EAU Guidelines on Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS)

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TABLE OF CONTENTS PAGE

1. INTRODUCTION 6
   1.1 Aim and objectives 6
   1.2 Panel composition 6
   1.3 Available publications 6
   1.4 Publication history 6
      1.4.1 Summary of changes 6

2. METHODS 7
   2.1 Introduction 7
   2.2 Review 7
   2.3 Patients to whom the Guidelines apply 7

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY 8

4. DIAGNOSTIC EVALUATION 9
   4.1 Medical history 9
   4.2 Symptom score questionnaires 1 0
      4.2.1 International Prostate Symptom Score 10
      4.2.2 International Consultation on Incontinence Questionnaire for MLUTS 10
      4.2.3 Danish Prostate Symptom Score 10
      4.2.4 Symptoms of Lower Urinary Tract Dysfunction Research Network 10
   4.3 Frequency volume charts and/or bladder diaries 11
   4.4 Physical examination and digital rectal examination 11
      4.4.1 Digital rectal examination and prostate size evaluation 11
   4.5 Urinalysis 11
   4.6 Prostate-specific antigen 12
      4.6.1 Prostate-specific antigen and the prediction of prostatic volume 12
      4.6.2 Prostate-specific antigen and the probability of PCa 12
      4.6.3 Prostate-specific antigen and the prediction of BPO-related outcomes 12
   4.7 Renal function measurement 13
   4.8 Post-void residual urine 13
   4.9 Uroflowmetry 14
   4.10 Imaging 14
      4.10.1 Upper urinary tract 14
      4.10.2 Prostate 14
         4.10.2.a Prostate size and shape 15
      4.10.3 Voiding cystourethrogram 15
   4.11 Urethrocystoscopy 15
   4.12 Urodynamics 16
      4.12.1 Diagnosing bladder outflow obstruction 16
      4.12.2 Videourodynamics 16
   4.13 Non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS 17
      4.13.1 Prostatic configuration/intravesical prostatic protrusion 17
      4.13.2 Bladder/detrusor wall thickness and ultrasound-estimated bladder weight 17
      4.13.3 Non-invasive pressure-flow testing 18
      4.13.4 The diagnostic performance of non-invasive tests in diagnosing bladder outlet obstruction in men with LUTS compared with pressure-flow studies 18
   4.14 Novel assessment 18
      4.14.1 Visual prostate symptom score 18
      4.14.2 MicroRNA 19
   4.15 Prostate cancer 19

5 DISEASE MANAGEMENT 20
   5.1 Conservative treatment 20
      5.1.1 Watchful waiting 20
      5.1.2 Behavioural and dietary modifications 20
      5.1.3 Practical considerations 20
   5.2 Pharmacological treatment 21

5.2.1 α1-Adrenoceptor antagonists (α1-blockers) 21
5.2.2 5α-reductase inhibitors 22
5.2.3 Muscarinic receptor antagonists 24
5.2.4 β3 agonist 25
5.2.5 Phosphodiesterase type 5 inhibitors 27
5.2.6 Plant extracts - phytotherapy 28
5.2.7 Combination therapies 30
5.2.7.a α1-blockers + 5α-reductase inhibitors 30
5.2.7.b α1-blockers + muscarinic receptor antagonists 32
5.2.7.c α1-blockers + Beta-3 agonist 33
5.2.7.d α1-blockers + Phosphodiesterase type 5 inhibitors 34
5.3 Surgical treatment of benign prostatic obstruction 35
5.3.1 Resection of the prostate 36
5.3.1.a Monopolar and bipolar transurethral resection of the prostate 36
5.3.1.b Holmium laser resection of the prostate 38
5.3.1.c Thulium:yttrium-aluminium-garnet laser vaporesection of the prostate 38
5.3.1.d Transurethral incision of the prostate 39
5.3.2 Enucleation of the