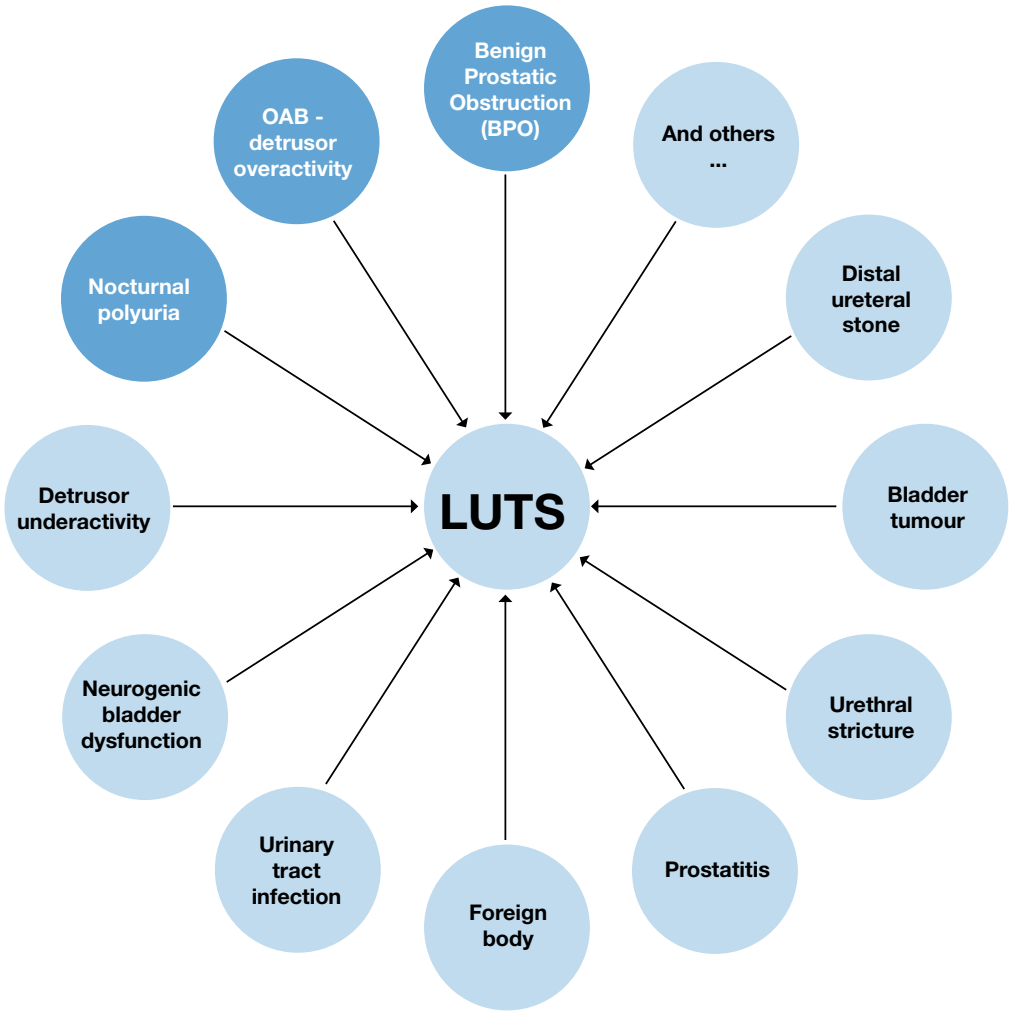
1. INTRODUCTION

Lower urinary tract symptoms (LUTS) represent one of the most common clinical complaints in adult men. The prevalence of LUTS increases with ageing (1,2). Estimates vary widely depending on the definitions and samples used, but most elderly men report having at least one LUTS.

LUTS can be divided into storage, voiding and post-micturition symptoms and have traditionally been related to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction (BPO), which is often associated with benign prostatic enlargement resulting from the histologic condition of benign prostatic hyperplasia (BPH) (3,4). Recent studies have shown, however, that LUTS are not necessarily related to prostatic pathologies. Various types of bladder dysfunction may also be involved in the pathogenesis of LUTS, which is sometimes urodynamically manifested as detrusor overactivity, impaired contractility (during the storage phase) and detrusor underactivity (during the voiding phase). In addition, many other conditions, both urological and non-urological, may also contribute to LUTS.

Figure 1.1 illustrates the many causes of LUTS. In any single person complaining of LUTS, it is common for more than one of these factors to be present. This multifactorial view of the aetiology of LUTS has led most experts to regard the whole urinary tract as a single functional unit. Because patients seek help for LUTS and not an underlying attribute of the prostate such as BPH or BPE, these updated guidelines have been written from the perspective of men who complain about a variety of bladder storage, voiding, and/or postmicturition symptoms. The recommendations made within the guidelines are based on the best available evidence.

Figure 1.1 Causes of male lower urinary tract symptoms (LUTS)



1.1 Methodology

The recommendations of these guidelines are based on a structured literature search using articles in English language published in the PubMed/Medline, Web of Science, and Cochrane databases between 1966 and 1st October 2013 for the Assessment section (Chapter 2) and between 1966 and 31 October 2012 for the Treatment chapters (3-6). The search terms included 'lower urinary tract symptoms', 'benign prostatic hyperplasia', 'detrusor overactivity', 'overactive bladder', 'nocturia', and 'nocturnal polyuria', in combination with the pre-specified diagnostic tests, the various treatment modalities and the search limits, 'humans', 'adult men', 'review', 'randomized clinical trials', 'clinical trials', and 'meta-analysis'. Each extracted article was separately analyzed, classified, and labelled with a Level of Evidence (LE), according to a classification system modified from the Oxford Centre for Evidence-based Medicine (LE: 1a, highest evidence level) to expert opinion (LE: 4, lowest evidence level) (5) (Table 1.1).

Table 1.1: Level of Evidence (LE)*

Level	Type of Evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative or correlation studies and case reports
4	Evidence obtained from expert committee reports or options or clinical experience of respected authorities

**Modified from (5).*

For Chapter 2 (Assessment), the Working Panel used the Delphi technique consensus approach. The Delphi method is based on the rationale that decisions captured systematically from a structured group of individuals (the Guidelines' Working Panel) are more valid than those from unstructured groups. When published information is scarce, experts can make inferences using other data from comparable contexts. Using bespoke software (www.acord.it), propositions were put to experts who voted their preference. The results for the group were then sent back anonymously to all participants, who were able to review their responses in the context of group-wide results. This practice conferred anonymity and allowed opinions to be expressed free from peer-group pressure. The web-based system offered to the participants the option to comment and justify their decisions anonymously. Having considered the view of the group, and reviewed the comments, a second round of anonymous voting took place. Experts were encouraged to revise their earlier answers in light of the replies of other Working Panel members. Three iterations of the process were used, during which the range of the answers decreased and the group converged towards the consensus 'correct' answer.

The Working Panel predetermined the consensus level at 77% (7 out of 9) using the Delphi process, such that consensus on and recommendation for any test required support from at least 77% of the panel members.

The Panel has classified diagnostic tests into three categories: 'must', 'should', and 'may'. 'Must' presents the highest level of obligation. 'Should' presents an intermediate level of obligation. 'May' expresses the lowest level of obligation.

Subsections for the various types of conservative treatments, drugs, and operations are presented in a homogeneous structure listing "mechanism of action", "available drugs with a table of key pharmacokinetic profiles", "efficacy" with a table of trials with the highest LE, "tolerability and safety", "practical considerations", and "recommendations" drawn from the relevant articles using a grade of recommendation (GR) according to a classification system modified from the Oxford Centre for Evidence-based Medicine (5).

Table 1.2: Grade of Recommendation (GR)*

Grade	Recommendation
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from (5)*

As much as possible, each recommendation is based on the strongest clinically relevant data. However, it should be noted that, when recommendations are graded, there is no automatic relationship between the Level of Evidence and Grade of Recommendation. The availability of randomized controlled trials (RCTs) may not necessarily translate into a Grade A recommendation if there are methodological limitations or a disparity in published results, uncertainty about the balance between desirable and undesirable effects, uncertainty or variability in patients' values and preferences, or uncertainty about whether the intervention represents a wise use of resources.

Alternatively, an absence of high-level evidence does not necessarily preclude a Grade A recommendation: if there is considerable clinical experience and consensus to support a high-level recommendation, a Grade A recommendation can be given. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical, financial or other reasons. In this case, unequivocal recommendations are considered helpful for the clinician. Whenever this occurs, it has been clearly indicated in the text with an asterisk, as 'upgraded based on Panel consensus'. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens and personal values and preferences when a Grade of Recommendation is assigned.

The Working Panel on the non-neurogenic male LUTS guidelines consists of experts with a urological and epidemiological background. Although the guidelines are written primarily for urologists, they can also be used by general practitioners, patients or other stakeholders. The Working Panel intends to update the content and recommendations, according to the given structure and classification systems regularly.

1.2 Patients to whom the guidelines apply

Recommendations apply to men aged 40 years or older who seek professional help for various non-neurogenic benign forms of LUTS for example, LUTS/BPO, detrusor overactivity/overactive bladder (OAB), or nocturnal polyuria. Men with lower urinary tract disease who do not fall into this category (e.g. concomitant neurological diseases, young age, prior lower urinary tract disease or surgery) usually require a more extensive work-up, which is not covered in these Guidelines, but may include several tests mentioned in the following section. EAU guidelines on LUTS due to neurologic diseases, urinary incontinence, urogenital infections, ureteral stones, or malignant diseases of the lower urinary tract have been developed by other EAU Working Panels (www.uroweb.org).

2. ASSESSMENT

2.1 Objectives of clinical assessment

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

- To consider the differential diagnoses, since the origin of male LUTS are multifactorial. For example, LUTS can be caused by BPO, bladder stones, detrusor overactivity, detrusor underactivity, distal ureteral stones, foreign body, neurological disease, nocturnal polyuria, prostatitis, urinary incontinence, urethral stricture, urinary tract infection (UTI), bladder cancer and others. Accordingly, the relevant EAU guidelines on the management of applicable conditions should be followed for individual patients.
- To define the clinical profile of men with LUTS in order to provide the best care. The assessment should be able to allocate patients for watchful waiting (WW), medical or surgical treatment and to identify men at risk of disease progression.

2.2 Medical History

*2.2.1 **Background information***

Earlier guidelines on male LUTS and/or BPH emphasize the importance of assessing the patient's history (6-8). A medical history aims to identify the potential causes of LUTS and relevant comorbidities, such as medical diseases (e.g. diabetes mellitus or insipidus, renal disease, heart failure) and neurological diseases (e.g. Parkinson's disease, multiple sclerosis, cerebrovascular disease, spinal cord injury, prolapsed intervertebral disc or impinging on the spinal cord).

In addition, it is recommended that current medication and lifestyle habits are reviewed as well as emotional and psychological factors. The Panel recognized the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no association

between the presence of LUTS and a higher prevalence of prostate cancer (PCa) compared with asymptomatic men (9,10).

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see 'symptom score questionnaires') should be assessed to objectify and quantify LUTS. The same symptom questionnaire should subsequently be discussed with the patient to assess therapeutic efficacy. Voiding diaries are particularly beneficial when assessing patients with bothersome storage LUTS, particularly nocturia (see Chapter 2.4 'frequency volume chart'). When relevant, potential erectile dysfunction and other forms of sexual dysfunction should be investigated, preferably with validated symptom questionnaires.

*2.2.2 **Recommendation***

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

**Upgraded based on Panel consensus.*

2.3 Symptom score questionnaires

*2.3.1 **Background information***

Symptom score questionnaires have been used increasingly since the 1970s to evaluate male LUTS (11) and have become a standard part of the assessment of male LUTS. Existing guidelines on male LUTS and/or BPH recommend using validated symptom score questionnaires (6-8). Several questionnaires are available; each is sensitive to changes in symptoms and can be used to monitor treatment (12-18).

*2.3.2 **The International Prostate Symptom Score (IPSS)***

The IPSS is an 8-item questionnaire, consisting of seven symptom questions and one quality-of-life (QoL) question (14).

The seven symptom questions assess (referring to the patient's previous month) a feeling of incomplete bladder emptying, weak stream, intermittency, and straining (voiding symptoms), as well as frequency, urgency and nocturia (storage symptoms). Response options range from 'Not at all' (0 points) to 'Almost always' (5 points) with a maximum total of 35 points. The IPSS score is calculated on the basis of symptom questions and categorized as 'asymptomatic' (IPSS 0 points), 'mildly symptomatic' (IPSS 1-7 points), 'moderately symptomatic' (IPSS 8-19 points), and severely symptomatic (IPSS 20-35 points). Limitation of the IPSS is its lack of assessment of symptom bother associated with each individual symptom question and of urinary incontinence and post-micturition symptoms.

*2.3.3 **The International Consultation on Incontinence Questionnaire (ICIQ-MLUTS)***

The ICIQ-MLUTS has been created from the ICS male questionnaire, which resulted from an outcome of the International Incontinence Society 'Benign Prostatic Hyperplasia' Study. It is a widely used and validated patient-completed questionnaire for evaluating MLUTS (15). It contains 13 items referring to hesitancy, straining to continue urination, strength of stream, intermittency, incomplete emptying, urgency, urge urinary incontinence, stress urinary incontinence, unexplained urinary incontinence, nocturnal enuresis, post-micturition dribble, nocturia and frequency. It is available in 17 languages and also includes subscales for nocturia and overactive bladder (OAB) scores. Bother scales are not incorporated in the overall score, but indicate the impact of individual symptoms for the patient.

*2.3.4 **Danish Prostate Symptom Score (DAN-PSS)***

The DAN-PSS is a symptom score (13) used mainly in Denmark and Finland. While the IPSS includes only one overall QoL question, the DAN-PSS and ICIQ-MLUTS include the assessment of bother of individual LUTS.

Symptom scores are helpful in quantifying the patient's LUTS and in identifying which type of symptoms (storage or voiding) are predominant, yet they are not disease-, age- or gender-specific, and are recommended in all patients during initial assessment. Symptom scores can also be used to monitor response to therapy.

*2.3.5 **Recommendation***

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

2.4 Frequency volume charts and bladder diaries

*2.4.1 **Background information***

The recording of the volume and time of each void by the patient is referred to as a frequency volume chart (FVC). The FVC is known as a bladder diary if it captures additional information such as fluid intake, use of pads, activities during recording, or symptom scores (3). Parameters that can be derived from the FVC include:

- voiding frequency;
- total voided volume, including the fraction of urine production during the night, known as nocturnal polyuria index (NPi);
- volume of individual voids (mean and range).

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 (19,20), so that the mean 24-hour frequency ranges widely which appears to increase with age. It is particularly relevant in nocturia, where it underpins the categorization of underlying mechanism(s) (21-23). Frequency volume charts are typically more accurate than patient recall (24,25), particularly regarding nocturia. However, the use of FVCs may cause a 'bladder training effect'. In addition, the nights may be atypical since FVC produces a range of variation in the frequency of nocturnal voids (26). To date, there is no agreement on standardizing the approach to deriving the above information in the evaluation of LUTS (27).

The duration of observation during FVC needs to be long enough to avoid sampling errors, but short enough to avoid non-compliance (27). Several studies have compared shorter durations of FVC (3 or 5 days) with longer periods (7 days) (28-33). A systematic review of the available literature published in 2007 recommended FVC should continue for 3 or more days (34). A recent phase 1 study of the development and validation of a urinary diary suggested that FVC should be performed for 4 days or more (35).

If the presenting complaint includes storage LUTS, it may be useful to consider turning the FVC into a bladder diary by adding extra content. Symptom scores may be beneficial in men with LUTS. However, there is no evidence to suggest that symptom scores in a diary are better than the separate one-off use of a questionnaire.

*2.4.2 **Recommendations***

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

2.5 Physical examination and digital-rectal examination (DRE)

*2.5.1 **Background information***

Physical examination should be performed focusing on:

- the suprapubic area to rule out bladder distention;
- the external genitalia to identify conditions that may cause or contribute to LUTS (e.g. urethral discharge, phimosis, meatal stenosis, penile cancer);
- the perineum/lower limbs to evaluate motor/sensory function.

Physical examination is especially useful in the differential diagnosis of LUTS.

Digital-rectal examination (DRE) is an important examination in men with LUTS to examine the dorsal surface of the prostate, consistency of prostatic parenchyma and prostate size. Despite its low value to diagnose PCa, it can still help to determine the coexistence of PCa when there are palpable nodes in the prostatic parenchyma (36) and abnormalities of anal sphincter tone. Finally, it enhances the capacity to estimate the prostate volume, which helps determine treatment options (e.g. 5α-reductase inhibitors [5-ARIs], TUIP, TURP and others; see Treatment chapters).

*2.5.2 **DRE and prostate size evaluation***

DRE is the simplest way to assess the prostate volume, but correct estimation of the prostatic volume by DRE is not easy to accomplish. To overcome this, investigators for the PLCO (Prostate, Lung, Colorectal and Ovarian Cancer) trial have described quality-control procedures for DRE examination (37).

It is well accepted that transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE. Roehrborn analyzed data from four studies in which estimations of prostate volume by DRE were compared with those performed by TRUS (38). Although different methods and criteria were used in the four

studies, it was concluded that underestimation of DRE increased with increasing TRUS volume, particularly if the volume was > 30 mL. For this reason, Roehrborn developed a model of visual aids to help urologists predict prostate volume more accurately (39). Similar models to assist training for DRE examinations have also been proposed by other groups (40). A community-based study found that DRE overestimates the volume in smaller prostates and underestimates the volume in larger prostates (41). However, it was concluded that DRE was sufficient to discriminate between prostate volumes > or < than 50 mL (41).

*2.5.3 **Recommendation***

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

2.6 Urinalysis

*2.6.1 **Background information***

LUTS are not only observed in patients with BPO, but may also be present in men with a UTI, whether related or not to BPE, and in patients with carcinoma of the bladder.

Urinalysis (dipstick or sediment) is an inexpensive test, which does not require sophisticated technical equipment. It must be included in the primary evaluation of any patient presenting with LUTS to determine conditions, such as UTI, diabetes mellitus, etc, based on abnormal findings (e.g. haematuria, proteinuria, pyuria, glucosuria, ketonuria, positive nitrite test). Once abnormal findings have been diagnosed, further evaluation is recommended according to the standards provided in other EAU guidelines, including guidelines on non-muscle invasive bladder cancer, muscle invasive and metastatic bladder cancer, upper urinary tract urothelial cell carcinoma, primary urethral carcinoma, or urological infections (42-45).

Urinalysis has traditionally been recommended in most guidelines worldwide for the primary management of patients with LUTS, suggestive of BPO due to the high prevalence of UTI/LUTS deterioration in the presence of UTI (46,47). It should be noted that there is very limited evidence to support these recommendations. However, even in the absence of controlled studies, there is general expert consensus that the benefits clearly outweigh the costs, although the use of urinalysis should always be associated with prognostic significance (48). Nevertheless, despite official guidelines and the widespread use of urinalysis among urologists (49), the value of urinary dipstick/microscopy for diagnosing UTI in patients with painless LUTS has recently been questioned (50).

*2.6.2 **Recommendation***

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

**Upgraded by Panel consensus.*

2.7 Prostate-specific antigen (PSA)

*2.7.1 **Background information***

Prostate-specific antigen (PSA) is a kallikrein-like serine protease produced almost exclusively by the epithelial cells of the prostate. The use of PSA has revolutionized the diagnosis of PCa. PSA is not considered as being disease-specific, but organ-specific. A rise in PSA may occur when prostatic carcinoma is present, but also in other non-malignant conditions including BPH.

*2.7.2 **PSA and the prediction of prostatic volume***

Several reports have demonstrated the reliability of measuring the PSA concentration for predicting prostate volume. Stamey et al. were the first to correlate PSA serum values and the volume of prostatic tissue (51). In the late 1980s, their research showed that the serum PSA contribution from BPH was 0.30 ng/mL per gram of prostate tissue and 3.5 ng/ml per cm3 of PCa tissue. The analysis of placebo-controlled multicentre BPH trials and a safety study (4,627 patients) showed that PSA had a good predictive value for assessing prostate volume, with areas under the curve ranging from 0.76 to 0.78 for various prostate volume thresholds (30 mL, 40 mL, and 50 mL). To achieve a specificity of 70% while maintaining a sensitivity between 65% and 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 (52).

Bohnen et al. reported a strong association between PSA and prostate volume in a large community-based study in The Netherlands (53). It was found that a PSA threshold value of 1.5 ng/mL could best predict a prostate volume of > 30 mL, with a positive predictive value (PPV) of 78%. Mochtar et al. showed in a population of men with LUTS that PSA has a good predictive value for assessing prostate enlargement with

area under receiver-operator characteristic curves (ROC) of 0.82 in the overall age groups of the PSA threshold values (54). Optimal serum PSA cut-off values for the overall study population, irrespective of age, are 2.0 ng/mL to detect a prostate volume > 30 mL and 2.5 ng/ml to detect a prostate volume > 40 mL. However, the determination of an exact individual prostate volume with PSA is not possible due to the relatively large standard deviation of the estimation curve in the study.

The prediction of prostate volume can also be based on total and free PSA. Both PSA forms were found to be able to predict the TRUS prostate volume (± 20%) in more than 90% of the cases (55). Recently, it was shown that the free PSA performed better than total PSA at predicting prostate volume. The free PSA with a threshold of 0.495 ng/mL correctly estimated a prostate volume of > 40 and < 40 mL in 71% and 66% of cases, respectively (56).

*2.7.3 **PSA and the probability of PCa***

The role of PSA in the diagnosis of PCa is presented by the *EAU Guidelines on Prostate Cancer* (36). The benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient, including the possibilities of false-positive and false-negative results, complications of subsequent TRUS-guided biopsy and false-negative biopsies, as well as the overdiagnosis and overtreatment of PCa.

*2.7.4 **PSA and the prediction of BPO-related outcomes***

The serum PSA concentration appeared to be a stronger predictor of prostate growth than prostate volume (57). In addition, the PLESS study showed that PSA also predicted the changes in symptoms, QoL/bother, and Q_{max} (58). In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression (59).

More importantly, in the placebo arms of large double-blind controlled studies, baseline serum PSA level consistently predicted the risk of acute urinary retention (AUR) and BPE-related surgery (60,61). The relationship between baseline serum PSA and the risk for BPH-related outcomes was also confirmed by the Olmsted County Study. It was found that the risk for treatment for LUTS and BPH in men with a baseline PSA of 1.4 ng/mL or greater was significantly higher (62). In a study of 302 men with moderate LUTS, it was found that PSA is significantly associated with BPO with significant likelihood ratios altering the probability of BPO (63). If the PSA is > 4 ng/mL, mild or definite BPO is likely (89%), whereas if the PSA is < 2 ng/mL, BPO is unlikely (33%). In an epidemiological study, elevated free PSA levels could predict clinical BPH, independent of total PSA levels (64). Patients with BPO appear to have a higher serum PSA level and larger prostate volumes compared to men without BPO (65). The positive predictive values of PSA for the detection of BPO was recently shown to be 68% (66).

*2.7.5 **Recommendation***

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

2.8 Renal function measurement

*2.8.1 **Background information***

Renal function may be assessed by serum creatinine levels or by determination of the estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention were more prevalent in patients with signs or symptoms of BPO (67). Even though BPO may be partly responsible for these complications, there is no conclusive evidence for BPO as the primary cause (67).

One study evaluated 246 men presenting with LUTS and found that approximately one in 10 (11%) had renal insufficiency (68). It was also shown that neither the symptom score nor the QoL assessment was associated with the serum creatinine concentration. When renal dysfunction was present, diabetes mellitus and hypertension were the most probable causes of the elevated creatinine concentration among patients of this group. This study also noted that it was rather rare to find patients with high creatinine levels due to BPO only (68).

Comiter et al. (69) reported a study in which the voiding dysfunction of a non-neurogenic aetiology did not appear to be a risk factor for elevated creatinine levels. In addition, in the MTOPS study, < 1% of men with LUTS presented with renal insufficiency (70). Koch et al. (71) studied the additional value of renal ultrasound (US) in the assessment of patients with male LUTS and concluded that only those with an elevated creatinine level require this investigation.

In the Olmsted County community-dwelling men, there was a cross-sectional association between signs and symptoms of BPO and chronic kidney disease (CKD). Prostatic enlargement was not associated with CKD (72).

In 2,741 consecutive patients who presented with LUTS, decreased maximum urinary flow rate and a history of hypertension and/or diabetes were significantly associated with CKD (73). Interestingly, a recent study demonstrated that Q_{max} correlated significantly with eGFR in middle-aged men with moderate-to-severe LUTS (74,75).

It has been shown that patients with renal insufficiency have an increased risk of developing post-operative complications compared to those with normal renal function (76). Bruskewitz et al. found that an isolated serum creatinine level could not predict the outcome after TURP, as measured by an improvement in the patient's QoL (77).

*2.8.2 **Recommendation***

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

**Upgraded by Panel consensus.*

2.9 Post-void residual urine

*2.9.1 **Background information***

Post-void residual (PVR) urine can be calculated by transabdominal US, bladder scan or catheterization. PVR is not necessarily associated with obstruction, since high PVR volumes can be both a consequence of obstruction and/or poor detrusor function (detrusor underactivity) (78,79).

At volumes of 50 mL, the diagnostic accuracy of PVR measurement has been shown to have a positive predictive value of 63% and a negative predictive value of 52% to determine bladder outflow obstruction (75). A large PVR measurement is not a contraindication to WW or medical therapy, although large PVR volumes may indicate bladder dysfunction and may predict a poor response to treatment and especially to WW. In both the MTOPS and ALTESS studies, a high baseline PVR was associated with an increased risk of symptom deterioration (60,61).

It has been suggested that the monitoring of changes in PVR over time may allow for identification of patients at risk of AUR (61). This is of particular importance for the management of patients receiving anticholinergic medication.

In contrast, baseline PVR has little prognostic value for the risk of BPE-related invasive therapy in patients taking an α_1-blocker or with WW (80). However, due to large test-retest variability and lack of outcome studies, it is currently impossible to establish a PVR threshold for treatment decision.

*2.9.2 **Recommendation***

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

2.10 Uroflowmetry

*2.10.1 **Background information***

Urinary flow rate assessment is a widely used basic non-invasive urodynamic test that evaluates the joint functioning of the lower urinary tract (i.e. bladder and outlet). Key parameters are maximum urinary flow rate (Q_{max}) and flow pattern.

Uroflowmetry parameters should ideally be evaluated when voiding volume is > 150 mL. If Q_{max} is normal (≥ 15 mL/s), physiological compensatory processes mean that BOO still cannot be completely excluded. This was shown by a prospective investigation of Q_{max} in patients with male LUTS. After the manual correction of artefacts, BOO was found to be present in < 1% of men (75). Q_{max} can also be subject to within-subject variation on either the same or different days (81,82); it is therefore useful to repeat uroflowmetry measurements when the voided volume is < 150 mL or Q_{max} or flow pattern is abnormal.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably, and is substantially influenced by diagnostic threshold values. A threshold value of Q_{max} of 10 mL/s had a specificity of 70%, a positive predictive value (PPV) of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15 mL/s was 38%, the PPV 67% and the sensitivity 82% (83). Thus, uroflowmetry alone is not suitable for the detection and quantification of BOO. Low Q_{max} can arise as a consequence of BOO (84), detrusor underactivity

or an underfilled bladder (85). Thus, it is limited as a diagnostic test because it is unable to discriminate between the underlying mechanisms in men with a low Q_{max}.

Specificity can be improved by repeated flow rate testing in individual patients. Uroflowmetry can be used for monitoring treatment outcomes (86) and correlating symptoms with objective findings.

*2.10.2 **Recommendation***

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

2.11 Imaging

*2.11.1 **Upper urinary tract***

2.11.1.1 Background information

Routine imaging of the upper urinary tract in men with LUTS is not recommended since these patients are not generally at an increased risk for upper tract malignancy or other abnormalities (including hydronephrosis, measurable degrees of renal insufficiency, renal cysts) when compared to the overall population (*see above*) (71,87-89).

Several arguments support the use of renal US in preference to intravenous urography (IVU). Compared to IVU, US allows for a better characterization of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, lower radiation dose and less side effects (88). A review of 10 reported studies involving over 2.1 million patients undergoing IVU found that the incidence of adverse effects due to contrast medium was approximately 6% of all patients, the incidence of serious adverse effects was 1 in 1,000-2,000, and the risk of dying from an allergic reaction was 1 in 100,000-200,000 investigations (90,91).

Low-osmolar contrast material (LOCM) resulted in a six-fold improvement in safety compared with high-osmolar contrast material (91). Furthermore, in patients with pre-existing renal failure, the use of LOCM reduces the risk of nephrotoxicity (91).

2.11.1.2 Recommendation

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

*2.11.2 **Prostate***

2.11.2.1 Background information

Imaging of the prostate can be performed using several imaging modalities including transabdominal US, TRUS, computed tomography, and magnetic resonance imaging (MRI). However, in daily routine practice, prostate imaging is mainly performed by TRUS or transabdominal US (88).

2.11.2.2 Prostate size and shape

Assessment of prostate size is important for the selection of the appropriate interventional treatment, i.e. open prostatectomy, enucleation techniques, transurethral resection, TUIP, or minimally invasive therapies. It is also important prior to treatment with 5-ARIs (36). Recent data suggest that the size of the prostate gland may predict which patients with LUTS will develop progressive symptoms and complications (70).

A large body of evidence documents the accuracy of TRUS in calculating the volume of the prostate. TRUS is superior to suprapubic (transabdominal) volume measurement as all three distances can be measured much more accurately by the transrectal approach (92,93). The presence of a median lobe protruding into the bladder may guide the treatment choice in patients scheduled for a minimally invasive treatment. Turkbey et al. reported that MRI could accurately assess prostate zonal volume (94). However, according to Park et al. MRI-based volume tends to overestimate the prostate volume compared to transrectal US-based volume (95). Dynamic contrast-enhanced MRI and diffusion MRI could also be used to distinguish between glandular and stromal prostatic tissues (96).

2.11.2.3 Recommendations

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

*2.11.3 **Prostatic configuration/intravesical prostatic protrusion (IPP)***

Prostatic configuration has been evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) (97). PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward 1 as the prostate becomes more circular. PCAR sensitivity was 77% for diagnosing BPO when PCAR was > 0.8 with 75% specificity. It seems clear that the more circular the prostate, the more likely there is to be BPO (97).

Ultrasound measurement of intravesical prostatic protrusion (IPP) has also been introduced. This is because it is thought that a protruding prostate median lobe into the bladder can cause a 'valve ball' type of BPO, with incomplete opening and disruption of the funnelling effect of the bladder neck (98). Intravesical prostatic protrusion represents the distance (in millimetres) between the tip of the prostate median lobe and bladder neck in the midsagittal plane, using a suprapubically positioned US scanner with the bladder filled with 150-250 mL of fluid. The IPP distance can be divided into three grades:

- grade I: 0-4.9 mm;
- grade II: 5-10 mm;
- grade III: more than 10 mm.

Chia et al. evaluated 200 patients with PFS and transabdominal US (98). It was found that IPP correlated well with BPO with a positive predictive value of 94% and a negative predictive value of 79%. IPP also correlated well with the severity of BPO as defined by the higher BOO (98). In addition, Keqin et al. found that IPP was positively correlated with prostate volume, detrusor overactivity, bladder compliance, detrusor pressure at maximum urinary flow, BOO index, and PVR but negatively correlated with Q_{max} (99). The authors concluded that IPP is a useful predictor for evaluating BPO and detrusor function. IPP also seems to predict successful outcome of trial without catheter (TWOC) after acute urinary retention (100,101).

However, more studies are required to confirm these results. No information with regard to intra- or inter-observer variability and learning curve is yet available. Other TRUS currently tested are using the intraprostatic resistance index as measured by Doppler analysis and the prostatic urethral angle (102).

Intravesical prostatic protrusion (IPP) may be a feasible option to diagnose 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 and currently no specific recommendations can be made.

*2.11.4 **Bladder/detrusor wall thickness and ultrasound-estimated bladder weight (UEBW)***

2.11.4.1 Background information

For bladder wall thickness (BWT) assessment, the entire diameter of the bladder wall is measured, which represents the distance between the hyperechogenic mucosa and the hyperechogenic adventitia. For detrusor wall thickness (DWT) assessment, the only measurement needed is the hypoechogenic detrusor sandwiched between the hyperechogenic mucosa and adventitia (103).

Manieri et al. found a significant correlation between BWT and PFS parameters. A threshold value of 5 mm at the anterior bladder wall with a bladder filling of 150 mL (via catheterization) was best at differentiating between patients with or without BOO. The study concluded that US BWT measurement appeared to be a useful predictor of BOO (104). Oelke et al. measured DWT at the anterior bladder wall with a bladder filling ≥ 250 mL in 160 LUTS/BPH patients (75). The DWT (threshold value for BOO ≥ 2 mm) had a positive predictive value of 94% and a specificity of 95%. There was an agreement of 89% between the results of DWT measurement and pressure-flow studies (75). Kessler et al. used threshold values of 2.0, 2.5, or 2.9 mm for DWT in 102 patients with LUTS and was able to correctly identify 81%, 89%, and 100% of patients with BOO, respectively (105).

The above-mentioned studies directly compared the value of BWT or DWT measurements with non-invasive BOO routine tests, although only Oelke et al. was a prospective study (75). All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or Qave of free uroflowmetry, measurements of PVR, prostate volume, or symptom severity. On the contrary, Blatt et al. could not demonstrate any difference in BWT between patients with normal urodynamics and those with BOO or detrusor overactivity; however, the study did not use a specific bladder filling volume for the measurement of BWT (106).

Disadvantages of the method include the lack of standardization in terms of threshold values and bladder fillings and varying results with different bladder fillings, as well as a lack of evidence to indicate which measurement (BWT or DWT) is best used (107). Measurement of BWT/DWT is therefore not currently part of the recommended diagnostic work-up of men with LUTS.

The concept of bladder weight (BW) as a measure of bladder wall hypertrophy has been introduced by Kojima (108). The same group compared US estimation of BW and PFS and found that UEBW could identify BOO with a diagnosis accuracy of 86.2% using a cut-off value of 35 g (109). UEBW could also be used as a reliable tool to monitor therapeutic effects on BPH patients in terms of the relief of BPO (108). More recently, Akino et al. prospectively followed-up 97 patients with LUTS under treatment with alpha-blockers (110). Thirty-seven of the patients eventually received surgery. Multivariate analysis revealed that severe LUTS and a high BW (≥ 35 g) were the risk factors for prostate/BPH surgery (110). The potential use of BW in daily practice is limited by the difficulty in accurately calculating BW and a lack of data limit.

Measurement of BWT or DWT and BW may be a feasible option to diagnose BOO in men with LUTS. The role of BWT, DWT and BW as a non-invasive alternative to PFS in the assessment of male LUTS or BOO is under evaluation and currently no specific recommendations can be made.

*2.11.5 **Other imaging modalities***

2.11.5.1 Urinary bladder voiding cysto-urethrogram

This investigation suffers from the fact that the information on the lower urinary tract is only indirect and gives, at best, only limited urodynamic information. It is therefore not recommended in the routine diagnostic work-up of men with LUTS. However, voiding cysto-urethrography may be useful for the detection of vesico-ureteral reflux, bladder diverticula, or PVR in selected patients.

2.11.5.2 Urethra

Retrograde urethrography gives only indirect information on BPE and adjacent structures. Therefore, it is not recommended in the routine assessment of patients, but it is recommended if urethral pathologies are suspected based on the initial evaluation. Retrograde urethrography may be useful for the evaluation and judgement of urethral strictures.

*2.11.6 **Urethrocystoscopy***

2.11.6.1 Background information

Patients with a history of microscopic or gross haematuria, urethral stricture, or associated risk factors (e.g. history of urethritis, urethral injury, urethral instrumentation, or previous urethral surgery), or bladder cancer who present with LUTS should undergo urethrocystoscopy during diagnostic evaluation.

Several studies have addressed whether findings of urethrocystoscopy correlate with functional data. Shoukry et al. evaluated 122 patients (mean age 64 years) with LUTS using uroflowmetry, symptom evaluation and urethrocystoscopy (111). The pre-operative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had an 'obstructive' maximum urinary flow rate.

Anikwe showed that there was no significant correlation ($p > 0.5$) 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 (112). There appeared to be a trend towards lower peak flow rates in men with higher degrees of bladder trabeculation (112). The largest study published on this issue correlated urethroscopic findings to urodynamic studies in 492 elderly men with LUTS (113). The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and grade of urethral occlusion) and urodynamic indices, detrusor overactivity and low compliance. It should be noted, however, that BOO was present in ~ 15% of patients with normal cystoscopic findings, while ~ 8% of patients had no obstruction, even in the presence of severe trabeculation (113).

The evaluation of a prostatic middle lobe in urethrocystocopic findings is necessary for the indication of certain interventional treatments, such as TUNA and TUMT.

2.11.6.2 Recommendation

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

2.11.7 ***Urodynamics (computer-urodynamic investigation)***

2.11.7.1 Background

In male LUTS, the most widespread urodynamic techniques employed are filling cystometry, which is used to assess the bladder storage phase, and pressure-flow studies, which is used to assess the voiding phase. The major aims of urodynamics are to explore the functional mechanisms of LUTS and to identify potential risk factors for adverse outcomes (for informed/shared decision-making). Most terms and disease conditions (e.g. detrusor overactivity, low compliance, BOO/BPO, detrusor underactivity) are defined by urodynamic investigation.

2.11.7.2 Diagnosing bladder outlet obstruction

Pressure-flow studies are the basis for the definition of BOO and are the primary objective of ascertaining its presence. BOO is characterized by increased detrusor pressure and decreased urinary flow rate during voiding and this constitutes the main clinical diagnostic criterion for BOO. BOO/BPO has to be differentiated from detrusor underactivity, which is defined as decreased detrusor pressure during voiding in combination with decreased urinary flow rate (3).

During the storage phase, urodynamic testing of OAB patients may identify detrusor overactivity (DO), which is a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. OAB is diagnosed from the patient's symptoms, based on the presence of urgency, usually with frequency and nocturia (3). Thus, the two terms OAB and DO are not interchangeable, since 21% of men with urinary urgency do not have DO (114), and DO can be asymptomatic. Studies have described an association between BOO and DO (115,116).

In men with LUTS attributed to BPE, DO was present in 61% of the patients (n = 1418) and independently associated with BOO grade and ageing. As the BOO grade increased and the patient got older, the prevalence of DO became higher, ranging from 50% in men without BOO to 83% in men with the most severe BOO (115). Additionally, the higher the BOO grade was, the earlier and with greater amplitude DO appeared (115). In men who did not have a clinically established diagnosis of BPO, DO was seen in 57%, BPO in 29%, other functional obstruction in 24%, and detrusor underactivity in 11% of patients (117). DO was found in 81% of patients with BPO and 39% of patients without BPO. BPO was found in 46% of the patients with DO and 12% of those without DO. Accordingly, there appeared to be no straightforward causal relationship between DO and BPO in men.

During the voiding phase, pressure-flow studies can distinguish between BOO and detrusor underactivity. The prevalence of detrusor underactivity in men with LUTS is about 11-40% (118,119). Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility (120,121).

No randomized studies were identified regarding the usefulness of cystometry for guiding clinical management in patients with LUTS. There are no published RCTs in men with LUTS and possible BPO that compare the standard practice investigation (uroflowmetry and PVR measurement) with pressure flow studies.

Due to the invasive nature of urodynamic testing due to catheter placement, computer-urodynamic investigation is generally only offered once conservative treatment has failed. The Working Panel attempted to suggest specific indications for PFS based on age, findings from the other diagnostic tests, and previous treatments. These include situations where the diagnosis of BPO is uncertain and there is the significant possibility that pathophysiology includes additional problems, such as detrusor overactivity during the storage phase or detrusor underactivity during the voiding phase.

Interestingly, the Working Panel allocated a different degree of obligation for PFS in men > 80 years and men < 50 years, which may reflect the lack of clear evidence. In addition, there was no consensus whether PFS should or may be performed when considering surgery in men with bothersome predominantly voiding LUTS and Q_{max} > 10mL/s, although the Panel recognized that with Q_{max} < 10 mL/s BOO is likely and pressure flow studies are not necessarily needed.

It should be emphasized that patients with neurological disease, including those with previous radical pelvic surgery should be assessed, according to the EAU Guidelines on Neurogenic Lower Urinary Tract Dysfunction (122).

2.11.7.3 Videourodynamics

The inclusion of intermittent synchronous radiograph imaging and filling of the bladder with contrast-medium for cystometry and PFS is termed videourodynamics. The test provides additional anatomical information. During filling, imaging is usually undertaken in the postero-anterior axis and shows bladder configuration (bladder trabeculation and diverticula), vesico-ureteral reflux and pelvic floor activity. During voiding, a 45º lateral projection is used and can show the exact location of obstruction. Videourodynamics is recommended where there is uncertainty regarding mechanisms of voiding LUTS.

2.11.7.4 Non-invasive pressure-flow testing

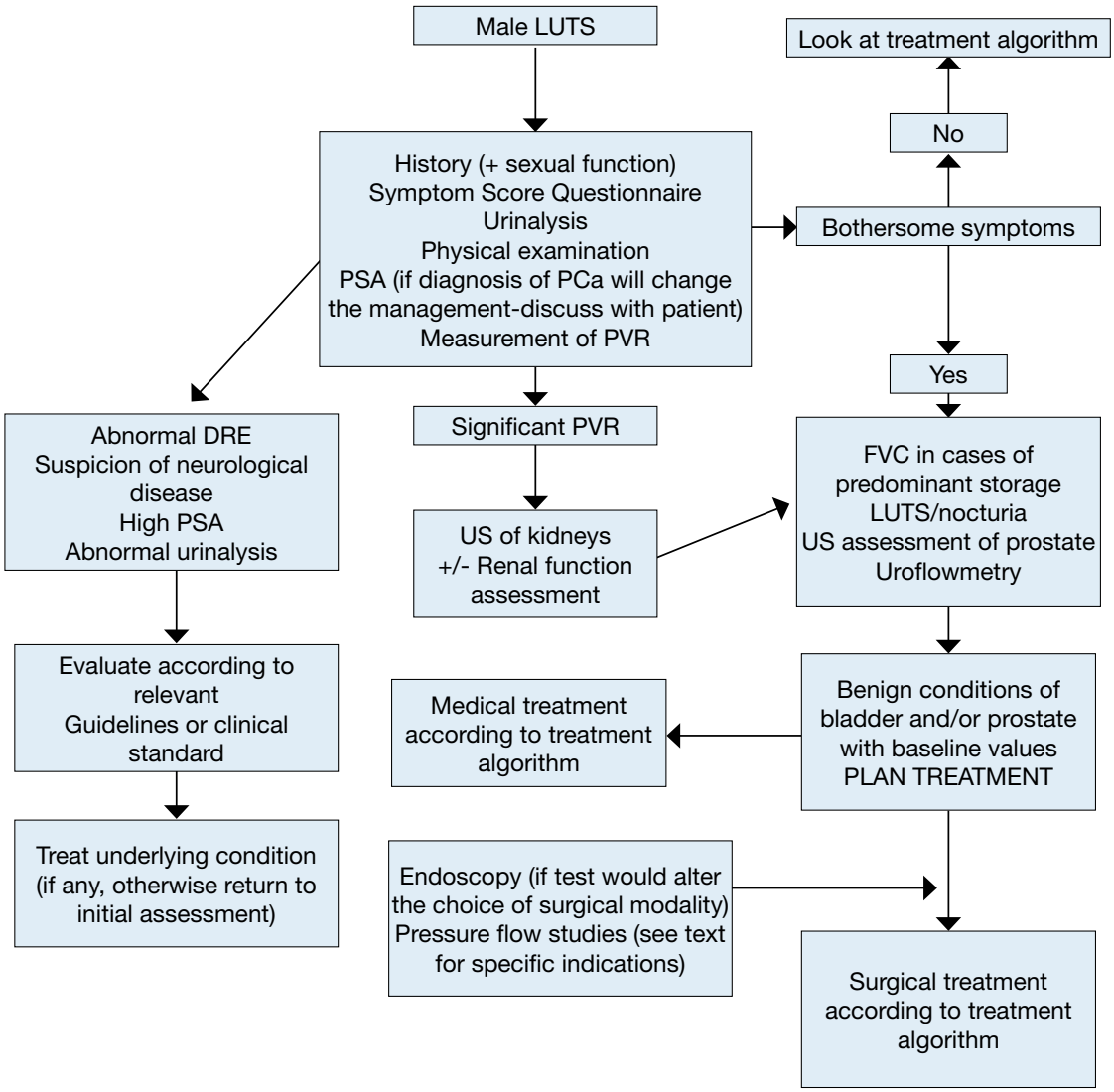
The perception that PFS may be poorly tolerated due to the invasive nature of testing led to the development of alternative approaches. The penile cuff method, in which flow is interrupted to estimate isovolumetric bladder pressure (123), shows promise, with good test/retest repeatability (124) and interobserver agreement (125), and a nomogram has been derived (126). A method in which flow is not interrupted is also under investigation (127).

The external condom method (128) agrees with invasive PFS in a high proportion (129). Resistive index (130) and prostatic urethral angle (131) have also been proposed, but are in the early stages of developing an evidence base. Ultrasound measurements of bladder or detrusor wall thickness, bladder weight, and intravesical prostatic protrusion have already been discussed in the imaging subchapter.

2.11.7.5 Recommendations

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

Figure 2.1: 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.

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3. CONSERVATIVE TREATMENT

Many men with lower urinary tract symptoms (LUTS) are not troubled enough by their symptoms to need drug treatment or surgical intervention. Most of these men can be managed conservatively by a process known as watchful waiting (WW). All men with LUTS should be formally assessed prior to any allocation of treatment in order to establish the severity of the LUTS and to differentiate between the great majority of men with so-called uncomplicated LUTS that pose no threat to life expectancy, and the more unusual presentation of complicated LUTS that might.

WW is a viable option for many men as, if left untreated, few will progress to acute urinary retention and complications such as renal insufficiency and stones (1,2). Similarly, some symptoms may improve spontaneously, while other symptoms can remain stable for many years (3).

A large study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed that those who had undergone surgery had improved bladder function compared with those in the WW group (flow rates and post-void residual [PVR] volumes), with the best results being in those with high levels of bother. Thirty-six per cent of patients crossed over to surgery in five years, leaving 64% doing well in the WW group (4).

Approximately 85% of men will be stable on WW at one year, deteriorating progressively to 65% at five years (5,6). The reason why some men deteriorate with WW and others do not is not well understood: increasing symptom bother and PVR volumes appeared to be the strongest predictors of failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

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 (3,6-8) 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 of or moderation in 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 optimizing 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 LE: 1b that self-management as part of WW reduces both symptoms and progression (7,8) (Table 3.1). Brown et al. (7) showed that men randomized to three self-management sessions in addition to standard care had better symptom improvement and improved quality of life at three and six months than men treated with standard care only. These differences were maintained at 12 months.

Table 3.1: Self-management as part of watchful waiting reduces symptoms and progression (7)

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

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

3.1 Practical considerations

The components of self-management have not been individually subjected to study. The above components of lifestyle advice have been derived from formal consensus methodology (9). Further research in this area is required.

3.2 Recommendations

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

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4. DRUG TREATMENT

4.1 α_1-Adrenoceptor antagonists (α_1-blockers)

4.1.1 Mechanism of action

Historically, it was assumed that α_1-blockers act by inhibiting the effect of endogenously released noradrenaline on smooth muscle cells in the prostate, thereby reducing prostate tone and bladder outlet obstruction (BOO). Contraction of the human prostate is mediated predominantly, if not exclusively, by α_{1A}-adrenoceptors (1). However, it has been shown that α_1-blockers have little effect on urodynamically determined bladder outlet resistance (2), and that treatment-associated improvement of lower urinary tract symptoms (LUTS) is correlated only poorly with obstruction (3).

There have therefore been discussions about the role of α_1-adrenoceptors located outside the prostate (e.g. urinary bladder and/or spinal cord) and other α_1-adrenoceptor subtypes (α_{1B}- or α_{1D}-adrenoceptors) as mediators of the beneficial effects of α_1-blockers. α_1-Adrenoceptors in blood vessels, other non-prostatic smooth muscle cells, and the central nervous system are considered to be mediators of adverse events during α_1-blocker treatment, and all three receptor subtypes seem to be involved. This concept has favoured the use of α_{1A}-selective adrenoceptor antagonists. However, it remains to be determined whether α_{1A}-selectivity is the only and main factor determining good tolerability.

4.1.2 Available drugs

Following the early use of phenoxybenzamine and prazosin in the treatment of LUTS/benign prostatic hyperplasia (BPH), five α_1-blockers are currently in mainstream use:

- alfuzosin HCL (alfuzosin)
- doxazosin mesylate (doxazosin)
- silodosin
- tamsulosin HCL (tamsulosin)
- terazosin HCL (terazosin).

Over a period of time, alfuzosin has been clinically available in Europe in three formulations, doxazosin and tamsulosin in two formulations each, and silodosin and terazosin in one formulation (Table 4.1). Although different formulations result in different pharmacokinetic behaviours and, perhaps, tolerability profiles, the overall clinical impact of the different formulations is modest. Indoramin and naftopidil are also available in a few countries, but there have been only limited clinical data for these agents at the time of the literature search and they will therefore not be discussed in these guidelines.

Table 4.1: Key pharmacokinetic properties and standard doses of α_1-blockers licensed in Europe for treating symptoms of BPH

Drug	t_{max} (hours)	$t_{½}$ (hours)	Recommended daily dose (mg)
Alfuzosin IR	1.5	4-6	3 x 2.5
Alfuzosin SR	3	8	2 x 5
Alfuzosin XL	9	11	1 x 10
Doxazosin IR	2-3	20	1 x 2-8
Doxazosin GITS	8-12	20	1 x 4-8
Silodosin	2.5	11-18	1 x 4-8
Tamsulosin MR	6	10-13	1 x 0.4
Tamsulosin OCAS	4-6	14-15	1 x 0.4
Terazosin	1-2	8-14	1 x 5-10

t_{max} = time to maximum plasma concentration; $t_{½}$ = elimination half-life; IR = immediate release; SR = sustained release; GITS = gastrointestinal therapeutic system; MR = modified-release; OCAS = oral-controlled absorption system.

4.1.3 Efficacy

Indirect comparisons between α_1-blockers and limited direct comparisons demonstrate that all α_1-blockers have a similar efficacy in appropriate doses (4). Although these improvements take a few weeks to develop fully, significant efficacy over placebo has been demonstrated within hours to days. α_1-Blockers have a similar

efficacy, expressed as a percentage improvement in International Prostate Symptom Score (IPSS), in patients with mild, moderate, or severe LUTS (5).

Controlled studies have shown that α_1-blockers typically reduce IPSS, after a placebo run-in period, by approximately 30-40% and increase the maximum flow rate (Q_{max}) by approximately 20-25% (Table 4.2). However, considerable improvements also occurred in the corresponding placebo arms (4,5). In open-label studies (without a run-in period), an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented (4,5).

Alpha$_1$-blockers are able to reduce both storage and voiding LUTS. Prostate size does not affect α_1-blocker efficacy in studies with follow-up periods of less than one year, but α_1-blockers do seem to be more efficacious in patients with smaller prostates (<40 mL) than in those with larger glands in longer-term studies (6-9).

Alpha$_1$-blocker efficacy is similar across age groups (5). α_1-Blockers neither reduce prostate size nor prevent acute urinary retention in long-term studies (6-8,10); some patients must therefore be treated surgically. Nevertheless, IPSS reduction and Q_{max} improvement during α_1-blocker treatment appears to be maintained over at least four years.

Table 4.2: Randomized, placebo-controlled trials with α_1-blockers in men with LUTS (drugs in chronological order; selection of trials)

Trials	Duration (weeks)	Treatment (daily dose)	Patients (n)	Change in symptoms (%)	Change in Q_{max} (mL/s)	PVR change (%)	LE
Jardin et al. (1991) (11)	24	Placebo Alfuzosin 3 x 2.5 mg	267 251	-32 [a] -42 [a,b]	+1.3 [a] +1.4 [a]	-9 -39 [a,b]	1b
Buzelin et al. (1997) (12)	12	Placebo Alfuzson 2 x 5 mg	196 194	-18 -31 [a,b]	+1.1 +2.4 [a,b]	0 -17 [a,b]	1b
van Kerrebroeck et al. (2000) (13)	12	Placebo Alfuzosin 3 x 2.5 mg Alfuzosin 1 x 10 mg	154 150 143	-27.7 -38.1 [a,b] -39.9 [a,b]	+1.4 +3.2 [a,b] +2.3 [a,b]	- - -	1b
MacDonald and Wilt (2005) (14)	4-26	Placebo Alfuzosin: all formulations	1039 1928	-0.9 [b] (Boyarski) [†] -1.8 [b] (IPSS) [†]	+1.2 [b]	-	1a
Kirby et al. (2001) (15)	13	Placebo Doxazosin 1 x 1-8 mg IR Doxazosin 1 x 4-8 mg GITS	155 640 651	-34 [a] -45 [a,b] -45 [a,b]	+1.1 [a] +2.6 [a,b] +2.8 [a,b]	- - -	1b
McConnell et al. (2003) (10)	234	Placebo Doxazosin 1 x 4-8 mg	737 756	-29 -39 [b]	+1.4 +2.5 [a,b]	- -	1b
Marks et al. (2009) (16)	12	Placebo Silodosin 1 x 8 mg	457 466	-16.0 -30.0[b]	+1.5 +2.6[b]	- -	1b
Chapple et al. (2011) (17)	12	Placebo Tamsulosin 1 x 0.4 mg Silodosin 1 x 8 mg	185 376 371	-25.0 -35.0[b] -37.0[b]	+2.9 +3.5 +3.7	- - -	1b
Cui et al. (2012) (18)	12	Placebo Tamsulosin 1 x 0.4 mg or 1 x 0.2 mg Silodosin 1 x 8mg or 2 x 4 mg	2543	sign. only vs placebo	sign. only vs placebo	- -	1a
Chapple et al. (1996) (19)	12	Placebo Tamsulosin MR 1 x 0.4 mg	185 364	-25.5 -35.1 [a,b]	+0.6 +1.6 [a,b]	-13.4 -22.4 [a]	1b

Lepor (1998) (20)	13	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin MR 1 x 0.8 mg	253 254 247	-28.1 -41.9 [a,b] -48.2 [a,b]	+0.5 +1.8 [a,b] +1.8 [a,b]	- - -	1b
Chapple et al. (2005) (21)	12	Placebo Tamsulosin MR 1 x 0.4 mg Tamsulosin OCAS 1 x 0.4 mg Tamsulosin OCAS 1 x 0.8 mg	350 700 354 707	-32 -43.2 [b] -41.7 [b] -42.4 [b]	- - - -	- - - -	1b
Wilt et al. (2002) (22)	4-26	Placebo Tamsulosin 1 x 0.4-0.8 mg	4122	-12 [b] (-1.1 Boyarski [†]) -11 [b] (-2.1 IPSS [†])	+1.1 [b]	-	1a
Brawer et al. (1993) (23)	24	Placebo Terazosin 1 x 1-10 mg	72 69	-11 -42 [a,b]	+1.2 +2.6 [a,b]	- -	1b
Roehrborn et al. (1996) (24)	52	Placebo Terazosin 1 x 1-10 mg	973 976	-18.4 -37.8 [a,b]	+0.8 [a] +2.2 [a,b]	- -	1b
Wilt et al. (2002) (25)	4-52	Placebo Terazosin (different doses)	5151	-37 [b] (-2.9 Boyarski [†]) -38 [b] (IPSS [†])	+1.7 [b]	-	1a

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

4.1.4 ***Tolerability and safety***

Distribution into lower urinary tract tissues, subtype selectivity, and the pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α_1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin, and are much less common for alfuzosin and tamsulosin (odds ratio for vascular-related adverse events 3.3, 3.7, 1.7 and 1.4, respectively; the latter two not reaching statistical significance [26]). In particular, patients with cardiovascular comorbidity and/or vaso-active co-medication may be susceptible to α_1-blocker-induced vasodilatation (27). In contrast, the frequency of hypotension with the α_{1A}-selective blocker silodosin is comparable with placebo (17).

Despite the long-standing and widespread use of α_1-blockers, an adverse ocular event termed intra-operative floppy iris syndrome (IFIS) was not discovered until 2005 in the context of cataract surgery (28). Although IFIS has been observed with all α_1-blockers, most reports are related to tamsulosin. In a recently published meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure, the authors found an increased risk for all the α_1-blockers investigated (29). However, the odds-ratio for IFIS was 393.1 for tamsulosin, 9.7 for alfuzosin, 6.4 for doxazosin and 5.5 for terazosin; so the odds-ratio is approximately 40-fold higher for tamsulosin than for the other α_1-blockers. It appears prudent not to initiate α_1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about previous or current α_1-blocker use.

A systematic review concluded that α_1-blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculation (30). Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that it is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. Abnormal ejaculation has been observed more frequently with tamsulosin and silodosin than with other α_1-blockers (31,32). Silodosin has the highest incidence of abnormal ejaculation; however, efficacy seems to be increased in patients experiencing abnormal ejaculation (32,33). Hence, the mechanism underlying abnormal ejaculation still remains to be elucidated.

4.1.5 ***Practical considerations.***

Alpha$_1$-blockers are often considered the first-line drug treatment of male LUTS because of their rapid onset of

action, good efficacy, and low rate and severity of adverse events. Ophthalmologists should be informed about α_1-blocker use prior to cataract surgery

4.1.6 ***Recommendation***

	LE	GR
Alpha$_1$-blockers can be offered to men with moderate-to-severe LUTS	1a	A

4.1.7 ***References***

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4.2 5α-Reductase inhibitors

*4.2.1 **Mechanism of action***

Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted primarily in the prostatic stroma cells from its precursor testosterone by the enzyme 5α-reductase, a nuclear-bound steroid enzyme (1). 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.

Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits 5α-reductase types 1 and 2 with similar potency (dual 5-ARI). However, the clinical role of dual inhibition remains unclear. 5α-Reductase inhibitors act by inducing apoptosis of prostate epithelial cells (2) leading to prostate size reduction of about 18-28% and circulating PSA levels of about 50% after 6-12 months of treatment (3). Mean prostate volume reduction and PSA decrease may be even more pronounced after long-term treatment.

*4.2.2 **Available drugs***

Two 5-ARIs are available for clinical use: dutasteride and finasteride (Table 4.3). The elimination half-time is longer for dutasteride (3-5 weeks). Both 5-ARIs are metabolized by the liver and excreted in the faeces. 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.

Table 4.3: 5α-reductase inhibitors licensed in Europe for treating benign prostatic enlargement (BPE) due to BPH; key pharmacokinetic properties and standard doses

Drug	t_{max} (hours)	$t_{½}$	Recommended daily dose
Dutasteride	1-3	3-5 weeks	1 x 0.5 mg
Finasteride	2	6-8 hours	1 x 5 mg

t_{max} = time to maximum plasma concentration; $t_{½}$ = elimination half-life.

*4.2.3 **Efficacy***

Clinical effects relative to placebo are seen after a minimum treatment duration of at least 6-12 months. After two to four years of treatment, 5α-reductase inhibitors reduce LUTS (IPSS) by approximately 15-30%, decrease prostate volume by approximately 18-28%, and increase Q_{max} of free uroflowmetry by approximately 1.5-2.0 mL/s in patients with LUTS due to prostate enlargement (Table 4.4) (4-13).

Indirect comparison between individual studies and one direct comparative trial indicate that dutasteride and finasteride are equally effective in the treatment of LUTS (3,14). Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates smaller than 40 mL (15). However, dutasteride seems to reduce IPSS, prostate volume, and the risk of acute urinary retention, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40 mL at baseline (16,17).

Comparative studies with α_1-blockers and a recent meta-analysis have demonstrated that 5α-reductase inhibitors reduce LUTS more slowly and that finasteride is less effective than either doxazosin or terazosin, but equally effective compared with tamsulosin (5,10,18-20). 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 in these patients at least as much as, or even more effectively than, the α_1-blocker tamsulosin (12,21,22). The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride.

5α-Reductase inhibitors, but not α_1-blockers, reduce the long-term (>1 year) risk of acute urinary retention (AUR) or need for surgery (8,10,23). In the Proscar Long-Term Efficacy and Safety Study, after four years, finasteride treatment reduced the relative risk of AUR by 57%, and surgery by 55%, compared with placebo (8). In the Medical Therapy of Prostatic Symptoms(MTOPS) study, a significant reduction in the risk of AUR and surgery in the finasteride arm compared with placebo was reported (68% and 64%, respectively) (10).

A pooled analysis of randomized 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%, relative to placebo in patients with moderately symptomatic BPH (24). Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Pooled phase 3 studies have shown a reduced relative risk of AUR (57%) and surgical intervention (48%) compared with placebo at two years (11). In addition, this reduction was maintained to four years during the open-label phase of the study (16).

The precise mechanism of action of 5α-reductase inhibitors in reducing disease progression remains to be determined, but it is most likely attributable to a reduction of bladder outlet resistance. Open-label trials have demonstrated relevant reductions of voiding parameters after computer-urodynamic re-evaluation in men who were treated for at least three years with finasteride (25,26).

Table 4.4: Randomized trials with 5α-reductase inhibitors in men with LUTS and benign prostatic enlargement due to BPH

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

Roehrborn et al. (2008) (12)	104	Tamsulosin 1 x 0.4 mg	1611	-27.4 [a]	+0.9	0	1b
		Dutasteride 1 x 0.5 mg	1623	-30.5 [a]	+1.9	-28 [b]	
Roehrborn et al. (2010) (13)	208	Tamsulosin 1 x 0.4 mg	1611	-23.2 [a]	+0.7	+4.6	1b
		Dutasteride 1 x 0.5 mg	1623	-32.3 [a]	+2.0	-28 [b]	

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

*4.2.4 **Tolerability and safety***

The most relevant adverse effects of 5α-reductase inhibitors are related to sexual function, and include reduced libido, erectile dysfunction and, less frequently, ejaculation disorders such as retrograde ejaculation, ejaculation failure, or decreased semen volume (3,10,13). The incidence of sexual dysfunction and other adverse events is low and even decreased with trial duration. Gynaecomastia (breast enlargement with breast or nipple tenderness) develops in approximately 1-2% of patients.

Data from two important trials on prostate cancer chemoprevention (the Prostate Cancer Prevention Trial and the Reduction by Dutasteride of Prostate Cancer Events trial) found a higher incidence of high-grade cancers in the 5-ARI arms than in the placebo arms (27,28). Although no causal relationship between 5-ARI and high-grade prostate cancer has been proven, men taking a 5α-reductase inhibitor should be followed up regularly using serial prostate-specific antigen (PSA) testing. Any confirmed increase in PSA while on a 5-ARI should be evaluated.

*4.2.5 **Practical considerations***

Treatment with 5α-reductase inhibitors should be considered only in men with moderate-to-severe LUTS and an enlarged prostate (>40 mL) or elevated PSA concentration (>1.4-1.6 ng/mL). Due to the slow onset of action, 5α-reductase inhibitors are suitable only for long-term treatment (many years). Their effect on the serum PSA concentration needs to be considered for prostate cancer screening. Of interest, 5α-reductase inhibitors (finasteride) might reduce blood loss during transurethral prostate surgery, probably due to their effects on prostatic vascularization (29).

*4.2.6 **Recommendations***

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

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4.3 Muscarinic receptor antagonists

*4.3.1 **Mechanism of action***

The main neurotransmitter of the urinary bladder is acetylcholine, which is able to stimulate muscarinic receptors (m-cholinoreceptors) on the surface of detrusor smooth muscle cells. However, muscarinic receptors are not only densely expressed on smooth muscle cells, but also on other cell types, such as epithelial cells of the salivary glands, urothelial cells of the urinary bladder, or nerve cells of the peripheral or central nervous system. Five muscarinic receptor subtypes (M1-M5) have been described in humans, of which the M2 and M3 subtypes are predominantly expressed in the detrusor. Although approximately 80% of these muscarinic receptors are M2 and 20% M3 subtypes, only M3 seems to be involved in bladder contractions in healthy humans (1,2). The role of M2 subtypes remains unclear. However, in men with neurogenic bladder dysfunction, and in experimental animals with neurogenic bladders or BOO, M2 receptors seem to be involved in smooth muscle contractions as well (3).

The detrusor is innervated by parasympathetic nerves which have their origin in the lateral columns of sacral spinal cord on the level S2-S4 which itself is modulated by supraspinal micturition centres. The sacral micturition centre is connected with the urinary bladder by the pelvic nerves which release acetylcholine after depolarization. Acetylcholine stimulates post-synaptic muscarinic receptors leading to G-protein mediated calcium release in the sarcoplasmatic reticulum and opening of calcium channels of the cell membrane and, finally, smooth muscle contraction. Inhibition of muscarinic receptors by muscarinic receptor antagonists inhibit/decrease muscarinic receptor stimulation and, hence, reduce smooth muscle cell contractions of the bladder. Antimuscarinic effects might also be induced or modulated by the urothelium of the bladder and/or by the central nervous system (4,5).

4.3.2 *Available drugs*

The following muscarinic receptor antagonists are licensed for treating overactive bladder/storage symptoms in men and women (Table 4.5):

- darifenacin hydrobromide (darifenacin)
- fesoterodine fumarate (fesoterodine)
- oxybutynin HCL (oxybutynin)
- propiverine HCL (propiverine)
- solifenacin succinate (solifenacin)
- tolterodine tartrate (tolterodine)
- trospium chloride.

Table 4.5: Antimuscarinic drugs licensed in Europe for treating overactive bladder/storage symptoms; key pharmacokinetic properties and standard doses

Drug	T_{max} [h]	$T_{½}$ [h]	Recommended daily dose [mg]
Darifenacin ER[a]	7	12	1 x 7.5-15
Fesoterodine[a,b]	5	7	1 x 4-8
Oxybutynin IR	0.5-1	2-5[c]	3-4 x 2.5-5
Oxybutynin ER	5	16	2-3 x 5
Propiverine	2.5	13	2-3 x 15
Propiverine ER	10	20	1 x 30
Solifenacin	3-8	45-68	1 x 5-10
Tolterodine IR[a]	1-3	2-10	2 x 1-2
Tolterodine ER[a]	4	6-10	1 x 4
Trospium IR	5	18	2 x 20
Trospium ER	5	36	1 x 60

t_{max} = time to maximum plasma concentration; $t_{½}$ = elimination half-life; ER = extended release (in some countries some manufacturers may have assigned different designators to the ER formulation); IR = immediate release.

[a]higher exposure can occur in CYP 2D6 poor metabolizers;

[b]only the active metabolite 5-hydroxy-methyl-tolterodine is detectable in blood after oral administration of fesoterodine;

[c]$t_{½}$ is age-dependent, values taken from (7).

Notes: the gel and patch formulations of oxybutynin have not been included in this table; detailed information on other pharmacokinetic parameters and their alteration in renal or hepatic impairment on drug metabolism and pharmacokinetic drug-drug interactions has been summarized (6); all data refer to drug use in adults; where applicable, pharmacokinetic properties may differ in paediatric populations.

4.3.3 *Efficacy*

Muscarinic receptor antagonists have been predominantly tested in females in the past because it was believed that LUTS in women are caused by the bladder and must therefore be treated with bladder-specific drugs. In contrast, it was believed that LUTS in men are caused by the prostate and need to be treated with prostate-specific drugs. However, there is no scientific data for that assumption (8). A sub-analysis of an open-label trial of 2,250 male or female patients with overactive bladder symptoms treated with tolterodine showed that age but not gender has a significant impact on urgency, frequency, or urgency incontinence (9).

The efficacy of the anticholinergic drug tolterodine, and lately also fesoterodine, was tested as a single agent in adult men with bladder storage symptoms (overactive bladder [OAB] symptoms) but without BOO (Table 4.6) (10-16). Maximum trial duration was 25 weeks, but most of the trials lasted for only 12 weeks.

Four post hoc analyses (two analyses with tolterodine extended release, one with solifenacin 5 mg, and one with fesoterodine 4 mg and 8 mg) of data from large randomized controlled trials (RCTs) on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men (11,12,16,17). It was demonstrated that tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency, and urgency-related voiding, as well as improve patient perception of treatment benefit compared

with placebo.

Solifenacin significantly improved mean patient perception of bladder condition scores, mean scores on the OAB questionnaire, and overall perception of bladder problems, and fesoterodine had significantly greater median percentage improvements in micturition frequency, urgency episodes, and urgency urinary incontinence (UUI) episodes, whereas significantly greater percentages reported a treatment response versus placebo.

In open-label trials with tolterodine, daytime frequency, nocturia, UUI, and IPSS were significantly reduced compared with baseline values after 12-25 weeks (10,15).

Few studies have investigated the efficacy of monotherapy with antimuscarinics for male patients with BOO and OAB symptoms with unsatisfactory findings. In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety study, patients who received tolterodine as monotherapy were significantly improved only in urge incontinence, but they did not show any significant improvement in urgency, IPSS (either total or storage subscore), or the overall percentage of patients reporting treatment benefit compared with placebo (13).

A further analysis showed that men with PSA levels of <1.3 ng/mL (smaller prostates) might profit more from antimuscarinic drugs (18). Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BOO (10,19). In a small RCT without placebo, patients in the propiverine hydrochloride arm experienced improvement in urinary frequency and urgency episodes compared with baseline (19). In an open-label study, tolterodine decreased the mean 24-hour micturition and nocturia, and mean American Urological Association Symptom Index scores improved significantly (10).

Table 4.6: Trials with antimuscarinic drugs only in elderly men with LUTS, predominantly with OAB symptoms (trials in chronological order)

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency (%)	Nocturia (%)	Urgency incontinence (%)	IPSS (%)	LE
Kaplan et al. (2005) (10)	25	Tolterodine 1 x 4 mg/d (after α-blocker failure)	43	-35.7[a]	-29.3[a]	-	-35.3[a]	2b
Roehrborn et al. (2006) (11)	12	Placebo	86	-4	-	-40	-	1b
		Tolterodine 1 x 4 mg/d	77	-12	-	-71[b]	-	
Kaplan et al. (2006) (12)	12	Placebo	374	-7.9	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-10.8[b]	-18.8	-	-	
Kaplan et al. (2006) (13)	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-85[b]	-54	
Dmochowski et al. (2007) (14)	12	Placebo	374	-5.6	-17.6	-	-	1b
		Tolterodine 1 x 4 mg/d	371	-8.7[b]	-18.8	-	-	
Höfner et al. (2007) (15)	12	Tolterodine 1 x 4 mg/d	741	-20[a]	-42.9 a	-100	-37.9[a]	2b
Herschorn et al. (2009) (16)	12	Placebo	124	-10.2	-	-59.3	-	1b
		Fesoterodine 1 x 4 mg/d	111	-13.2[b]	-	-84.5[b]	-	
		Fesoterodine 1 x 8 mg/d	109	-15.6[b]	-	-100[b,c]	-	

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

4.3.4 ***Tolerability and safety***

Muscarinic receptor antagonists are generally well tolerated and associated with approximately 3-10% of withdrawals, which is not significantly different from placebo in most studies. Compared with placebo, drug-related adverse events appear with higher frequency for dry mouth (up to 16%), constipation (up to 4%), micturition difficulties (up to 2%), nasopharyngitis (up to 3%), and dizziness (up to 5%).

Increase of post-void residual (PVR) urine in men without BOO is minimal and not significantly different from placebo (0-5 mL vs -3.6-0 mL). Nevertheless, fesoterodine 8 mg showed higher post-void residuals (+20.2 mL) than placebo (-0.6 mL) or fesoterodine 4 mg (+9.6 mL) (16). The incidence of urinary retention in men without BOO was comparable with placebo in trials with tolterodine (0-1.3% vs 0-1.4%). In men undergoing fesoterodine 8 mg treatment, 5.3% had symptoms suggestive of urinary retention, which was higher than with 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.

Antimuscarinic drugs are not recommended in men with BOO because of the theoretical decrease of bladder strength that might be associated with PVR urine or urinary retention. A 12-week placebo-controlled safety study dealing with men who had mild to moderate BOO (median BOO index in the placebo or tolterodine group 43 cm H_2O and 49 cm H_2O, respectively) demonstrated that tolterodine significantly increased the amount of PVR urine (49 mL vs 16 mL) but was not associated with increased events of acute urinary retention (3% in both study arms) (20). The urodynamic effects of tolterodine included significantly larger bladder volumes to first detrusor contraction, higher maximum cystometric bladder capacity, and decreased bladder contractility index. Maximum urinary flow remained unchanged in both the tolterodine and placebo groups. This single trial indicated that the short-term treatment with antimuscarinic drugs in men with BOO is safe (20).

4.3.5 ***Practical considerations***

Although not all antimuscarinic agents have been tested in elderly men with LUTS and OAB symptoms, they are all likely to present similar efficacy and adverse events. Long-term studies on the efficacy of muscarinic receptor antagonists in men with LUTS are not yet available. These drugs should therefore be prescribed with caution, and regular re-evaluations of IPSS and PVR urine is advised.

4.3.6 ***Recommendations***

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

4.3.7 ***References***

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4.4 Phosphodiesterase 5 inhibitors (with or without α_1-blockers)

4.4.1 Mechanism of action

Nitric oxide (NO) represents an important non-adrenergic, non-cholinergic neurotransmitter in the human body and is involved in signal transmission in the human urinary tract. NO is synthesized from the amino acid L-arginine by NO synthases, which are classified based on their original tissues of detection as neuronal, endothelial, and immune cell (inducible) NOS.

After being synthesized, NO diffuses into cells and stimulates the synthesis of cyclic guanosine monophosphate (cGMP) mediated by the enzyme guanylyl-cyclase. cGMP can activate protein kinases, ion channels, and cGMP-binding phosphodiesterases (PDEs), leading to smooth muscle cell relaxation via depletion of intracellular Ca^{2+} and desensitization of contractile proteins (1). The effects of cGMP are terminated by PDE isoenzymes catalysing the hydrolysis of cGMP to an inactive form. PDE inhibitors increase the concentration and prolong the activity of intracellular cGMP, thereby reducing smooth muscle tone of the detrusor, prostate and urethra.

So far, 11 different PDEs have been identified, with PDE types 4 and 5 predominating in the transition zone of the human prostate, bladder and urethra (2,3). NO and PDEs might also be involved in the micturition cycle by inhibiting reflex pathways in the spinal cord and neurotransmission in the urethra, prostate or bladder (4). It has also been proposed that PDE inhibitors increase blood perfusion and oxygenation of the lower urinary tract, but their exact mechanism of action remains to be determined.

*4.4.2 **Available drugs***

Although three selective oral PDE5 inhibitors (sildenafil citrate [sildenafil], tadalafil, and vardenafil HCl [vardenafil]) have been licensed in Europe for the treatment of erectile dysfunction, and clinical trials of all of them have been conducted in patients with male LUTS, only tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS (Table 4.7). The available PDE5 inhibitors differ primarily in their pharmacokinetic profiles (5). All PDE5 inhibitors are rapidly resorbed from the gastrointestinal tract, have high protein-binding in plasma, are metabolized primarily by the liver and eliminated predominantly in the faeces. However, their half-lives differ markedly. PDE5 inhibitors are taken on-demand by patients with erectile dysfunction, but tadalafil is also registered for once-daily use in lower dose (5 mg) than for on-demand use.

Table 4.7: PDE5 inhibitors licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

Drugs	t_{max} (hours)	$t_{½}$ (hours)	Daily doses in clinical trials of patients with male LUTS
Sildenafil	1 * (0.5-2)	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1 * (0.5-2)	4-5	2 x 10 mg

*t_{max} = time to maximum plasma concentration; $t_{½}$ = elimination half-life; *dependent on food intake (i.e. slower resorption of the drug and an increase in t_{max} by approximately 1 hour after a fatty meal).*

*4.4.3 **Efficacy***

A post hoc analysis of patients with erectile dysfunction treated with sildenafil initially showed that the PDE5 inhibitor was also capable of significantly improving concomitant LUTS and increasing bladder symptom-related quality of life (QoL), as measured by the IPSS questionnaire (6,7). LUTS improvement was found to be independent of improvement of erectile function.

Randomized, placebo-controlled trials on the efficacy of all three of the oral PDE5 inhibitors available have been published in the past few years, investigating changes in symptoms (IPSS), uroflowmetry parameters (Q_{max}), and PVR urine (8-24). Significant LUTS reduction has been documented with tadalafil as early as after one week of treatment (19). The maximum trial duration was 52 weeks in an open-label trial with tadalafil (16). Randomized, placebo-controlled trials demonstrated that all PDE5 inhibitors significantly and consistently reduced IPSS by approximately 17-37% (Table 4.8). Both bladder storage and voiding symptoms decreased during treatment with PDE5 inhibitors. PDE5 inhibitors also significantly improved QoL compared with placebo-treated patients. Q_{max} of free uroflowmetry increased in a dose-dependent fashion, but was not significantly different compared with placebo in the majority of trials.

Table 4.8: Efficacy of PDE5 inhibitors in adult men with LUTS who participated in high level clinical trials

Trials	Duration (weeks)	Treatment	Patients	IPSS	Q_{max} (mL/s)	PVR (mL)	LE
McVary et al. 2007 (8) ‡	12	Placebo	180	-1.93	+0.16	-	1b
		Sildenafil 1 x 50-100 mg/ day or 1 x 50-100 mg before sexual intercourse	189	-6.32 *	+0.32	-	
Kaplan et al. 2007 (9)‡	12	Alfuzosin 1 x 10 mg/day	20	-2.7 (-15.5%) †	+1.1 †	-23 †	1b
		Sildenafil 1 x 25 mg/day	21	-2.0 (-16.9%) †	+0.6	-12	
		Alfuzosin 1 x 10 mg/day + Sildenafil 1 x 25 mg/day	21	-4.3 (-24.1%) †	+4.3 †	-21 †	
Tuncel et al. (2010) (10)‡	8	Sildenafil 1 x 25 mg, 4 x/ week	20	-28.1%	+3.7 †	-15.2 †	1b
		Tamsulosin 1 x 0.4 mg	20	-36.2%°	+3.2 †	-26.2 †°	
		Sildenafil 1 x 25 mg, 4 x/week + Tamsulosin 1 x 0.4 mg/day	20	-40.1%°	+5.7 †•°	-33.3 †°	
McVary et al. 2007 (11)	12	Placebo	143	-1.7 (-9.3%)	+0.9	-2.6	1b
		Tadalafil 1 x 5-20 mg/day	138	-3.8 (-21.7%) *	+0.5	+1.4	
Roehrborn et al. 2008 (12)	12	Placebo	212	-2.3 (-13.3%)	+1.2	+4.81	1b
		Tadalafil 1 x 2.5 mg/day	209	-2.7 (-22.2%) *	+1.4	+12.1	
		Tadalafil 1 x 5 mg/day	212	-4.9 (-28.2%) *	+1.6	+6.6	
		Tadalafil 1 x 10 mg/day	216	-5.2 (-29.1%) *	+1.6	+10.6	
		Tadalafil 1 x 20 mg/day	209	-5.2 (-30.5%) *	+2.0	-4	
Bechara et al. 2008 (13)	6	Tamsulosin 1 x 0.4 mg/day	15	-6.7 † (-34.5%)	+2.1 †	-35.2 †	1b
		Tamsulosin 1 x 0.4 mg/day + tadalafil 1 x 20 mg/day	15	-9.2 †a (-47.4%)	+3.0 †	-38.7 †	
Liguori et al. 2009 (14) ‡	12	Alfuzosin 1 x 10 mg/day	22	-5.2 † (-27.2%)	+1.7 †	-	1b
		Tadalafil 1 x 20 mg every 2 days	21	-1.3 (-8.4%)	+1.2 †	-	
		Alfuzsosin 1 x 10 mg/day + Tadalafil 1 x 20 mg every 2 days	23	-6.3 † (-41.6%)	+3.1 †	-	
Porst et al. 2009 (15)‡	12	Placebo	115	-2.1	+1.9	-6.8	1b
		Tadalafil 1 x 2.5 mg/day	113	-3.6 *	+1.4	+8.6 *	
		Tadalafil 1 x 5 mg/day	117	-4.2 *	+1.7	-1.8	
		Tadalafil 1 x 10 mg/day	120	-4.7 *	+1.3	+3.8	
		Tadalafil 1 x 20 mg/day	116	-4.7 *	+2.0	-14	

Donatucci et al. (2011) (16)‡	52	Tadalafil 1 x 5 mg/day	427	-5.0† (with ED: -5.3 (29.3%)) † (without ED: -4.5 (25.3%)) †	-	-18.9	2a
Porst et al. (2011) (17)‡	12	Placebo	164	-3.6 (-21.7%)	+1.1	+4.5	1b
		Tadalafil 1 x 5 mg/day	161	-5.6* (-32.8%)	+1.6	+ 8.8	
Egerdie et al. (2012) (18)‡	12	Placebo	200	-3.8 (-20.9%)	+1.2	-3.0	1b
		Tadalafil 1 x 2.5 mg/day	198	-4.6 (-25.3%)	+1.7*	-8.4	
		Tadalafil 1 x 5 mg/day	208	-6.1* (-33%)	+1.6	-2.0	
Oelke et al. (2012) (19)‡	12	Placebo	172	-4.2 (-24.1%)	+1.2	-1.2	1b
		Tadalafil 1 x 5 mg/day	171	-6.3* (-36.6%)	+2.4*	-4.6	
		Tamsulosin 1 x 0.4 mg/day	168	-5.7* (-33.9%)	+2.2*	10.2	
Yokoyama et al. (2012) (20)‡	12	Placebo	154	-3.0 (-17.9%)	+2.2	-1.2	1b
		Tadalafil 1 x 2.5 mg/day	151	-4.8* (-28.9%)	+1.6	-0.1	
		Tadalafil 1 x 5 mg/day	155	-4.7* (-27.3)	+1.3	-2.9	
Stief et al. 2008 (21)	8	Placebo	113	-3.6 (-20%)	+1.0	+1.92	1b
		Vardenafil 2 x 10 mg	109	-5.8 (-34.5%) *	+1.6	-1.0	
Gacci et al. (2012) (22)‡	12	Tamsulosin 1 x 0.4 mg/day + placebo	30	-3.7 (-18.1%)	+0.1	-4.9	1b
		Tamsulosin 1 x 0.4 mg/day + Vardenafil 1 x 10 mg/day	30	-5.8• (-31%)	+2.6	-10.2	
Gacci et al. (2012) (23)	6-12	Placebo	964				1a
		PDE5 inhibitor (any)	2250	Δ -2.8*	0.0	-	
		α_1-blocker	107				
		α_1-blocker + PDE5 inhibitor	109	Δ -1.8•	Δ +1.5•	-	

IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate during free uroflowmetry; PVR = post-void residual urine;
‡trial included patients with both erectile dysfunction and LUTS;
**significant compared with placebo ($p \leq 0.05$);*
†significant compared with baseline ($p \leq 0.05$ [indexed wherever evaluated]);
°significant compared with PDE5 inhibitor alone;
•significant compared with α1-blocker alone.

In contrast to the evidence-based medicine level 1b trials listed in Table 4.8, two single-centre uroflowmetry studies documented significant and clinically relevant improvements of Q_{max} and Qave following oral administration of 50 mg or 100 mg sildenafil in up to 76% of men (mean Q_{max} increase 3.7-4.3 mL/s or 24-38%) (25,26). PVR urine remained unchanged in the majority of the trials. A recent meta-analysis (3,214 men with a median follow-up of 12 weeks) reported that monotherapy with a PDE5 inhibitor achieved a significant

improvement in the International Index of Erectile Function (IIEF) score (+5.5) and IPSS (-2.8), but no significant improvement in Q_{max} was found (0.00) compared with placebo (23).

With regard to tadalafil 5 mg, it was found significantly to reduce IPSS by 22-37% (4.7-6.6 IPSS points; IPSS points relative to placebo: 2.1-4.4) (15,19). Significant LUTS (IPSS) reduction has been documented with tadalafil as early as 1 week after the beginning of treatment. In the latter RCT, not included in the meta-analysis just cited, a statistically significant increase in Q_{max} with tadalafil compared with placebo (+2.4 mL/s) was reported for the first time (19). Tadalafil had no significant impact on PVR.

Only five trials (two studies with tadalafil 20 mg, two studies with sildenafil 25 mg, and one with vardenafil 20 mg) have evaluated the combination of α-blockers with PDE5 inhibitors (9,10,13,14,22). These trials were conducted in a small number of patients and with a limited follow-up of 6-12 weeks. A meta-analysis of the five RCTs available showed that the combination of α-blockers and PDE5 inhibitors significantly improved Q_{max} (+1.5 mL/s), IPSS (-1.8) and IIEF score (+3.6) compared with the use of α-blockers alone (23). However, because only tadalafil 5 mg has been licensed, data on combinations of PDE5 inhibitors and other LUTS medications are considered insufficient.

*4.4.4 **Tolerability and safety***

PDE5 inhibitors in general can cause headache, flushing, dizziness, dyspepsia, nasal congestion, myalgia, hypotension, syncope, tinnitus, conjunctivitis, or altered vision (blurred, discoloration). Tadalafil, the only PDE5 inhibitor with a license for treating male LUTS, causes most frequently (prevalence 2-3%) headache, back pain, dizziness, and dyspepsia (19). The probability of developing priapism or acute urinary retention is considered minimal.

PDE5 inhibitors are contraindicated in patients using nitrates or the potassium channel opener nicorandil because of additional vasodilatation, which might cause hypotension, myocardial ischaemia in patients with coronary artery disease, or cerebrovascular strokes (5). In addition, none of the PDE5 inhibitors should be given to patients who:

- are taking the α_1-blockers doxazosin or terazosin
- have unstable angina pectoris
- have had a recent myocardial infarction (during the previous three months) or stroke (during the previous six months)
- have myocardial insufficiency New York Heart Association stage >2
- have hypotension
- have poorly controlled blood pressure
- have significant hepatic or renal insufficiency
- have, or have had after previous use of PDE5 inhibitors, non-arteritic anterior ischaemic optic neuropathy with sudden loss of vision.

Caution is advised if PDE5 inhibitors are used together with other drugs that are metabolized by the same hepatic elimination pathway (CYP3A4), which is associated with an increased serum concentration of the PDE5 inhibitor.

*4.4.5 **Practical considerations***

To date, only tadalafil 5 mg once daily has been officially licensed for the treatment of male LUTS with or without erectile dysfunction. Therefore, only tadalafil should be used clinically for the treatment of male LUTS. The meta-analysis of PDE5 inhibitors suggested that younger men with low body mass index and more severe LUTS profit the most from treatment with PDE5 inhibitors (23).

Long-term experience with tadalafil in patients with LUTS is limited to one trial, and therefore judgement about its efficacy or tolerability >1 year is not possible. There is limited information at present about the reduction of prostate size and no information on the slowing of disease progression. Insufficient information is available about combinations between PDE5 inhibitors and other LUTS medications.

4.4.6 *Recommendations*

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

4.4.7 *References*

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4.5 Plant extracts - phytotherapy

*4.5.1 **Mechanism of action***

Phytotherapy comprises the medical use of various extracts of different plants. Which of the components of the extracts are responsible for the relief of symptoms in male LUTS remains controversial. The most important compounds are believed to be phytosterols, ß-sitosterol, fatty acids, and lectins (1). In vitro studies have shown that plant extracts:

- 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, 5α-reductase, muscarinic cholinoceptors, dihydropyridine receptors and vanilloid receptors
- improve detrusor function
- neutralize free radicals (1-3).

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

*4.5.2 **Available drugs***

Herbal drug preparations are made of roots, seeds, pollen, bark or fruits, and can be made from a single plant (monopreparations) or a combination of extracts of two or more plants (combination preparations). A large

number of different plants are used for the preparation of extracts, the most widely used being:

- *Cucurbita pepo* (pumpkin seeds)
- *Hypoxis rooperi* (South African star grass)
- *Pygeum africanum* (bark of the African plum tree)
- *Secale cereale* (rye pollen)
- *Serenoa repens* (syn. Sabal serrulata; berries of the American dwarf palm, saw palmetto)
- *Urtica dioica* (roots of the stinging nettle).

Various producers use different extraction techniques, distribute active ingredients with different qualitative and quantitative properties, or combine two or more herbal compounds in one pill. The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects, and so the effects of one brand cannot, therefore, be extrapolated to others (4). To complicate matters further, even two different batches of the same product from the same producer might contain different concentrations of active ingredients and cause different biological effects (5). Thus the pharmacokinetic properties can differ significantly between different plant extracts.

4.5.3 ***Efficacy***

Each class of plant extract is discussed separately for the above-mentioned reasons (Table 4.9). Whenever possible, the brand name is mentioned to demonstrate possible differences between products. In general, no phytotherapeutic agent has been shown to reduce prostate size significantly, and no trial has proven a reduction of BOO or a decrease in disease progression.

Cucurbita pepo: Only one trial has evaluated the efficacy of pumpkin seed extract (Prosta Fink™ forte) in patients with BPH-LUTS (6). A total of 476 patients were randomly assigned to placebo or Prostat Fink™ forte. After a follow-up of 12 months, IPSS and daytime voiding frequency were significantly reduced in the pumpkin seed group. However, uroflowmetry parameters (Q_{max}), PVR urine, prostate volume, PSA concentration, nocturia and QoL were not statistically different between the groups.

Hypoxis rooperi: These phytopharmacological extracts contain a mixture of phytosterols bonded with glycosides, of which ß-sitosterol is the most important compound (Harzol™, Azuprostat™). Four randomized, placebo-controlled trials with durations of between four and 26 weeks were published and summarized in a Cochrane report (7). Daily doses of plant extracts ranged from 60 mg to 195 mg. Two trials evaluated symptoms (8,9) and all four trials investigated Q_{max} and PVR urine. A meta-analysis calculated weighted mean differences of -4.9 IPSS points, +3.9 mL/s in terms of Q_{max} and -28.6 mL in terms of PVR urine in favour of ß-sitosterol. Prostate size remained unchanged in all trials. No further trials have been carried out since the Cochrane report was published in 2000.

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

Secale cereale: A Cochrane report dealt with the clinical results of the main *Secale cereale* product Cernilton™. It comprised 444 men who were enrolled in two placebo-controlled and two comparative trials (Tadenan™, Paraprost™) lasting between 12 and 24 weeks (11). Men treated with Cernilton™ were twice as likely to report a benefit from therapy than those treated with placebo (RR 2.4). However, there were no significant differences between Cernilton™ and placebo with regard to Q_{max}, PVR urine, or prostate volume. No additional placebo-controlled trial with a monopreparation of Secale cereale has been published since the Cochrane report in 2000.

Serenoa repens/Sabal serrulata: A recently updated Cochrane report summarized the clinical results of 30 randomized trials comprising 5,222 men (12). Serenoa repens (mainly Permixon™ or Prostaserene™) was compared as a mono- or combination preparation with placebo, other plant extracts (*Pygeum africanum, Urtica dioica*), the 5-ARI finasteride, or the α-blocker tamsulosin. Mean follow-up of these trials varied between four and 60 weeks. The Cochrane report concluded that *Serenoa repens* was not superior to placebo, finasteride, or tamsulosin with regard to IPSS improvement, Q_{max}, or prostate size reduction. Similar levels of IPSS or Q_{max}

improvements in trials with finasteride or tamsulosin might be interpreted as treatment equivalence (13). For nocturia, Serenoa repens was significantly better than placebo (mean weighted difference -0.78).

Urtica dioica: Two trials compared the efficacy of stinging nettle monopreparations with placebo (14,15). One trial investigated 246 men with BPH-LUTS over a period of 52 weeks (14). Only IPSS decreased significantly in the phytotherapy group (Bazoton™ uno), whereas Q_{max} and PVR urine were not statistically different between the groups at the end of the trial. The second trial investigated 620 patients with BPH-LUTS over a period of 26 weeks (15). IPSS, Q_{max} and PVR urine significantly improved compared with placebo.

Combination preparations: Various trials have been carried out, especially with the extract combination of *Sabal serrulata* and *Urtica dioica* (PRO 160/120, Prostatgutt™ forte). A 24-week placebo-controlled trial demonstrated a significant improvement in IPSS in the phytotherapy arm (-2 IPSS points difference) (16); Q_{max} reduction was similar in both groups. A 24-week open label extension trial of the same patients, in which all patients were treated with PRO 160/120, showed similar improvements of IPSS at week 48 in both groups (-7 IPSS points). A second trial, in which PRO 160/120 was randomized against finasteride, showed similar results for IPSS and Q_{max} in both groups (17).

Table 4.9: Trials with plant extracts in patients with BPH-LUTS (selection; in alphabetical order)

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

Lopatkin et al. (2005) (16)	24	placebo	126	-4	+1.9	-	1b
		Sabal cerrulata + *Urtica dioica* (Prostatgutt™ forte)	127	-6[b]	+1.8	-	
Sökeland & Albrecht (1997) (17)	48	finasteride	244	-5.6	+2.8	-17.1	1b
		Sabal cerrulata + *Urtica dioica* (Prostatgutt™ forte)	245	-4.8	+2.0	-10.2	

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

*4.5.4 **Tolerability and safety***

Side-effects during phytotherapy are generally mild and comparable to placebo with regard to severity and frequency. Serious adverse events were not related to study medication. Gastrointestinal complaints were the most commonly reported side-effects. In formulations with *Hypoxis rooperi*, erectile dysfunction appeared in 0.5% of patients. Trial withdrawals were almost equal in both placebo and phytotherapy groups.

*4.5.5 **Practical considerations***

Phytotherapeutic agents are a heterogeneous group of plant extracts used to improve LUTS/BPH. Phytotherapy remains problematic to use because of different concentrations of the active ingredient(s) in different brands of the same phytotherapeutic agent. Hence, meta-analyses of extracts of the same plant do not seem to be justified and results of these analyses have to be interpreted with caution.

*4.5.6 **Recommendations***

The guidelines committee has not made any specific recommendations on phytotherapy for the treatment of male LUTS because of the heterogeneity of the products, lack of regulatory framework, and the considerable methodological problems associated with the published trials and meta-analyses.

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4.6 Vasopressin analogue - desmopressin

*4.6.1 **Mechanism of action***

The antidiuretic hormone arginine vasopressin (AVP) plays a key role in body water homeostasis and the control of urine production by binding to the V2 receptor in the renal collecting ducts. AVP increases water re-absorption as well as urinary osmolality, and decreases water excretion as well as total urine volume. AVP might be used therapeutically to manipulate the amount of urine excreted, although AVP also has V1 receptor-mediated vasoconstrictive/hypertensive effects and a very short serum half-life, which makes the hormone unsuitable for the treatment of nocturia/nocturnal polyuria.

*4.6.2 **Available drugs***

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and antidiuretic properties, but has no relevant V1 receptor affinity or hypertensive effects. Desmopressin may be used by intravenous infusion, nasal spray, tablet or 'melt' formulation. Nasally or orally administered desmopressin is rapidly absorbed, and later excreted 55% unchanged by the kidneys (1). Desmopressin has been used for more than 30 years in the

treatment of diabetes insipidus or primary nocturnal enuresis, and it has been approved in most European countries for the treatment of nocturia secondary to nocturnal polyuria in adult patients (Table 4.10). After intake before sleeping, excretion of urine during the night decreases and, therefore, the urge to void is postponed and the number of voids at night reduced (2,3). The clinical effects, in terms of the decrease in urine volume and increase in urine osmolality, last for approximately 8-12 hours (2).

Table 4.10: Antidiuretics licensed in Europe for treating nocturia due to nocturnal polyuria; key pharmacokinetic properties and standard doses

Drug	t_{max} (hours)	$t_{½}$ (hours)	Recommended daily dose before sleeping at night
Desmopressin tablet	1.0-2.0	3.0	1 x 0.1-0.4 mg orally
Desmopressin oral lyophilisate (MELT)	0.5-2.0	2.8	1 x 60-240 µg sublingually
Desmopressin nasal spray	1.0	0.4-4.0	1 x 10-40 µg nasally

t_{max} = time to maximum plasma concentration; $t_{½}$ = elimination half-life.

*4.6.3 **Efficacy***

The majority of clinical trials have used desmopressin in an oral formulation. A dose-finding study showed that the nocturnal urine volume/nocturnal diuresis was more greatly reduced by oral desmopressin 0.2 mg than 0.1 mg. However, this study also showed that a 0.4 mg dose taken once before sleeping had no additional effects on the nocturnal diuresis compared with a 0.2 mg dose (4). In the pivotal clinical trials, the drug was titrated from 0.1 mg to 0.4 mg according to the individual clinical response.

Desmopressin significantly reduced nocturnal diuresis by approximately 0.6-0.8 mL/min (-40%), decreased the number of nocturnal voids by approximately 0.8-1.3 (-40%), and extended the time until the first nocturnal void by approximately 1.6-2.1 hours (Table 4.11). Furthermore, desmopressin significantly reduced night-time urine volume as well as the percentage of urine volume excreted at night (5-7).

A meta-analysis of the available RCTs found that desmopressin significantly reduced the overall number of nocturnal voids and significantly increased the hours of undisturbed sleep in comparison with placebo. However, these RCTs were conducted in extremely heterogeneous populations with variable dosages (8).

The clinical effects of desmopressin were more pronounced in patients with more severe nocturnal polyuria and bladder capacity within the normal range at baseline. The 24-hour diuresis remained unchanged during desmopressin treatment (9). The clinical effects were stable over a follow-up period of 10-12 months and returned to baseline values after cessation of the trial (7). A significantly higher proportion of patients felt fresh in the morning after desmopressin use (odds ratio 2.71) (6).

Table 4.11: Clinical trials with desmopressin in adult men with nocturnal polyuria

Trials	Duration (weeks)	Treatment, i.e. oral daily dose before bedtime unless otherwise indicated	Patients (n)	Change nocturnal urine volume (mL/min)	Change nocturnal voids (n)	Time to first void (hours)	LE
Asplund et al. (1998) (4)	3	1 x 0.1 mg	23*	-0.5 (-31%)	-	-	2b
		1 x 0.2 mg	23*	-0.7 (-44%)	-	-	
		2 x 0.2 mg	23*	-0.6 (-38%)	-	-	
Cannon et al. (1999) (10)	6	Placebo	20	-	+0.1 (+3%)	-	1b
		1 x 20 µg intranasal	20	-	-0.3 (-10%)	-	
		1 x 40 µg intranasal	20	-	-0.7 (-23%)[a]	-	
Asplund et al. (1999) (9)	2	Placebo	17*	-0.2 (-11%)	-0.2 (-11%)	+0.2	1b
		1 x 0.1-0.4 mg	17*	-0.8 (-44%)[a]	-0.8 (-42%)[a]	+1.6	
Chancellor et al. (1999) (11)	12	1 x 20-40 µg intranasal	12	-	-1.8 (-50%)	-	2b
Mattiasson et al. (2002) (5)	3	Placebo	65	-0.2 (-6%)	-0.5 (-12%)	+0.4	1b
		1 x 0.1-0.4 mg	86	-0.6 (-36%)[a]	-1.3 (-43%)[a]	+1.8[a]	
Kuo 2002 (12)	4	1 x 0.1 mg	30*	-	-2.72 (-48.5%)	-	2b
Rembratt et al. (2003) (13)	0.5	1 x 0.2 mg	72*	-0.5	-1.0	+1.9	2b
van Kerrebroeck et al. (2007) (6)	3	Placebo	66	-	-0.4 (-15%)	+0.55	1b
		1 x 0.1-0.4 mg	61	-	-1.25 (-39%)[a]	+1.66[a]	
Lose et al. (2004) (7)‡	52	1 x 0.1-0.4 mg	132	-	-2	+2.3	2b
Wang et al. (2011) (14)	52	Placebo	58		-	-	1b
		1 x 0.1 mg	57	Δ141 mL	-	+0.50a	
Weiss et al. (2012) (15)‡	4	Placebo	90	-125 mL	-0.84	40 min	1b
		1 x 10 µg	82	-125 mL	-0.54	48 min	
		1 x 25 µg	87	-163 mL	-0.83	61 min	
		1 x 50 µg	77	-286 mL[a]	-1.13	72 min	
		1 x 100 µg	80	-306 mL[a]	-1.38[a]	100 min[a]	

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

4.6.4 Tolerability

The absolute number of adverse events associated with desmopressin treatment were higher than with placebo but usually mild in nature. The most frequent adverse events in short-term (up to three weeks) and long-term studies (12 months) were headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth and hyponatraemia (serum sodium concentration of <130 mmol/L). These events were comparable with the established safety profile of desmopressin in the treatment of polyuria due to other conditions. Peripheral oedema (2%) and hypertension (5%) were reported in the long-term treatment trial (7).

Hyponatraemia was observed mainly in patients aged 65 years or older, and occurred less frequently in men than in women of the same age (3). Hyponatraemia of all degrees, not necessarily associated with symptoms, occurs in 5.0-7.6% of patients soon after treatment initiation (16,17). The risk of developing hyponatraemia significantly increases with age (odds ratio 1.16 per year of age), lower serum sodium concentration at baseline (odds ratio 0.76), and higher basal 24-hour urine volume per bodyweight (odds ratio 1.09) (16). The risk of hyponatraemia in patients younger than 65 years is less than 1%, whereas the risk for older patients increases to 8% with normal sodium concentration, and up to 75% in patients with low sodium concentration at baseline (16). A recently published subanalysis suggests that oral doses of 50-100µg desmopressin (melt) are safe in men (18).

The treatment of men aged 65 years or older should therefore not be initiated without monitoring the serum sodium concentration. At the time of treatment initiation or dose change, older men with normal values of serum sodium should be monitored by Na+ measurement at day three and day seven of treatment, as well as one month later. If serum sodium concentration has remained normal and no dose adjustment is intended, Na+ should be monitored every three to six months thereafter (19). Furthermore, patients should be informed about the prodromal symptoms of hyponatraemia, such as headache, nausea or insomnia.

*4.6.5 **Practical considerations***

Desmopressin should be 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 every week until maximum efficacy is reached. The recommended maximum oral daily dose is 0.4 mg/day. Patients should avoid drinking fluids at least one hour before using desmopressin and for eight hours after dosing. Serum sodium concentrations should be monitored at day three and day seven after starting therapy, and regularly thereafter. In men aged 65 years or older, desmopressin should not be used if the serum sodium concentration is below the normal value.

*4.6.6 **Recommendation***

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

*4.6.7 **References***

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4.7 Combination therapies

4.7.1 α_1-blockers + 5α-reductase inhibitors

4.7.1.1 Mechanism of action

Combination therapy of α_1-blockers and 5α-reductase inhibitors aims to combine the differential effects of both drug classes to create synergistic efficacy in symptom improvement and prevention of disease progression.

4.7.1.2 Available drugs

Combination therapy consists of an α_1-blocker (alfuzosin, doxazosin, tamsulosin or terazosin; for pharmacokinetic properties see Section 3.1.2) together with a 5-ARI (dutasteride or finasteride; for pharmacokinetic properties see Section 3.2.2).

The α_1-blocker exhibits clinical effects within hours or days, whereas the 5-ARI needs several months to develop significant clinical efficacy. Of all the drug combinations possible, finasteride together with alfuzosin, doxazosin or terazosin, and dutasteride together with tamsulosin, have so far been tested in clinical trials. Both compounds show class effects with regard to efficacy and adverse events. No differences in the pharmacokinetic or pharmacodynamic properties of the drugs have been reported when used in combination compared with singly.

4.7.1.3 Efficacy

Several studies have investigated the efficacy of combination therapy against the efficacy of an α_1-blocker, 5-ARI or placebo alone (Table 4.12). Initial studies with follow-up periods of between six and 12 months used symptom (IPSS) change as their primary endpoint (1-3). These trials consistently demonstrated that the α_1-blocker was superior to finasteride in symptom reduction, whereas the combination treatment was not superior to the α_1-blocker alone. In studies that included a placebo arm, the α_1-blocker was consistently more effective than placebo, whereas finasteride was consistently not more effective than placebo. Data from the one-year timepoint of the MTOPS (Medical Therapy of Prostatic Symptoms) study, which have been published but not specifically analysed for this timepoint, showed similar results (4).

More recently, the four-year data analysis from MTOPS, as well as the two- and four-year results from the Combination of Avodart and Tamsulosin (CombAT) trials, have been reported (4-6). The latter trial included older men with larger prostates and higher serum PSA concentrations, and therefore appears to represent men at greater risk of disease progression. In contrast to earlier studies with only 6-12 months of follow-up, long-term data have demonstrated that combination treatment is superior to monotherapy with regard to symptom

reduction and improvement in Q_{max}, and superior to α-blocker in reducing the risk of acute urinary retention and the need for surgery (4-6).

The CombAT study demonstrated that combination treatment is superior to either monotherapy with regard to symptom improvement and Q_{max} starting from month nine, and superior to α_1-blocker with regard to the reduction in the risk of acute urinary retention and the need for surgery after month eight (6). The different results between the CombAT and MTOPS trials appear to arise from different inclusion and exclusion criteria rather than from the types of α_1-blockers or 5α-reductase inhibitors used.

Discontinuation of the α_1-blocker after six to nine months of combination therapy was investigated by an RCT and an open-label multicentre trial (7,8). The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months (7). After cessation of the α_1-blocker, almost three-quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A more recently published trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy (finasteride plus α_1-blocker) (8). LUTS improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference -0.44). However, the main limitations of those studies include the short duration of the combination therapy and the short follow-up period after discontinuation.

In both the MTOPS and CombAT trials, combination therapy was shown to be superior to monotherapy in preventing overall clinical progression as defined by an IPSS increase of at least four points, acute urinary retention, urinary tract infection, incontinence, or an increase in serum creatinine >50% compared with baseline values. 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) (4). 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 67.8%, BPH-related surgery by 70.6%, and symptom deterioration by 41.3% compared with tamsulosin, after four years (6).

Table 4.12: Randomized trials using α_1-blocker, 5α-reductase inhibitor, and the combination of both drugs in men with LUTS and benign prostatic enlargement due to BPH

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

Note: references 5 and 6 reflect different timepoints in the same study
IPSS = International Prostate Symptom Score; Q_{max} = maximum urinary flow rate (free uroflowmetry).
[a]*significant compared with baseline (indexed wherever evaluated);*
[b]*significant compared with placebo;*
[c]*significant compared with α-blocker monotherapy;*
[d]*significant compared with 5α-reductase inhibitor monotherapy.*

4.7.1.4 Tolerability and safety

Adverse events for both drug classes have been reported with combination treatment (4-6).The adverse events observed during combination treatment were typical of α_1-blockers and 5α-reductase inhibitors. The frequency of adverse events was significantly higher for combination therapy for most adverse events.

4.7.1.5 Practical considerations

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

4.7.1.6 Recommendation

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

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4.7.2 α_1-blockers + muscarinic receptor antagonists

4.7.2.1 Mechanism of action

Combination therapy comprising an α-blocker together with a muscarinic receptor antagonist aims to antagonize both α_1-adrenoceptors and muscarinic cholinoreceptors (M2 and M3) in the lower urinary tract, thereby using the efficacy of both drug classes to achieve synergistic effects.

4.7.2.2 Available drugs

Combination treatment consists of an α_1-blocker (alfuzosin, doxazosin, tamsulosin or terazosin; for pharmacokinetic properties see Chapter 3.1.2) together with a muscarinic receptor antagonist (darifencacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine or trospium chloride; for pharmacokinetic properties see Chapter 3.3.2). However, not all the possible combinations have been tested in clinical trials yet. No differences in the pharmacokinetic or pharmacodynamic properties of the drugs have been reported when used in combination compared with singly.

4.7.2.3 Efficacy

Several RCTs and prospective studies have evaluated the efficacy of the combination of α_1-blockers and muscarinic receptor antagonists, either as an initial treatment in men with OAB and presumed benign prostatic obstruction, or as a sequential treatment in men with persistent storage symptoms despite treatment with an α_1-blocker (1-10) (Table 4.13). The duration of the longest trial was 25 weeks, but the majority of trials lasted

only 4-12 weeks. One trial used the α_1-blocker naftopidil (not registered in most European countries) with and without anticholinergic agents (11).

Combination treatment was more efficacious in reducing voiding frequency, nocturia, or IPSS compared with α_1-blockers or placebo alone. Combination treatment significantly reduced UUI episodes, as well as urgency, and significantly increased QoL (4). Overall, symptom improvement in the combination therapy arm was significantly higher than with placebo regardless of PSA serum concentration, whereas tolterodine alone significantly improved symptoms predominantly in men with a serum PSA concentration of less than 1.3 ng/mL (12).

Persistent LUTS during α_1-blocker treatment can be significantly reduced by the additional use of a muscarinic receptor antagonist (add-on approach), especially when detrusor overactivity had been demonstrated (6-9). Two systematic reviews (no statistical analyses were provided) of studies on the efficacy and safety of antimuscarinic agents (including tolterodine, oxybutynin, propiverine, solifenacin, trospium, and fesoterodine) for the treatment of LUTS, including OAB in men, supported that combination treatment provides significant benefit to those men (13,14).

Table 4.13: Efficacy of muscarinic receptor antagonists together with α_1-blockers

Trials	Duration (weeks)	Treatment	Patients	Voiding frequency (%)	Nocturia (%)	IPSS (%)	LE
Saito et al. (1999) (1)	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5	-	1b
		Tamsulosin 1 x 0.2 mg/d + propiverine 1 x 20 mg/d	75	-44.7	-44.4[a]	-	
Lee et al. (2005) (3)	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
		Doxazosin 1 x 4 mg/d + propiverine 1 x 20 mg/d	131	-27.5[a]	-46.7	-50.7	
Kaplan et al. (2006) (4)	12	Placebo	215	-13.5	-23.9	-44.9	1b
		Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9[b]	
		Tolterodine 1 x 4 mg/d + tamsulosin 1 x 0.4 mg/d	217	-27.1[b]	-39.9[b]	-66.4[b]	
MacDiarmid et al. (2008) (5)	12	Tamsulosin 1 x 0.4 mg/d + placebo	209	-	-	-34.9	1b
		Tamsulosin 1 x 0.4 mg/d + oxybutynine 1 x 10 mg/d	209	-	-	-51.9[b]	
Kaplan et al. (2005) (7) ‡	25	Tolterodine 1 x 4 mg/d	43	-35.7[a]	-29.3 [a]	-35.3	2b
Yang et al. (2007) (8) ‡	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7[a]	2b
Chapple et al. (2009) (9)‡	12	Tolterodine ER 4.0 mg/d + α-blocker	283	-15.8[b]	-29.4	-25.1	1b
		Placebo + α-blocker	292	-10.5	-23.5	-23.5	
Kaplan et al. (2009) (10) ‡	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2[a]	-	-29	1b
		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1[a]	-	-31.8	

IPSS = International Prostate Symptom Score; ER = extended-release.
[a]significant compared with baseline ($p \leq 0.05$, indexed wherever evaluated); [b]significant reduction compared with placebo ($p < 0.05$); ‡persisting LUTS during α1-blocker treatment (add-on approach).

4.7.2.4 Tolerability and safety

Adverse events of both drug classes are reported with combination treatment with α_1-blockers and muscarinic receptor antagonists. The most frequently reported side-effect in all trials was xerostomia. Some side-effects (e.g. xerostomia or ejaculation failure) may appear with increased frequency and cannot simply be explained by adding together the frequencies of the adverse events of either drug.

Combination studies of α_1-blockers and antimuscarinics that measured PVR volume showed an increase in PVR (though not clinically significant), and the risk of AUR seems to be low (13,14). It remains unknown which men are at risk of developing PVR urine or urinary retention during the combination treatment.

A recent RCT investigated the safety in terms of maximum detrusor pressure and Q_{max} of the combination of solifenacin (6 mg and 9 mg) with tamsulosin in men with LUTS and BOO compared with placebo (15). At the end of treatment, the combination therapy was not inferior to placebo for the primary urodynamic variables; Q_{max} was increased versus placebo (15).

4.7.2.5 Practical considerations

Class effects are likely to be responsible for increased efficacy and QoL in patients treated with an α_1-blocker and muscarinic receptor antagonist. Trials used mainly storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Therefore, measuring PVR urine is recommended during combination treatment to assess increased PVR or urinary retention.

4.7.2.6 Recommendations

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

4.7.2.7 References

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5. SURGICAL TREATMENT

5.1 Transurethral resection of the prostate (TURP) and transurethral incision of the prostate (TUIP)

5.1.1 ***Mechanism of action***

Transurethral resection of the prostate (TURP) was first performed in 1932. Since then the basic principles behind TURP have stayed the same. It is still, primarily, the removal of tissue from the transition zone of the prostate to reduce benign prostatic obstruction (BPO) and, secondly, to reduce LUTS.

TURP is still regarded as the current surgical standard procedure for the treatment of LUTS secondary to BPO in prostates between 30 and 80 mL. However, there is no strong evidence in the literature regarding the upper size limit of the prostate suitable for TURP. The suggested threshold sizes reflect the Panel's expert opinion, which is based on the assumption that this limit depends on the surgeon's experience, resection speed, and choice of resectoscope size.

During the last 10 years, the number of TURPs performed has shown a steady decline from 81% of all surgery for benign prostatic hypertrophy (BPH) in the USA in 1999 to only 39% by 2005. This is due to the combined effect of fewer prostatic operations and the availability of procedures that are minimally invasive (1).

Transurethral incision of the prostate (TUIP) was initially described by Orandi in 1969. TUIP reduces LUTS secondary to BPO by splitting the bladder outlet without tissue removal. This technique has been rediscovered and may replace TURP as the surgical therapy of choice of treatment in selected men with benign prostate enlargement (BPE), especially men with prostate sizes ≤ 30 mL and without prostate middle lobes.

Urinary tract infections (UTIs) should be treated prior to TURP or TUIP (2,3). The routine use of prophylactic antibiotics in TURP has been well evaluated with a considerable number of RCTs. Three systematic reviews of the available RCTs have all shown that antibiotic prophylaxis is beneficial (4-6). Antibiotic prophylaxis was found to significantly reduce bacteriuria, fever, sepsis, and the need for additional antibiotics after TURP. There was also a trend towards higher efficacy with short-course antibiotic administration compared to a single-dose regimen (4). However, further studies are required to define the optimal antibiotic regimen and cost-effectiveness of antibiotic prophylaxis in TURP.

5.1.2 ***Efficacy***

In 1999, a meta-analysis of 29 RCTs found a mean decrease in LUTS of 70.6% and a mean increase in Q_{max} by 125% after TURP (7). In a recent analysis of 20 contemporary RCTs published between 2005 and 2009 and a maximum follow-up of 5 years, TURP resulted in a substantial improvement in mean Q_{max} (+162%) and a significant reduction in mean IPSS (-70%), mean QoL scores (-69%), and mean PVR urine (-77%) (8). TURP also delivers durable clinical outcomes as shown by studies with a long follow-up of 8 to 22 years. There are no similar data on durability for any other surgical treatment for BPO (9). One study with a mean follow-up of

13 years after TURP reported a significant and sustained decrease in most symptoms and an improvement in urodynamic parameters. Subjective and objective failures were associated with detrusor underactivity rather than re-development of BPO (10). Another study in 577 men, who underwent TURP, reported excellent functional outcomes with a mean IPSS of 4.9 and a mean QoL score of 1.2 after 10 years of follow-up (11).

A meta-analysis of short- and long-term data from 10 RCTs comparing TUIP with TURP found similar LUTS improvements and lower but not significant improvements in Q_{max} for TUIP patients with small prostates but without enlarged prostate median lobes (12). Table 5.1 presents RCTs that compared TUIP with TURP (12-19). The results found that post-void residual (PVR) volume decreased by 60.5% (95% CI: 48-71) after TURP (7). However, although the decrease in PVR after TUIP varied between the studies, PVR was always lower after TUIP compared to TURP.

5.1.2.1 Re-treatment rate

A second prostatic operation, usually also TURP, has been reported at a constant rate of approximately 1-2% per year. A review analyzing 29 RCTs found a re-treatment rate of 2.6% (96% CI: 0.5-4.7) after a mean follow-up of 16 months (7). In a recent large-scale study of 20,671 men, who underwent TURP in Austria, the overall reported re-treatment rates (including secondary TURP, urethrotomy and bladder neck incision) were 5.8%, 12.3%, and 14.7%, at 1, 5, and 8 years of follow-up, respectively (20). The incidence of secondary TURP was 2.9%, 5.8% and 7.4%, for the same follow-up periods (20). A meta-analysis of six trials showed that the need for re-operation was more common after TUIP (18.4%) than after TURP (7.2%) (relative risk [RR]: 2.40) (12).

*5.1.3 **Tolerability and safety***

Mortality following prostatectomy has decreased constantly and significantly during the past decades and is less than 0.25% in contemporary series (7,21,22). In the most recent study of 10,654 men who underwent TURP, peri-operative mortality (during the first 30 days) was 0.1% (23). The possibility of an increased long-term risk of mortality after TURP compared to open surgery has been raised by Roos et al. (21). However, these findings have not been replicated by others (24-26). Recently, data from 20,671 TURPs and 2452 open prostatectomies (OP) showed that the 8-year incidence of myocardial infarction was identical after TURP (4.8%) and OP (4.9%). Similarly, both short-term and long-term mortality rates after TURP and OP were almost identical, including at 90 days (0.7% vs 0.9%, respectively), at 1 year (2.8% vs 2.7%), at 5 years (12.7% vs 11.8%) and at 8 years (20% vs 20.9%) (20).

The risk of transurethral resection (TUR) syndrome has also decreased during recent decades to less than 1.1% (7,22). Risk factors associated with TUR syndrome are excessive bleeding with an opening of venous sinuses, prolonged operation time, large prostates, and past or present nicotine abuse (27). No cases of TUR syndromes were recorded in patients undergoing TUIP. The incidence of blood transfusion following TURP in the analysis of 29 RCTs (*see above*) was 8.6% (95% CI: 3.9-13.4) (7). Contemporary real-life data from 10,654 TURP procedures reported procedure-related bleeding requiring blood transfusion in 2.9% of patients (23). The risk of bleeding following TUIP was negligible (7). Similar results for TURP complications were reported by an analysis of contemporary RCTs that had used TURP as a comparator: bleeding requiring blood transfusion 2% (range: 0-9%), TUR syndrome 0.8% (range: 0-5%), AUR 4.5% (range: 0-13.3%), clot retention 4.9% (range: 0-39%), and urinary tract infection (UTI) 4.1% (range: 0-22%) (8).

Long-term complications comprise urinary incontinence (1.8% after TUIP vs 2.2% after TURP), urinary retention and UTIs, bladder neck stenosis (4.7% after TURP), urethral stricture (3.8% after TURP vs 4.1% after TUIP), retrograde ejaculation (65.4% after TURP vs 18.2% after TUIP), and erectile dysfunction (6.5% after TURP) (7).

*5.1.4 **Practical considerations***

TURP and TUIP are both effective primary treatments for men with moderate-to-severe LUTS secondary to BPO. The choice between TURP and TUIP should be based primarily on prostate volume, with prostates < 30 mL suitable for TUIP and prostates 30-80 mL for TURP. UTIs should be treated prior to TURP or TUIP (6).

No studies on the optimal cut-off value are available, but the rate of complications increased with prostate size (23). The upper limit for size depends on the experience of the surgeon and is mostly suggested as 80 mL.

*5.1.5 **Modifications of TURP: bipolar TURP***

5.1.5.1 Mechanism of action

One of the most important recent improvements in TURP is the incorporation of plasmakinetic bipolar technology. Bipolar TURP (B-TURP) addresses the fundamental flaw of monopolar TURP (M-TURP) by allowing performance in normal saline (NaCl 0.9%) irrigation. Contrary to M-TURP systems, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed at the resection site

between an active and a return pole attached to a single support on the resectoscope (28). Prostatic tissue removal during B-TURP is identical to monopolar TURP. B-TURP requires less energy/voltage because there is a smaller amount of interpolated tissue (i.e. less resistance). Energy from the active pole (resection loop) is transmitted to the saline solution resulting in the excitation of sodium ions to form plasma corona. Once plasma is established, molecules can be easily cleaved under relatively low voltage, enabling tissue resection. During coagulation, the heat dissipates within vessel walls creating sealing coagulum/collagen shrinkage.

To date, five types of bipolar resection devices have been developed: the plasmakinetic (PK) system Gyrus (ACMI Southborough, MA, USA), Vista Coblation/controlled tissue resection (CTR) system (ACMI, Southborough, MA, USA) [withdrawn], transurethral resection in saline (TURis) system (Olympus, Tokyo, Japan), Storz (Karl Storz Endoscope, Tuttlingen, Germany), and Wolf (Richard Wolf GmbH, Knittlingen, Germany) (28). The devices differ in the way in which bipolar current flow is delivered to achieve the plasmakinetic effect. As with other endoscopic operations, UTIs should be treated before the procedure and prophylactic antibiotic therapy is advised.

5.1.5.2 Efficacy

B-TURP is the most widely and thoroughly investigated alternative to M-TURP. A meta-analysis based on 17 RCTs concluded that no clinically relevant differences exist in short-term efficacy (up to 12 months) in terms of IPSS (weighted mean difference [WMD]: 0.05; 95% CI: -0.40-0.51), QoL score (WMD: 0.04; 95% CI: -0.17-0.24) and Q_{max} (WMD: 0.72 mL/s; 95% CI: 0.08-1.35) (29). Two subsequent RCT-based meta-analyses supported these conclusions, which despite the relatively low trial quality appear reliable and currently reflect the best available evidence (8,30). A contemporary update of a meta-analysis detected 16 additional RCTs published during the last 3 years (33 RCTs; 3601 randomized patients in total) and updated pooled results are still awaited (31).

The RCTs published so far (Table 5.2) have follow-ups > 12 months (range: 18-60 months) showing no differences in terms of IPSS and Q_{max} between B-TURP and M-TURP at midterm (32-36).

5.1.5.3 Tolerability and safety

TUR syndrome has not been reported with B-TURP, due to the use of physiological saline irrigation fluid and reduced fluid absorption during the procedure. A number of RCTs have suggested that urethral strictures are more common with B-TURP, with possible contributory factors being a larger resectoscope size (27F), the type of return electrode, and higher current densities (28). However, a meta-analysis based on 17 RCTs found that there were no differences in urethral stricture and bladder neck contracture rates between M-TURP and B-TURP (29). Mid-term RCTs evaluating the urethral stricture and bladder neck contracture rates (follow-up > 12 months) also found no differences between B-TURP and M-TURP (32-38). In addition, B-TURP was preferable due to a more favourable peri-operative safety profile, including the elimination of TUR syndrome, less bleeding, with lower clot retention and blood transfusion rates, and shorter times for irrigation, catheterization, and possibly hospitalization (29). These findings were supported by the two subsequent RCT-based meta-analyses (8,30).

Regarding the impact of B-TURP on sexual function, several RCTs (39) and a focused RCT, using the erectile function domain of the International Index of Erectile Function (IIEF-ED), have shown that M-TURP and B-TURP have a similar effect on EF (40). Recently, a comparative evaluation of the effects on the overall sexual function, quantified with IIEF-15, was completed in an international, multicentre, double-blind RCT setting (41). No differences were detected between B-TURP and M-TURP at 12 months of follow-up in any aspect of the overall sexual function (EF, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) (41).

5.1.5.4 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 a lower peri-operative morbidity (29). The duration of improvements with B-TURP was documented in a number of RCTs with a follow-up > 12 months. Midterm results (up to 5 years) of B-TURP safety and efficacy are comparable with those of M-TURP. The choice of B-TURP should currently be based on the availability of the bipolar armamentarium, the surgeon's experience, and the patient's preference.

5.1.6 *Recommendations*

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

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

Table 5.1: Efficacy and safety of transurethral resection of the prostate (TURP) or transurethral incision of the prostate (TUIP) in level 1 trials at 12 or 24 months. Absolute and relative changes compared to baseline with regard to symptoms (Madson-Iverson or IPSS) and maximum urinary flow rate (Q_{max})

Trials	Intervention	Patients (N)	Absolute decrease (%) in symptoms at 12 months		Q_{max} (mL/s) at 12 months		Blood trans-fusion	Re-operation rate at 12 months	LE
			Absolute	(%)	Absolute	(%)	(%)	(%)	
Dorflinger et al. (1992) (13)	TURP	31	-11.6 [a]	-88 [a]	+22.9 [a, b]	+294 [a, b]	13	3.2 [b]	1b
	TUIP	29	-12.6 [a]	-85 [a]	+16.3 [a]	+223 [a]	0 [c]	20.7	
Jahnson et al. (1998) (14)	TURP	43	-13 [a]	-82 [a]	+19.5 [a, b]	+229 [a, b]	2.4	7.1 [b]	1b
	TUIP	42	-11.8 [a]	-77 [a]	+13.8 [a]	+148 [a]	0	23.2	
Riehmann et al. (1995) (15)	TURP	61	-9.5 [a]	-67 [a]	no significant difference between groups			16	1b
	TUIP	56	-10 [a]	-63 [a]				23	
Saporta et al. (1996) (16)	TURP	20	-9.4 [a]	-63 [a]	+17.3 [a]	+266 [a]		0 [b]	1b
	TUIP	20	-9.3 [a]	-64 [a]	+14.6 [a]	+197 [a]		15	
Soonwalla et al. (1992) (17)	TURP	110			+20.1 [a]	+251 [a]	34.5		1b
	TUIP	110			+19.5 [a]	+246 [a]	0 [c]		
Tkoocz et al. (2002) (18)	TURP	50	-12 *[a]	-70*	6.9 *[a]	+255 [a]			1b
	TUIP	50	-13 *[a]	-77*	7.6 *[a]	+222 [a]			
Lourenco et al. (2009) (12)	TURP	345	no significant difference between groups		no significant difference between groups		28.3	7.2 [b]	1a
	TUIP	346					1.1 [c]	18	
Yang et al. (2001) (19)	TURP	403	-11.2 to -13	-63 to -82	+17.3 to +22.9 [b]	+266 to +352 [b]	25.1	5.5	1a
	TUIP	392	-10 to -13.5	-63 to -83	+13.8 to +16.3	+189 to +223	0.87 [c]	9.3	

** = 24 months post operatively; a = significantly different compared to baseline; b = significantly different in favour of TURP; c = significantly different in favour of TUIP.*

Table 5.2: Mid-term (follow-up longer than 12 months) results from randomized controlled trials comparing monopolar transurethral resection of the prostate (TURP) with bipolar TURP

Trials	Intervention	Patients (N)	Follow-up (months)	Decrease symptoms		Q_{max} (mL/s)		Urethral stricture	Bladder neck Contracture	LE
				Absolute	[%]	Absolute	[%]	[%]	[%]	
Autorino et al. 2009 (32)	M-TURP	31	48	-17.9[a]	-74[a]	+15.0[a]	+242[a]	6.5	3.2	1b
	B-TURP (Gyrus)	32		-17.3[a]	-72[a]	+12.7[a]	+179[a]	3.1	3.2	
Chen et al. 2010 (33)	M-TURP	50	24	-18.0[a]	-83[a]	+16.9[a,b]	+214[a]	6.0	4.0	1b
	B-TURP (TURis)	50		-19.1[a]	-84[a]	+18.4[a]	+259[a]	4.0	2.0	
Geavlette 2011 (34)	M-TURis	170	18	-15.9[a]	-66[a]	+14.2	+222	5.1	4.1	1b
	B-TURP (TURis)	170		-16.1[a]	-67[a]	+14.5[a]	+238[a]	6.3	3.4	
Xie et al. 2012 (35)	M-TURP	79	60	-16.2[a]	-71[a]	+15.2[a]	+157[a]	5.1	10.1	1b
	B-TURP (Gyrus)	78		-16.6[a]	-70[a]	+16.5[a]	+167[a]	5.1	5.1	
Mamoulakis et al. 2012 (36)	M-TURP	108	36	-16.0[a]	-69[a]	+10.8[a]	+126[a]	9.3	1.9	1b
	B-TURP (Autocon)	122		-15.4[a]	-66[a]	+10.7[a]	+122[a]	8.2	6.6	

[a] = *Significantly different compared to baseline.*

5.1.7 ***References***

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5.2 Open prostatectomy

*5.2.1 **Mechanism of action***

Open prostatectomy is the oldest surgical treatment modality for moderate-to-severe LUTS secondary to BPO. Obstructive prostatic adenomas are enucleated using the index finger, either from the inside of the bladder (Freyer procedure) or through the anterior prostatic capsule (Millin procedure). Removal of prostatic tissue resolves BPO and, secondarily, LUTS.

A known urinary tract infection should be treated before surgery (1,2). The routine use of prophylactic antibiotics remains controversial. However, antibiotics are recommended in patients upon catheterization prior to surgery.

5.2.2 *Efficacy*

Open prostatectomy is the treatment of choice for large glands (> 80-100 mL). Associated complications include large bladder stones or bladder diverticula (3-5). Three recent RCTs have shown that Holmium laser enucleation and PVP lead to similar outcomes compared to open prostatectomy in men with large glands (> 70, 80 and 100 mL) at a significantly lower complication rate (6-8).

The results of open prostatectomy studies for treating BPH-LUTS or BPO are summarized in Table 5.3. Open prostatectomy results in reduction of LUTS by 63-86% (12.5-23.3 IPSS points), improvement of the IPSS-QoL score by 60-87%, mean increase of Q_{max} by 375% (range: 88-677%; in absolute terms +16.5-20.2 mL/s), and reduction of PVR by 86-98% (6-10).

A favourable long-term outcome is common after open prostatectomy. Efficacy is maintained after long-term observation for more than 5 years (7-9) (Table 5.4).

5.2.3 *Tolerability and safety*

Mortality following open prostatectomy has decreased significantly during the past two decades and is less than < 0.25% in contemporary series (10) (Table 5.4). The estimated need for blood transfusion is about 7-14% (8-10).

Long-term complications are urinary incontinence and bladder neck stenosis and urethral stricture. The risk of developing stress incontinence is up to 10% (3), while the risk for developing bladder neck contracture and urethral stricture is about 6% (6-8).

5.2.4 *Practical considerations*

Open prostatectomy is the most invasive but also the most effective and durable procedure for the treatment of LUTS/BPO. Only holmium enucleation delivers similar results but with less morbidity (6,8). In the absence of an endourological armamentarium and a holmium laser, open prostatectomy is the surgical treatment of choice for men with prostates > 80 mL, who have absolute indications for surgery or experience moderate-to-severe LUTS, secondary to BPO, who have been treated insufficiently by drugs.

5.2.5 *Recommendations*

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

Table 5.3: Results of open prostatectomy studies for treating BPH-LUTS or BPO

Studies	Duration (weeks)	Patients (*n*)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Kuntz et al. 2008 (8)	260	32	-18.2	86	21.4	677	-287	98			1b
Skolarikos et al. 2008 (7)	78	60	-12.5	63	7	86	-77	86	-86	88	1b
Naspro et al. 2006 (6)	104	39	-13.2	62	15.9	291					1b
Varkarakis et al. 2004 (9)	151	232	-23.3	84	16.5	329	-104	90			3
Gratzke et al. 2007 (10)		868			13	218	-128	88	85	88	2b

IPSS = International Prostate Symptom Score; LE = level of evidence; n = number of patients; PVR = post-void residual urine; Q_{max} = maximum urinary flow rate (free uroflowmetry).

Table 5.4: Tolerability and safety of open prostatectomy

	Peri-operative mortality (%)	Postoperative stress incontinence (%)	Re-operation for BPO (%)
Kuntz *et al*. 2008 (8)	0	0	0
Skolarikos *et al*. 2008 (7)	0		0
Naspro *et al*. 2006 (6)	0	2.5	0
Varkarakis *et al*. 2004 (9)	0	0	
Gratzke *et al*. 2007 (10)	0.2		

BPO = benign prostatic obstruction

*5.2.6 **References***

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5.3 Transrethral microwave therapy (TUMT)

*5.3.1 **Mechanism of action***

Microwave thermotherapy of the prostate works by emitting microwave radiation through an intra-urethral antenna in order to deliver heat into the prostate. Tissue is destroyed by being heated at temperatures above cytotoxic thresholds (> 45°C) (coagulation necrosis). Heat is mainly produced by electrical dipoles (water molecules) oscillating in the microwave field and electric charge carriers (ions) moving back and forth in the microwave field. It is thought that the heat generated by TUMT also causes apoptosis and denervation of alpha-receptors, thereby decreasing the smooth muscle tone of the prostatic urethra.

Transurethral microwave therapy is a registered trademark of Technomed Medical Systems, the pioneer of microwave thermotherapy. Currently, the main devices in the field of microwave thermotherapy are the Prostatron™ device (Urologix, Minneapolis, MN, USA), Targis™ (Urologix, Minneapolis, MN, USA),

CoreTherm™ (ProstaLund, Lund, Sweden), and TMx-2000™ (TherMatrx Inc, Northbrook, ILL, USA). Most published data on thermotherapy has been about the Prostatron device.

Conceptually, TUMT devices are all similar in delivering microwave energy to the prostate with some type of feedback system. All TUMT devices consist of a treatment module that contains the microwave generator with a temperature measurement system and a cooling system. The main difference between TUMT devices is the design of the urethral applicator. The applicator consists of a microwave catheter connected to the module, which is inserted into the prostatic urethra. Differences in the characteristics of applicators have a significant effect on the heating profile (1). Other less important differences between TUMT devices are found in the catheter construction, cooling systems, treatment time, and monitoring of TUMT effects (2).

*5.3.2 **Efficacy***

A systematic review of all available RCTs on TUMT attempted to assess therapeutic efficacy (Table 5.5) (3) in different TUMT devices and software, including Prostatron (Prostatsoft 2.0 and 2.5) and ProstaLund Feedback. Weighted mean differences were calculated with a 95% CI for the between-treatment differences in pooled means. The review found that TUMT was somewhat less effective than TURP in reducing LUTS. The pooled mean symptom score for men undergoing TUMT decreased by 65% in 12 months compared to 77% in men undergoing TURP, which is a WMD of -1.0 in favour of TURP. TURP achieved a greater improvement in Q_{max} (119%) than TUMT (70%), with a WMD of 5.08 mL/s in favour of TURP (3). TUMT also improved IPSS symptom scores (WMD: -4.20) and peak urinary flow (WMD: 2.30 mL/s) in the one comparison with α-blockers (3).

Similarly, a pooled analysis of three studies (two RCTs and one open label) of ProstaLund Feedback TUMT (PLFT) with 12-month follow-up showed that the responder rate was 85.3% in the PLFT group and 85.9% in the TURP group (4). In addition, pooled IPSS data indicated a subjective, non-inferior improvement with PLFT compared to TURP (4). However, one-sided 95% CI analysis showed that the non-inferiority of PLFT compared to TURP did not reach the predetermined level, even though both PLFT and TURP appeared to improve Q_{max} significantly.

Previously, urinary retention was considered to be a contraindication for TUMT. Nowadays, level 2b evidence studies have reported an 80-93% success rate for TUMT, defined as the percentage of patients who regained their ability to void spontaneously (5-7). However, these studies had a short follow-up ($\leq$ 12 months), which makes it difficult to estimate the durability of TUMT outcome in patients with retention. In a study with a longer follow-up of up to 5 years, treatment failure was 37.8% in the retention group, with a cumulative risk of 58.8% at 5 years (8). One RCT compared TUMT with the α_1-blocker, terazosin (9). After 18 months' follow-up, treatment failure in the terazosin-treated patients (41%) was significantly greater than in TUMT patients (5.9%), with TUMT also achieving a greater improvement in IPSS and Q_{max} (10).

Low-energy TUMT has disappointing results for durability. Several studies have reported a re-treatment rate after low-energy TUMT as high as 84.4% after 5 years (11-14), while other studies have reported re-treatment rates of 19.8-29.3% after high-energy TUMT, though with a lower mean follow-up of 30-60 months (15-18). The re-treatment rate due to treatment failure has also been estimated by a systematic review of randomized TUMT trials (3). The trials had different follow-up periods and the re-treatment rate was expressed as the number of events per person per year of follow-up. The re-treatment rate was 0.075/person years for patients treated by TUMT and 0.010/person years for TURP.

However, a prospective, randomized, multicentre study after 5 years has obtained comparable clinical results with TUMT to those seen with TURP. The study compared TUMT (PLFT; the Core-Therm device) and TURP (19). No statistically significant differences were found in Q_{max} and IPSS between the two treatment groups at 5 years. In the TUMT group, 10% needed additional treatment versus 4.3% in the TURP arm. These data suggest that, at 5 years, clinical results obtained with PLFT-TUMT were comparable to those seen after TURP. It should be noted that most durability studies have a high attrition rate; in this study, less than half of the initial group of patients treated were analyzed at 4-5 years. In addition, patients who remained in the study were likely to represent the best data (responders).

*5.3.3 **Tolerability and safety***

Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. Pooled morbidity data of randomized studies comparing TUMT and TURP have been published (3,4,20). In the Cochrane systematic review of RCTs comparing TURP with TUMT, it was shown that catheterization time, incidence of dysuria/urgency, and urinary retention were significantly less with TURP, whereas the incidence of hospitalization, haematuria, clot retention, transfusions, TUR syndrome, and urethral strictures were significantly less for TUMT (3). Sexual dysfunction and re-treatment rates for strictures of the meatus, urethra, or bladder neck were higher after TURP than after TUMT.

5.3.4 *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. Because of the low peri- and post-operative morbidity and no need for anaesthesia, TUMT is a true outpatient procedure and an alternative for older patients with comorbidities and those at risk for anaesthesia or otherwise unsuitable for invasive treatment (21). Independent baseline parameters that predict an unfavourable outcome include small prostates, mild-to-moderate bladder outlet obstruction, and a low amount of energy delivered during treatment (22). However, it should be remembered that predictive factors for particular devices cannot necessarily be applied to other devices.

5.3.5 *Recommendations*

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

Table 5.5: Efficacy of TUMT. Absolute and relative changes compared to baseline are listed for symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume (PVol)

Trials	Duration (weeks)	Patients (n)	Change IPSS (absolute [%])	Change Q_{max} (mL/s, [%])	Change QoL (absolute [%])	Change PVR (absolute [%])	Change PVol (absolute [%])	LE
Hoffman et al. (2012) (3)	52	322	-12.7[a] (-65.0)	5.6[a] (70.0)	-2.4[a] (58.5)	NA	NA	1a
Gravas et al. (2005) (4)	52	183	-14.5[a] (-69.0)	8.4[a] (109.0)	-2.97[a] (70.9)	NA	-17.0 [a] (-33.0)	1b
Mattiasson et al. (2007) (19)	260	100	-13.6[a] (-61.5)	3.8[a] (50.0)	-3.2[a] (-74.4)	-36.0 (-34.0)	-4.0 (-8.1)	1b
Floratos et al. (15)	156	78	-8.0[a] (-40.0)	2.7[a] (29.3)	-2.0[a] (-50.0)	NS	NA	1b
Thalmann et al. (2002) (17)	104	200	-20.0[a] (-87.0)	7.0[a] (116.6)	-4.0[a] (-80.0)	-143 [a] (-84.1)	-17.7 [a] (-30.7)	2b
Miller et al. (2003) (18)	260	150	-10.6[a] (-47.0)	2.4[a] (37.0)	-2.3[a] (-54.7)	NA	NA	2b
Trock et al. (2004) (23)	208	541	-8.9[a] (-42.7)	2.8[a] (35.0)	-2.1[a] (-50.1)	NA	NA	2b

a = significant compared to baseline (indexed whenever evaluated); LE = level of evidence; n = number of patients; NS = not significant; NA = not available.

5.3.6 *References*

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5.4 Transurethral needle ablation (TUNA™) of the prostate

*5.4.1 **Mechanism of action***

The transurethral needle ablation (TUNA™) device delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. Needles are placed under direct vision using an attachment to the standard cystoscope. The energy induces coagulation necroses in the prostatic transition zone resulting in prostate volume reduction and BPO reduction/resolution. There may also be a poorly understood neuromodulatory effect. TUNA™ is carried out under anaesthetic (local or general) or sedation.

*5.4.2 **Efficacy***

Several, non-randomized, clinical trials have documented the clinical efficacy of TUNA™ with a fairly consistent outcome (3-7). Symptomatic improvement has ranged from 40-70%. Improvements in Q_{max} vary widely from 26-121% in non-retention patients. A recent report with 5 years' follow-up in 188 patients demonstrated symptomatic improvement in 58% and improved flow in 41%. However, 21.2% of patients required additional treatment (8).

TUNA™ has been compared with TURP in randomized studies (8-11), with varying follow-up. The studies found both TUNA™ and TURP produced symptomatic improvement. However, TURP produced greater symptom improvement and a better quality of life than TUNA™, as well as a significant improvement in Q_{max} after TUNA™ (Table 5.6). More detailed comparisons between TUNA™ and TURP can be found in some very high quality and comprehensive, systematic reviews and meta-analyses (12,13). A meta-analysis of two randomized trials, two non-randomized protocols, and 10 single-arm studies conducted on TUNA™ showed that it achieved a 50% decrease in the mean IPSS and a 70% improvement in Q_{max} from baseline at 1 year after treatment (12). A more recent meta-analysis of 35 studies (9 comparative, 26 non-comparative) confirmed these results (13). TUNA™ significantly improved IPSS and Q_{max} with respect to baseline values, but in comparison with TURP this improvement was significantly lower at 12 months. TURP versus TUNA™ differences in means were -4.72 and 5.9 mL/s for the IPSS and Q_{max}, respectively (13).

Clinical studies on the impact of TUNA™ on BPO (14,15) have demonstrated a statistically significant decrease in maximum detrusor pressure or detrusor pressure at Q_{max}, even though a number of patients were still obstructed following TUNA™ therapy. There is no convincing evidence that prostate size is significantly reduced following TUNA™ (6). Recent reports have suggested that gadolinium-enhanced MRI can be used to assess TUNA™-related treatment effects (16).

As most studies have been short-to-medium term in duration, there are concerns about the durability of effects. Even short-term (12 months), up to 20% of patients treated with TUNA™ need to be re-treated with TURP (1). A recent French report described a failure rate (incorporating re-treatment) of up to 50% over a 20-month period (17). TUNA™ has a significant higher re-treatment rate compared with TURP (odds ratio [OR]: 7.44 [2.47-22.43]). The overall re-treatment rate after TUNA™ was 19.1% (95% CI: 18.7-39.7), as calculated in an analysis of 17 non-comparative studies (13).

5.4.3 *Tolerability and safety*

TUNA™ can be performed as a day-case procedure under local anaesthesia or intravenous sedation (1). Post-operative urinary retention with a mean duration of 1-3 days is seen in 13-42% of patients; within 1 week, 90-95% of patients are catheter-free (1). Bladder storage symptoms are common for the first 4-6 weeks after the operation (2). TUNA™ is associated with fewer adverse events compared with TURP, including mild haematuria, urinary infections, strictures, incontinence, ED, and ejaculation disorders (OR: 0.14; 95% CI: 0.05-0.41) (13).

5.4.4 *Practical considerations*

TUNA™ is unsuitable for prostates > 75 mL or isolated bladder neck obstruction. Because TUNA™ cannot effectively treat prostatic middle lobes, it remains unclear whether men with large middle lobes will benefit from this treatment. There is anecdotal evidence for TUNA™ in men receiving aspirin and anti-coagulants. TUNA™ can be performed as a day-case procedure and is associated with fewer side effects compared to TURP (e.g. bleeding, ED, urinary incontinence). However, there remain concerns about the durability of the effects achieved by TUNA™.

5.4.5 *Recommendations*

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

Table 5.6: Summary of comparative level of evidence (LE) 1 data for TUNA™ versus TURP (13)

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

IPSS = International Prostate Symptom Score; LE = level of evidence; Q_{max} = maximum urinary flow rate; PVR = post-void residual urine.

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

5.4.6 *References*

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5.5 Laser treatments of the prostate

*5.5.1 **Holmium laser enucleation (HoLEP) and Holmium laser resection of the prostate (HoLRP)***

5.5.1.1 Mechanism of action

The holmium:yttrium-aluminium garnet (Ho:YAG) laser with a wavelength of 2140 nm is a pulsed solid-state laser that is promptly absorbed by water and water-containing tissues. This means that the area of tissue coagulation and the resulting tissue necrosis is limited to 3-4 mm, which is enough to obtain adequate haemostasis (1). Holmium laser resection of the prostate (HoLRP) or holmium laser enucleation of the prostate (HoLEP) results in BPO relief and, secondarily, in LUTS reduction.

5.5.1.2 Efficacy

In a meta-analysis of studies comparing HoLRP with TURP, no difference in symptom improvement could be detected at 6 or 12 months post operatively. However, HoLRP achieved a significantly greater increase in Q_{max}

compared with TURP with a WMD of 4.8 mL/s (Table 5.7) (2). One RCT comparing TURP with HoLRP with a minimum follow-up of 4 years showed no difference in urodynamic parameters between the two techniques after 48 months (3). Three meta-analyses that analyzed RCTs comparing HoLEP and TURP reported a significantly longer operation time for the laser operation. Symptom improvement was comparable or superior with HoLEP (Table 5.7) (4-6). Furthermore, Q_{max} at 12 months was significantly better with HoLEP (4-6). One RCT comparing photoselective vaporization 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 (7).

Available RCTs indicated that in large prostates HoLEP was as effective as open prostatectomy for improving micturition (8,9), with equally low re-operation rates after 5 years (5% vs 6.7%, respectively) (8). One RCT comparing HoLEP with TURP in a small number of patients who completed the 7-year follow-up found that the functional long-term results of HoLEP were comparable with TURP; no HoLEP patient required re-operation for recurrent BPH (10). A retrospective study of 949 patients treated with HoLEP with the longest follow-up (up to 10 years; mean follow-up: 62 months) reported durable functional results. Bladder neck contracture, urethral stricture, and re-operation due to residual adenoma occurred in 0.8%, 1.6%, and 0.7% of patients, respectively (11).

5.5.1.3 Tolerability and safety

No major intra-operative complications have been described. Dysuria is the most common peri-operative complication (1,4). Compared to TURP, HoLRP has a significantly shorter catheterization time and shorter hospitalization time (2,12). Potency, continence, and major morbidity at 48 months were identical between HoLRP and TURP (13). Retrograde ejaculation occurred in 75-80% of patients; no post-operative impotence has been reported (1).

Three meta-analyses found that HoLEP resulted in a significantly shorter catheterization time and hospital stay, reduced blood loss, and fewer blood transfusions, but had a longer operation time compared with TURP (4-6). In a meta-analysis, no statistically significant differences were noted between HoLEP and TURP for urethral stricture (2.6% vs 4.4%), stress urinary incontinence (1.5% vs 1.5%; p = 0.980), and re-intervention (4.3% vs 8.8%; p = 0.059) (5). Pooled data from large case series (total of 1847 patients) showed low complication rates including peri-operative mortality (0.05%), transfusion (1%), UTI (2.3%), urethral stricture/bladder neck stenosis (3.2%), and re-operation (2.8%) (14). Similarly, available RCTs indicated that HoLEP was better than open prostatectomy for blood loss, catheterization, and hospitalization time (8,9).

HoLEP has been safely performed in patients using anticoagulant medication (15,16). In a study of 83 patients treated with HoLEP, blood transfusion was required in seven patients (8%), including one who had stopped oral anticoagulation treatment (OAT), five on low molecular-weight heparin substitution, and one who was on full anticoagulation (15). A retrospective study compared the safety results of HoLEP between 39 patients who were on anticoagulant therapy (13 on coumadin and 25 on aspirin) at the time of their surgery, and 37 who were controls (16). No transfusions were required in any of their 76 patients and the bleeding complication rates between the coumadin, aspirin, and control groups were not significantly different (16). Short-term studies showed that patients with urinary retention could be successfully treated with HoLEP (17,18).

The impact on ED and retrograde ejaculation is comparable between HoLEP and TURP/OP (19,20). The overall EF did not decrease from baseline in either group while three quarters of sexually active patients had retrograde ejaculation after HoLEP.

5.5.1.4 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 (21,22).

5.5.2 ***532 nm ('Greenlight') laser vaporization of prostate***

5.5.2.1 Mechanism of action

The kalium-titanyl-phosphate (KTP) and the lithium triborate (LBO) lasers are both derived from the neodymium:YAG (Nd:YAG) laser. The addition of a KTP or LBO crystal to the laser resonator converts the Nd:YAG wavelength from 1064 nm to 532 nm. Laser energy is absorbed within the tissue by haemoglobin, which acts as an intracellular chromophore, and not by the water. Vaporization leads to immediate removal of prostatic tissue, relief of BPO, and, secondarily, reduction of LUTS. In 2013, three different Greenlight lasers were in use: the 80-W (KTP), 120-W HPS (LBO), and the 180-W XPS (LBO) laser systems. They differ in maximum power output, fibre design, and maximum energy application.

5.5.2.2 Efficacy

Numerous studies, predominantly with 80-W lasers, have been published in recent years. A meta-analysis of the nine available RCTs comparing PVP using the 80-W and 120-W lasers with TURP was performed in 2012 (Table 5.7) (23). No differences were found in Q_{max} and IPSS between PVP and TURP, but only three RCTs provided sufficient 12-month data to be included in the meta-analysis (24-26).

The longest RCT using the 80-W KTP laser has a follow-up of only 12 months (24). A case series of 246 patients who completed the 5-year follow-up showed that functional outcomes after the 80-W KTP laser were durable with an overall re-treatment rate of 8.9% at 5 years due to recurrent adenoma (7.7%) and bladder neck stenosis (1.2%) (27). Another case series of 500 patients treated with the 80-W system with a mean follow-up of 30.6 months (5.2-60.6 months) reported a re-treatment rate of 14.8% due to recurrent or persisting adenoma (6.8%), bladder neck strictures (3.6%), or urethral strictures (4.4%) (28).

Significant improvements in voiding parameters at a follow-up of 12 months were demonstrated with urodynamic investigation (29). At 12 months' follow-up, the mean urethral opening pressure (Pdetopen; 76.2 vs 37.4 cm H_2O) and detrusor pressure at Q_{max} ($Pdet_{max}$; 75 vs 36.6 cm H_2O) were significantly reduced compared to baseline. The Q_{max} improved by 113% (mean 18.6 mL/s) compared to pre-operative Q_{max} (mean 7.9 mL/s) (29). 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, whereas the percentage reductions in PSA level and prostate volume were significantly higher in the TURP group (30). Reoperation rate was significantly higher after PVP (11% vs 1.8%; p = 0.04) (30). Similar improvement of IPSS, QoL, Q_{max}, or urodynamic parameters was reported from two RCTs with a maximum follow-up of 24 months (25,31).

No RCTs had been published on the 180-W Greenlight laser until the end of the literature search (October 2012). A multicentre case series of the 180-W laser demonstrated comparable safety and symptom improvement compared with the former Greenlight laser systems (32). Interestingly, transurethral enucleation of the prostate using a 120-W HPS Greenlight laser in combination with a 600-m side-fire laser fibre has been described (33).

5.5.2.3 Tolerability and safety

The meta-analysis of the RCTs comparing the 80-W and 120-W lasers with TURP showed a significantly longer operating time but significantly shorter catheterization time and length of hospital stay after PVP (23). Post-operative blood transfusions and clot retention were significantly less with PVP. No difference was noted in the occurrence of post-operative urinary retention, infection, meatal stenosis, urethral stricture, or bladder neck stenosis (23).

Studies of the Greenlight laser have indicated that the procedure seems to be safe and beneficial for high-risk patients under anticoagulation treatment (34-38). There were no thromboembolic or bleeding complications and no blood transfusions were required. In one study, anticoagulated patients had significantly higher rate of transient post-operative bladder irrigation (17.2%) compared with patients treated with Greenlight laser without taking anticoagulants (5.4%) (34). In addition, in one study, three out of 162 patients required blood transfusion due to delayed bleeding within 30 days from the procedure (37). Safety in patients with urinary retention, or prostates > 80 mL was shown in various prospective non-randomized trials (38-40).

The impact of Greenlight laser on sexual function seems to be similar to that of TURP. One RCT reported a 56.7% and 49.9% rate of retrograde ejaculation for the patients treated with TURP and Greenlight PV, respectively (41). In addition, no difference was reported between patients undergoing OP/TURP and Greenlight PV with regard to erectile function (EF) (42,43). Sexual function in terms of International Index of Erectile Function (IIEF-5) was investigated 149 patients treated with either the 80-W (63 cases) or the 120-W Greenlight laser (86 cases) (44). The overall mean IIEF-5 scores were comparable before and after surgery, indicating that sexual function appeared to be 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. There was no difference in erectile function between patients who underwent an 80-W or 120-W procedure (44).

5.5.2.4 Practical considerations

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

*5.5.3 **Diode laser vaporization of the prostate***

5.5.3.1 Mechanism of action

In diode lasers, a semiconductor is used to generate the laser light. The wavelength of the laser beam depends on the semiconductor material used. For the application in prostate surgery, diode lasers with a wavelength of 940 nm, 980 nm, 1318 nm, and 1470 nm are available, and they are absorbed by both water and haemoglobin (45). Depending on wavelength, power output, and fibre design, diode lasers can be used for vaporization in

non-contact and contact mode and enucleation.

5.5.3.2 Efficacy

A major drawback of all studies on diode laser vaporization is the lack of RCTs in comparison with TURP or open prostatectomy and the short follow-up period (up to 12 months). Case series, as well as two comparative studies, of a 980-nm diode laser to the 120 W HPS laser are available (46-55). IPSS, QoL, Q_{max}, and PVR improved significantly in all diode laser studies compared with the baseline value. Compared with the 120-W HPS laser, the improvement of IPSS, QoL, Q_{max}, and PVR was similar at 6 months and 12 months (46,49).

A small RCT with a 6 months' follow-up comparing laser enucleation using a 1318-nm diode laser with B-TURP reported similar efficacy and safety results (Table 5.7) (56). Operative time, blood loss, catheterization, and hospitalization time were in favour of laser enucleation.

5.5.3.3 Tolerability and safety

Studies on diode lasers indicate a high level of intra-operative safety. The application of the 980-nm diode laser showed no intra-operative bleeding, whereas with the 120-W HPS laser, bleeding was reported in 11% and 13% of the cases (46,49). Notably, in these two studies, anticoagulants or platelet aggregation inhibitors were taken in 23.6% and 52% of the diode laser cases compared with 25% and 43% of the cases in the 120-W HPS group (46,49). Comparable haemostatic properties are also reported for the 1470-nm diode laser (52).
During the post-operative course, a significantly higher rate of dysuria with sloughing tissues occurs after the 980-nm diode laser compared with the 120-W HPS laser (46,49). The modification of the 980-nm diode laser fibre with a quartz head led to a significant reduction of dysuria lasting > 1 month from 42% to 17% (53). Re-operation due to bladder neck stricture and obstructive necrotic tissue (33% vs 4%) and the persistence of stress urinary incontinence (9.1% vs 0%) were significant higher after 980-nm diode laser compared with 120-W HPS laser (46,49). In contrast, two cohort studies of the 980-nm diode laser reported no re-operations but only after 3 and 6 months (50,55). After treatment with the1470-nm diode laser, re-operation in 2 of 10 patients was necessary during the 12 months after surgery (52).

5.5.3.4 Practical considerations

Diode lasers lead to immediate, subjective, and objective improvements of LUTS due to BPO and appear to be safe due to their haemostatic properties. Based on the short follow-up, the lack of RCTs compared to TURP or open prostatectomy, and controversial data on the re-treatment rate, diode lasers cannot be recommended as a standard treatment option for BPO.

5.5.4 ***Thulium:yttrium-aluminium-garnet laser***

5.5.4.1 Mechanism of action

In thulium:YAG (Tm:YAG) lasers, a wavelength of approximately 2000 nm is emitted in continuous-wave mode. The target chromophore is water. The laser is primarily used in front-fire applications: the continuous-wave output of the Tm:YAG allows smooth incision of tissue (45).

Four different techniques have been described: Tm:YAG vaporization of the prostate (ThuVaP), Tm:YAGvaporesection (ThuVaRP), Tm:YAGvapoenucleation (ThuVEP), and Tm:YAG laser enucleation of the prostate (ThuLEP). ThuVEP follows a HoLEP-like approach, and ThuLEP consists mainly of blunt dissection of the tissue.

5.5.4.2 Efficacy

A major drawback of all studies on thulium lasers is the limited number of RCTs compared to TURP and the lack of RCTs compared to open prostatectomy. No data beyond a follow-up of 18 months are available yet. One RCT and one non-RCT compared ThuVaRP with M-TURP (57,58), while one RCT comparing ThuVaRP and B-TURP was published recently (59). In summary, all studies show a comparable improvement of symptoms and voiding parameters. There are only few case studies on ThuVEP showing a significant improvement in IPSS, Q_{max}, and PVR after treatment (60-63). Interestingly, a comparative study showed that both 120-W and 200-W ThuVEP had an equivalent efficacy and safety at 12-months of follow-up (62). ThuLEP and HoLEP were compared in one RCT with 18-months of follow-up (Table 5.7) (64). Symptom improvement, an increase in Q_{max}, and a reduction in PVR volume sustained and were comparable between ThuLEP and HoLEP (64).

5.5.4.3 Tolerability and safety

Thulium laser prostatectomy shows high intra-operative safety in RCTs (57,59,64), as well as in case series in patients with large prostates (60) and for anticoagulation therapy or bleeding disorders (61). Catheterization time, hospital stay, and blood loss were significantly shorter compared to TURP (57-59). In one RCT, operation

time was longer with ThuLEP compared with HoLEP, whereas blood loss was reduced with ThuLEP (64). The rate of post-operative urethral strictures after ThuVaRP was 1.9%, the rate of bladder neck contracture was 1.8%, and the reported re-operation rate was 0-7.1% during the 9- to 12-months of follow-up (57,58,65). Urethral stricture after ThuVEP occurred in 1.6% of the patients, and the overall re-treatment rate was 3.4% after a mean follow-up of 16.5 months (66). No urethral and bladder neck strictures after ThuLEP were reported during the 18-month follow-up (64).

5.5.4.4 Practical considerations

The limited number of RCTs evaluating thulium laser applications for the surgical management of BPO and the limited follow-up (up to 18 months) do not permit final conclusions regarding the long-term efficacy of thulium laser prostatectomy.

5.5.5 ***Recommendations***

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

Table 5.7: Efficacy of different lasers for the treatment based on the highest-quality study for each of the treatment options. Absolute and relative changes compared to baseline, with regard to symptoms (AUA-SI/IPSS) and maximum urinary flow rate (Q_{max})

Trials	Duration (months)	Patients (N)	Surgery	Change symptoms (IPSS)			Change Q_{max} (mL/s)			LE
				Absolute	[%]	WMD	Absolute	[%]	WMD	
Tooher et al. 2004 (2)	12	231	HoLRP	NA	NA	-0.4	NA	NA	+4.2	1a
			TURP	NA	NA		NA	NA		
Tan et al. 2007 (5)	12	232	HoLEP	-17.5 to -21.7	-81 to -83	NA	+13.4 to +23.0	+160 to +470	+0.59	1a
		228	TURP	-17.7 to -18.0	-76 to -82		+10.1 to +21.8	+122 to +370		
Lourenco et al. 2008 (4)	12	277	HoLEP	-17.7 to -21.7	-82 to -92	-0.82	+13.4 to +23.0	+160 to +470	+1.48	1a
		270	TURP	-17.5 to -18.7	-81 to -82		+10.1 to +21.8	+122 to +370		
Thangasamy et al. 2012 (23)	12	176	KTP (80-W and 120-W)	-15.9 to -16.1	-64 to -66	-0.7	+9.8 to +14.5	+111 to +181	+1.1	1a
		164	TURP	-14.1 to -14.4	-56 to -63		+10.5 to +13.7	+118 to +154		
Lusuardi et al. 2011 (56)	6	30	Diode laser enucleation	-22.7	-84		+14.8	+218		1b
		30	B-TURP	-21	-83		+15.2	+237		
Xia et al. 2008 (57)	12	52	ThuVaRP	-18.4	-84		+15.7	+196		1b
		48	TURP	-16.9	-81		+15.8	+190		

Peng et al. 2013 (59)	3	50	ThuVaRP	-13.2	-65		+16.2	+205		1b
		50	B-TURP	-12.1	-63		+16.2	+198		
Zhang et al. 2012 (64)	18	71	ThuLEP	-19.4	-79		+16.6	+244		1b
		62	HoLEP	-16.6	-73		+16.9	+232		

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

5.5.6 ***References***

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5.6 Prostatic stents

5.6.1 ***Mechanism of action***

The use of an endoprosthesis to preserve luminal patency is a well-established concept, with Fabian in 1980 first describing stenting of the prostatic urethra to relieve BPO (1). Prostatic stents were primarily designed as an alternative to an indwelling catheter in patients unfit for surgery because of comorbidity. However, prostatic stents have also been assessed by several studies as a primary treatment option in patients without significant comorbidities (2,3).

A prostatic stent requires a functioning detrusor, so that the bladder still has the ability to empty itself. This is in contrast to an indwelling catheter, which drains the bladder passively (4). Stents can be temporary or permanent. Permanent stents are biocompatible, allowing epithelialization, so that eventually they become embedded in the urethra. Temporary stents do not epithelialize 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 (MIT) (4).

*5.6.2 **Efficacy***

There have been several small case studies on a range of stents of different designs and materials, which have provided a low level of evidence for their use. Table 5.8 describes the most important studies (2,5-9).

All studies during follow-up have observed a significant attrition rate. There is only one RCT that has compared two versions of a blind-placement prostatic stent (BPS) for BPO (10), and there have been no studies comparing stents with sham or other treatment modalities. The BPS system is a temporary stent consisting of a soft silicone stent, retrieval line, and delivery device, with the difference between BPS-1 and BPS-2 being an additional 2-cm bulbar segment. This bulbar segment results in a significantly lower migration rate with BPS-2 (5%) compared with BPS-1 (85%), but the bulbar segment also caused significant discomfort (10). BPS-2 also has better symptom scores and voiding function than BPS-1, but only Q_{max} reached statistical significance. The results from this study appear to indicate that stent design has a critical role in the efficacy and safety of prostatic stents (10).

The main representative of the permanent stents is the UroLume prosthesis. A systematic review identified 20 case series, with a total of 990 patients who received the UroLume stent (11). These trials with a varying follow-up reported relevant symptom improvement; IPSS decreased by 10-12.4 points (11). Additionally, mean Q_{max} increased by 4.2-13.1 mL/s following stent insertion.

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, with the mean Q_{max} ranging from 8.8 to 20 mL/s (11). At 12 years of follow-up, the mean IPSS, Q_{max} and PVR were 10.82, 11.5 mL/s and 80 mL, respectively (11,12).

The best data on non-epithelializing prostatic stents are provided by a systematic review of the efficacy of Memokath, a self-expanding metallic prostatic stent (13). A total of 14 case series with 839 patients were reviewed. The Memokath stent reduced IPSS by 11-19 points. However, assessments were made at different times after stent placement; similarly, stent insertion resulted in a Q_{max} increase of 3-11 mL/s (13).

*5.6.3 **Tolerability and safety***

In general, stents are subject to misplacement, migration, and poor tolerability because of exacerbation of LUTS and encrustation (4). The main adverse events immediately following stent placement include perineal pain or bladder storage symptoms. It can be difficult to remove permanent stents in cases of stent migration, stent encrustation, or epithelial ingrowth, and general anaesthesia is usually needed in these cases.

Removal of a temporary stent is achieved by pulling the retrieval suture until the stent is completely retracted or by using graspers under endoscopic guidance.

The systematic review of the UroLume reported a 16% failure rate (104/666) within 12 months of insertion, mainly due to stent misplacement or migration (37%) or recurrent obstructive or irritative LUTS (14%). The overall failure rate at 5 years was 27% (50/188 stents), although many patients were lost to follow-up or died with the stent in situ (11). In the study with the longest follow-up, 18% of the patient population (11 men) completed 12 years of follow-up with the Urolume stent in situ, whereas 29 stents were removed (failure rate, 47%) and 22 patients (34%) died of diseases not related to male LUTS.

*5.6.4 **Practical considerations***

The side effects and high migration rate of prostatic stents mean they have a limited role in the treatment of moderate-to-severe LUTS secondary to BPO. Prostatic stents remain an alternative to transurethral catheterization for men who have (recurrent) urinary retention and are at high risk for surgery. Temporary stents can provide short-term relief from LUTS secondary to BPO in patients temporarily unfit for surgery or after minimally invasive treatment (4).

*5.6.5 **Recommendation***

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

Table 5.8: Efficacy of stents: key studies

		Symptoms		Q_{max} (mL/s)		Failure rate (follow-up in months)	LE
Stent	***n***	**Pre-operative**	**Post-operative**	**Pre-operative**	**Post-operative**		
Urolume (P) (2)	91	14.1	4.7	9.3	17.1	Overall	3
	44	R	4.6	R	13.7	15.5% (18 mos)	
Memotherm (P) (5)	123	24.0	6.1*	7.4	16.1*	4% (48 mos)	3
TITAN (P) (6)	85	15.9[a]	9.33[1]	8.59*	11.43[1]	Overall	3
	59	18.0	5.21	R	11.34	19% (24 mos)	
Spanner (T) (7)	30	22.3	7.1	8.2	11.6	0% (2 mos)	3
Memokath (T-P) (8)	211	20.3	8.2[2]	NA	NA	23% (7 y)	3
Horizon Bell-shaped (T) (9)	108	22.0	15.0	9.1	9.6	46% (3 mos)	3

Q_{max} = maximum urinary flow rate (free uroflowmetry); (P) = permanent stent; R = retention; (T) = temporary stent; NA = not available.

** = immediately after insertion; [a] = Madsen score; [1] = at 2 years; [2] = at 3 months.*

*5.6.6 **References***

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5.7 Emerging operations

*5.7.1 **Intraprostatic ethanol injections***

5.7.1.1 Mechanism of action

Absolute (dehydrated, 95-98%) ethanol is injected into the prostatic parenchyma for the treatment of LUTS secondary to BPO. The precise mechanism of action in both humans and animals remains unclear. The use of ethanol was investigated in the canine model and demonstrated the ability of ethanol to cause inflammation, coagulative necrosis with protein denaturation and cell membrane lysis, and, finally, atrophy and ablation of prostatic tissue resulting in cavity formation (1-4). Tissue necrosis was typically wedge-shaped (4). The volume of injected ethanol correlated only moderately with the size of tissue necrosis (4). Intra-prostatic cavity formation appeared in the canine model after 7 days (3).

Liquid dehydrated ethanol or ethanol gel is injected into the prostatic parenchyma with a 20-22 gauge needle either transurethrally, transperineally, or transrectally. The transurethral approach (TEAP or TUEIP) has been used more often (5-15) than the transperineal (11,16,17) or transrectal approaches (11).

Specific devices have been developed for the transurethral delivery of ethanol (InecTx™ in the USA and Prostaject™ in Europe) (18). There is no consensus on the number of injection sites or injection volumes, which depend on total prostate volume, urethral length and/or presence of a prostate median lobe, and have ranged from 2 mL to 25 mL of ethanol per patient in different studies (with the injection volume being up to 42% of the volume of the prostate).

Local anaesthesia supplemented by conscious sedation may be considered, although regional or general anaesthesia was chosen by most patients. The procedure is usually completed within approximately 30 minutes. Most patients need an indwelling catheter after the procedure.

5.7.1.2 Efficacy

Several open trials (5-17) have been published, with most having investigated men refractory to medical treatment. Only one trial investigated patients with urinary retention (10). None of these trials were randomized against TURP or other minimally invasive procedures for LUTS/BPH or BPO. Mean follow-up varied among studies from 3 to 54 months.

Most trials demonstrated a significant reduction in symptoms (IPSS: -41% to -71%) and PVR (-6% to -99%) as well as a significant improvement in the maximum urinary flow rate (Q_{max}: +35% to +155%) and QoL (IPSS-QoL: -47% to -60%) (Table 5.9). Prostate volume decreased significantly in approximately half of the trials (-4% to -45%). After an initial strong reduction in prostate volume, prostate size had increased again by 1-2 years post-operatively, although LUTS and maximum urinary flow remained significantly improved (8). No predictive efficacy parameter or dose-response relationship has been found (9,12).

A considerable number of re-treatments have been reported within the first year after the procedure (usually treated by a second ethanol injection, TURP, or open prostatectomy). Little is known about the durability of clinical effects later than 1 year after the operation; one trial with a mean follow-up of 3 years showed a re-treatment rate of 41% (8).

5.7.1.3 Tolerability and safety

Frequently reported adverse events included: perineal or abdominal discomfort/pain, bladder storage symptoms (≤ 40%), haematuria (≤ 40%), urinary tract infection or epididymitis, and urinary retention. Less frequently reported (< 5%) adverse events included: decreased libido, retrograde ejaculation, urgency urinary incontinence, urethral stenosis, and ED.

Animal studies revealed a high percentage of urethral sphincter damage and stress urinary incontinence when ethanol was injected via the perineal route (1), but these complications have not been reported in humans (16,17). One man developed a big bladder stone within 6 months after treatment, most probably due to calcification of necrotic prostatic masses (19). Two cases of severe complications after ethanol injections have been reported; bladder necrosis required cystectomy and urinary diversion (9).

5.7.1.4 Practical considerations

Ethanol injections are considered a minimally invasive treatment option for patients with moderate-to-severe LUTS secondary to BPO. However, the mechanism of action, patient selection, and application of ethanol (number of injection sites and injection volume) have not been well investigated. In addition, severe adverse events occurred in some patients (9) and long-term results are sparse. Intraprostatic ethanol injections are therefore regarded as experimental procedures for use only in trials. RCTs with long-term follow-up comparing ethanol injections with TURP, other minimally invasive procedures, or drugs are needed to judge adequately the value of this treatment modality.

5.7.1.5 Recommendation

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

Table 5.9: Results of intra-prostatic ethanol injections for treating BPH-LUTS or BPO in men refractory to medical treatment or in urinary retention

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Goya *et al.* 1999 (5)	12	10	-10.9[a]	-47	+5.1[a]	+64	-79.8[a]	-62	-2.1	-4	3
Savoca *et al.* 2001 (16)	24	8	-11[a]	-52	+5[a]	+46	-103[a]	-79	n/a	n/a	3
Ditrolio *et al.* 2002 (6)	52	15	-1 6.5	-74	+6.2	+109	n/a	n/a	-21.6	-45	3
Plante *et al.* 2002 (7)	52	5	-9.6[a]	-41	+3.2	+32	-7.6	-6.4	-15.8[a]	-30	2b
Chiang *et al.* 2003 (17)	12 (24)	11	-9.2[a]	-52	+8.2[a]	+155	-203.2[a]	-88	-2.2	-5	3
Goya *et al.* 2004 (8)	156	34	-8.7[a]	-40	+4.4[a]	+65	-65[a]	-70	+2.1	+4	3
Grise *et al.* 2004 (9)	52	115 (94)	-10.3[a]	-50	+3.5[a]	+35	n/a	n/a	-7.4[a]	-16	2b
Mutaguchi *et al.* 2006 (10)[†]	64	16	Spontaneous voiding in 87.5% Mean PVR 60 mL						-19.7[a]	-34	3
Larson *et al.* 2006 (11)	52	65	-9.4[a]	-44	+2.8[a]	+33	n/a	n/a	n/a	n/a	3
Plante *et al.* 2007 (12)*	24	79	-10.6 to -13.4[a]	-47 to -55	+3.2 to +8.1[a]	+37 to +94	-1.2 to -27.3[a]	-1 to -26	-5.6 to -11.2[a]	-13 to -25	2b
Magno *et al.* 2008 (13)	52	36	-13.3[a]	-47	+9.2[a]	+154	-286.4[a]	-99	-12.7	-19	3
Sakr *et al.* 2009 (14)	208	35	-12.1[a]	-55	+11[a]	+186	-32.6[a]	-47	-2.8[a]	-5	3

Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume.
*a = significant compared with baseline (indexed whenever evaluated); † = patients with urinary retention; * = three study arms comparing transurethral, transrectal and transperineal injections.*

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5.7.2 ***Intra-prostatic botulinum toxin injections***

5.7.2.1 Mechanism of action

Botulinum toxin (BTX) is the exotoxin of the bacterium *Clostridium botulinum*. This 150 kDa toxin is the most potent neurotoxin known in humans, and causes botulism (food-borne, wound or infant). Seven subtypes of BTX are known (types A-G), of which subtypes A and B have been manufactured for use in humans.

Experience with intra-prostatic injections for the treatment of LUTS/BPO exists only for BTX-A. The precise mechanism of action has been evaluated in experimental animals, but it is not fully understood. BTX-A blocks the release of neurotransmitters (e.g. acetylcholine or noradrenaline) from pre-synaptic nerves (1). BTX-A directly or indirectly reduces LUTS by induction of apoptoses of prostatic (epithelial) cells leading to tissue atrophy and prostate size reduction (2-4), inhibition of sensory neurons in the prostate and reduction of afferent signals to the central nervous system (3), and/or relaxation of smooth muscle cells in the prostatic parenchyma and reduction of BPO (4-6). Down-regulation of alpha1a-adrenergic receptors in the prostate may contribute to smooth muscle cell relaxation (3). The latter two mechanisms are summarized as chemical denervation that possibly has a negative influence on prostate growth.

Under US visualization, BTX-A can be injected into the prostatic parenchyma transperineally, transurethrally or transrectally, using a 21-23 gauge needle. The most frequently described approach is the transperineal approach (7-13), while the transurethral (5) and transrectal routes (14,15) have been used less often. Botox™ (Allergan, Irving, CA, USA) was used in all but one study (13).

Different therapeutic doses (100-300 U Botox™ or 300-600 U Dysport™) and dilutions (25-50 U Botox™/mL or 75 U Dysport™/mL) were used in various studies, but doses and dilutions have not been systematically tested. Doses of 100 units Botox™ have been suggested for prostate sizes < 30 mL, 200 units for sizes between 30 mL and 60 mL, and 300 units for sizes > 60 mL (9). For Dysport™, 300 units for prostate sizes < 30 mL, and 600 units for sizes > 30 mL were used (13). Most patients were treated without anaesthesia, local anaesthesia, or sedation.

5.7.2.2 Efficacy

A review of the available RCTs or prospective observational studies (until 2010) on the use of intraprostatic injection of BoNTA for LUTS/BPH showed an improvement in IPSS in 20 studies; this reduction was statistically significant in 13 studies (16). Similarly, Q_{max} increased in all series, reaching statistical significance in 14 studies. The reduction in prostate volume varied between the different series and was statistically significant in 18 studies.

Duration of the effects of treatment was also variable, ranging from 3 to 30 months (16). In patients with urinary retention before BoNTA injections, most men could void spontaneously within 1 month (Table 5.10). In two recent RCTs comparing several BoNTA doses, no differences were observed between groups in term of efficacy (17,18). In addition, the results from the largest placebo-controlled study on the efficacy of different doses of BoNTA (100 U, 200 U, and 300 U) in men with LUTS/BPH have been published (19). No significant difference between the BoNTA and placebo arms was observed in terms of IPSS, QoL, and Q_{max} at week 12 (19).

Little is known about the long-term effects and durability of the treatment; prostate volume seemed to increase again after 6-12 months (11,14) despite stable improvements in symptoms, Q_{max} and PVR. Re-treatment rates with BTX-A were as high as 29% (11).

Table 5.10: Results from initial studies on intra-prostatic botulinum toxin (Botox™) injections for treating LUTS/BPH, BPO or urinary retention

Trials	Duration (weeks)	Patients (n)	Change in symptoms (IPSS)		Change in Q_{max}		Change in PVR		Change in prostate volume		LE
			Absolute	%	mL/s	%	mL	%	mL	%	
Maria *et al.* 2003 (7)*	52	30	-14.4[a,b]	-62	+6.9[a,b]	+85	-102[a,b]	-81	-32[a,b]	-61	1b
Chuang *et al.* 2005 (8)*	40	16	-9.8[a]	-52	+5.3[a]	+73	-41	-60	-3[a]	-16	3
Kuo 2005 (5)†	24	10	Spontaneous voiding in 100% of patients		+4.0[a]	+53	-206[a]	-85	-17[a]	-24	3
Chuang *et al.* 2006 (9)*	52	41	-11[a]	-57	+4.1[a]	+59	-68	-42	-7[a]	-13	3
Park *et al.* 2006 (10)*	24	23	-9.3[a]	-39	+2.0[a]	+28	-49[a]	-45	-7[a]	-14	3
Chuang *et al.* 2006 (4)	12	8	-15[a]	-79	+6.5[a]	+73	-155.5	-88	-12.1[a]	-20	3
Silva *et al.* 2008 (14)†*	12 (24)	21 (10)	Spontaneous voiding in 80% of patient		+11.4	n/a	Mean PVR 66 mL		-20[a]	-29	3
Brisinda *et al.* 2009 (11)*	120	77	-13[a]	-54	+5.9[a]	+69	-65[a]	-71	-27.2[a]	-50	3
Kuo and Liu 2009 (12)*	52	30	-7.1[a]	-46	+2.3[a]	+27	+21	+23	-13[a]	-14	1b
Silva *et al.* 2009 (15)†*	72	11	Spontaneous voiding in 100% of patients		+10.5	n/a	Mean PVR 58 mL		-9.2[a]	-11	3
Nikoobakht *et al.* 2010 (13)‡	52	72	-11.3[a]	-57	+7.7[a]	+122	-34[a]	-68	n/a		3

Absolute and relative changes compared with baseline are listed with regard to symptoms (IPSS), maximum urinary flow rate (Q_{max}), post-void residual urine (PVR), and prostate volume.
*a = significant compared with baseline (indexed whenever evaluated); b = significant compared with placebo (saline solution) or alpha1-blockers; † = patients with acute or chronic urinary retention; * = Botox™; ‡ = Dysport™.*

5.7.2.3 Tolerability and safety

BoNTA injections were well tolerated in all studies. The main reported complications after treatment included dysuria, haematuria, epididymitis, prostatitis, and grade 2-3 events (unspecified) among 35% of patients in the series (16). In addition, patients may receive a transurethral catheter or perform clean intermittent catheterization during the early post-operative period (1 week to 1 month) (8,14,20). Intraprostatic injection of BoNTA in patients with BPE seem to have no impact on sexual function (16,21).

5.7.2.4 Practical considerations

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

5.7.2.5 Recommendation

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

5.7.2.6 References

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5.8 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. Table 5.11 provides differential information about conservative, medical and surgical treatment options described in the EAU Guidelines on Non-neurogenic Male LUTS. Note that treatment modalities may be combined leading to different effects.

Table 5.11: Speed of onset and influence on basic parameters with conservative, medical or surgical treatment modalities for the management of non-neurogenic male LUTS

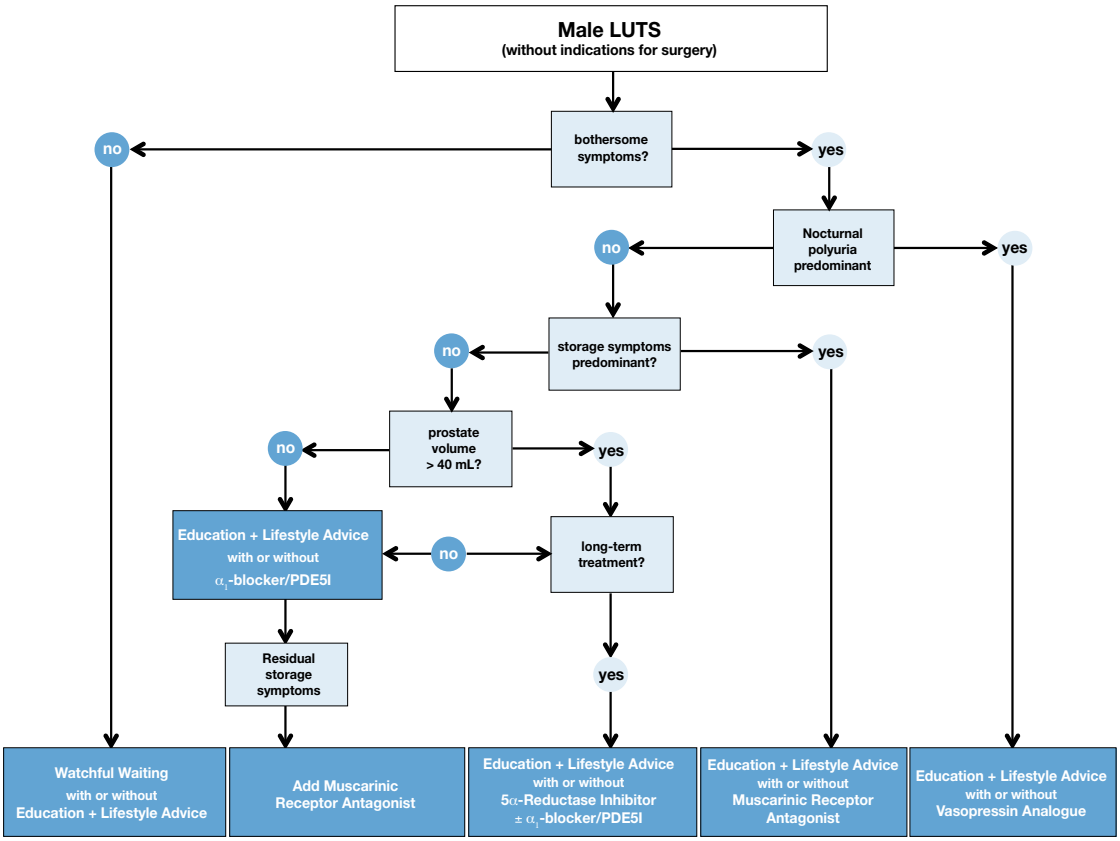
Treatment	Speed of Onset	LUTS (IPSS)	Uroflowmetry (Q_{max})	Prostate size	PVR	Disease progression
Conservative and drug treatments						
Watchful waiting, behavioural treatment	months	+ (-1.3 to -5.7 points)	-	-	-	?
α1-adrenoceptor antagonists	days	++ (-31 to -48.2%)	++ (+1.4 to +3.2 ml/s)	-	- / + (-17 to -39%)	+++ (symptoms)
5α-reductase inhibitors	months	+ (-13.3 to -38.6%)	++ (+1.4 to +2.2 ml/s)	+ - ++ (-15 to -28%)	-	+++ (retention)
Muscarinic receptor antagonists	Weeks	++ (storage symptoms) (-35.3 to -54%)	-	-	+ (0 to +49ml)	?
PDE5 inhibitors (tadalafil)	Days	++ (-17 to -37%)	- / +	-	- / + (+9 to -19 ml)	?
α1-adrenoceptor antagonists + 5α-reductase inhibitors	Days	++ (-38 to -49.7%)	++ (+2.3 to 3.8 ml/s)	+ -++ (-11.9 to -27.3%)	- / +	+++ (symptoms + retention)
α1-adrenoceptor antagonists + muscarinic receptor antagonists	Days	++ (-31.8 to -66.4%)	++	-		?
Surgical treatments		**After catheter removal**				
TURP-TUIP	Hours	++++ (-63 to -88%)	++++ (+6.9 to 22.9 ml/s)	+++	++++	++++
Open prostatectomy	Hours	++++ (-62 to -86%)	++++ (+7.0 to +21.4 ml/s)	++++ (-88%)	++++ (-86 to -98%)	++++
TUMT	Weeks	+++ (-40 to -87%)	+++ (+2.4 to 8.4 ml/s)	++ (-8.1 to -33.0%)	++ (-34 to -84.1%)	+++
TUNA™	Weeks	+++ (-45 to -56%)	+++ (+4.7 to 6.5 ml/s)	++	+ (-20 ml or -22%)	++
HoLEP/HoLRP	Hours	++++ (-66 to -92%)	++++ (+10.9 to 23.0 ml/s)	++++ (-34 to -54%)	++++ (-68 to -98%)	++++
KTP/Greenlight	Days	+++ (-31 to -75%)	+++ (+4.7 to 14.9 ml/s)	+++ (-44 to -63%)	+++ (-57 to -91%)	+++
Diode laser	hours	+++ (-55 to -84.3%)	+++ (+5.1 to 13.7 ml/s)	+++ (-30.3 to -58.1%) PSA based reduction	+++ (-58.1 to -87.7%)	+++
Thulium LaserThuVaP, ThuVaRP, and ThuVEP	hours	+++ (-63 to -85.4%)	+++ (+12.8 to 18.7 ml/s)	+++ (-35.7 to -88%) PSA based reduction	+++ (-72.4 to -94.4%)	+++
Prostate stents	hours	++ (-10 to -19 points)	++ (+3 to 13.1 ml/s)	-	+++	?

- no influence; + mild influence; ++ moderate influence; +++ strong influence; ++++ very strong influence; ? unknown

BTX: Botulinum Toxin; HoLEP: Holmium Laser Enucleation of the Prostate; HoLRP: Holmium Laser Resection of the Prostate; IPSS: International Prostate Symptom Score; KTP: K+-titanyl-phosphate, "greenlight" laser vaporization; LUTS: Lower Urinary Tract Symptoms; PDE5 inhibitor: phosphodiesterase 5 inhibitor; PVR: Post-Void Residual urine; ThuVaP: Tm:YAG vaporisation of the prostate; ThuVaRP: Tm:YAG vaporesection; ThuVEP: Tm:YAG vapoenucleation; TUMT: Transurethral Microwave Therapy; TUNA™: Transurethral Needle Ablation; TUIP: Transurethral Incision of the Prostate; TURP: Transurethral Resection of the Prostate.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 5.1 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles.

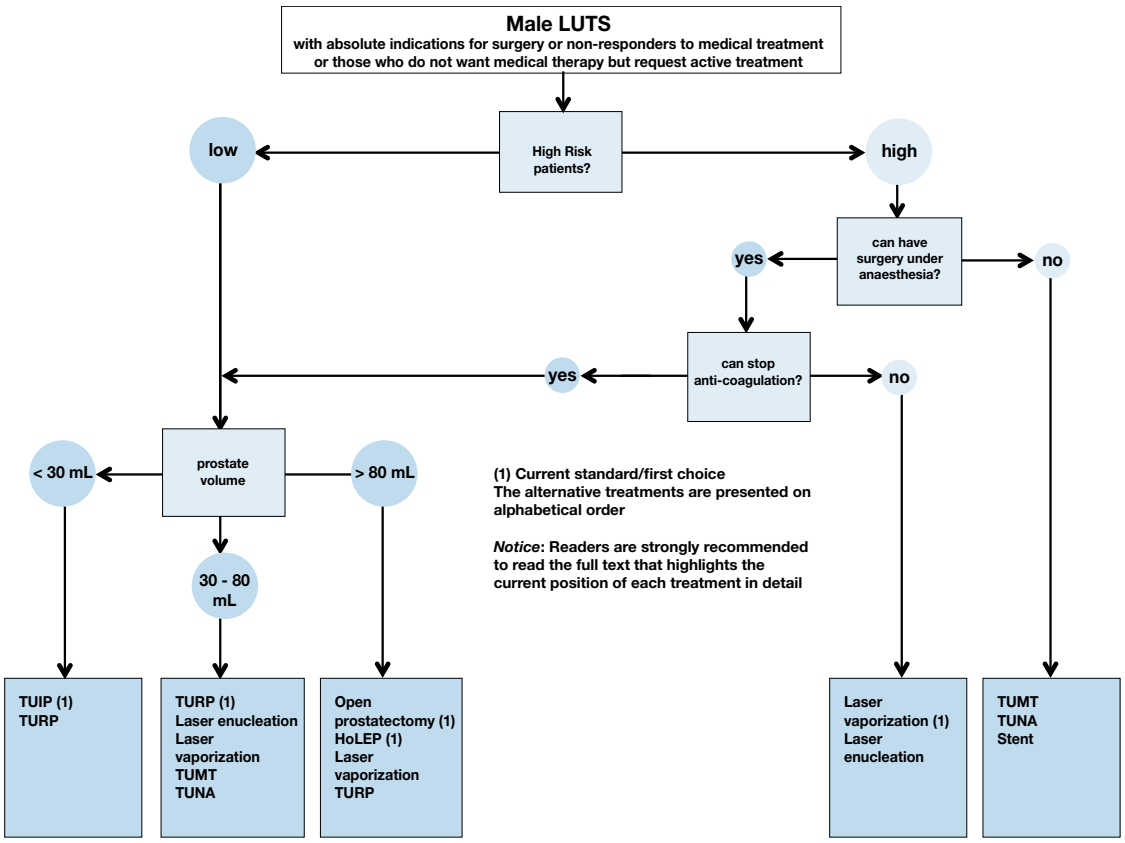
Figure 5.1: Treatment algorithm of male LUTS using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation. Note that patients' preferences may result in different treatment decisions.



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 patients' profiles is provided in Figure 5.2.

Figure 5.2: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size



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

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

Patients who elect to pursue a WW policy should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume.

6.2 Medical treatment

Patients receiving α_1-blockers, muscarinic receptor antagonists, phosphodiesterase 5 inhibitors or the combination of α_1-blockers + 5-α reductase inhibitors or muscarinic receptor antagonists should be reviewed 4-6 weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following tests are recommended at follow-up visits: IPSS, uroflowmetry, and PVR volume.

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

Men taking a 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is > 10 years and if a diagnosis of prostate cancer could alter management. A new baseline PSA should be determined at month 6, and any confirmed increase in PSA while on a 5-ARIs should be evaluated.

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

6.3 Surgical treatment

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

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

6.4 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

7. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

AUR	acute urinary retention
AVP	arginine vasopressin
BOO(I)	bladder outlet obstruction (index)
BPE	benign prostatic enlargement
BPH	benign prostatic hyperplasia
BPO	benign prostatic obstruction
BWT	bladder wall thickness
cGMP	cyclic guanosine monophosphate
CKD	chronic kidney disease
CombAT	combination of avodart® and tamsulosin
DAN-PSS	Danish prostate symptom score
DHT	dihydrotestosterone
DO	detrusor overactivity
DRE	digitorectal examination
DWT	detrusor wall thickness
eNOS	endothelial NOS
ER	extended release
FVC	frequency volume chart
GITS	gastrointestinal therapeutic system
HoLEP	Holmium Laser Enucleation
HoLRP	Holmium Laser Resection of the Prostate
ICIQ	international consultation on incontinence questionnaire
IFIS	intra-operative floppy iris syndrome
IPP	intravesical prostatic protrusion
IPSS	international prostate symptom score
IR	immediate release
IVP	intravenous pyelogram
LUTS	lower urinary tract symptoms
MR	modified release
MRI	magnetic resonance imaging
MTOPS	medical therapy of prostatic symptoms
NAION	non-arteritic anterior ischemic optic neuropathy
NO	Nitric oxide
NOS	NO synthases
nNOS	neuronal
n.s.	not significant
OAB	overactive bladder
OCAS	oral controlled absorption system
PDE	phosphodiesterase
PFS	pressure flow study
PPV	positive predictive value
PSA	prostate specific antigen
PVR	post-void residual urine
Qave	average urinary flow rate (free uroflowmetry)
Q_{max}	maximum urinary flow rate during free uroflowmetry
QoL	quality of life
RCT	randomized controlled trial
RR	relative risk
SHBG	sexual hormone binding globulin
SR	sustained release
t_{max}	time to maximum plasma concentration
$t_{½}$	elimination half-life
TURP	transurethral resection of the prostate
ThuVaP	Tm:YAG vaporization of the prostate
ThuVaRP	Tm:YAGvaporesection
ThuLEP	Tm:YAG laser enucleation of the prostate
ThuVEP	Tm:YAGvapoenucleation

TRUS	transrectal ultrasound (of the prostate)
TWOC	trial without catheter
UDS	urodynamic study
UEBW	ultrasound-estimated bladder weight
UTI	urinary tract infection
WW	watchful waiting

Conflict of interest

All members of the Male LUTS Guidelines working 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 European Association of Urology website. This guidelines document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation, and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.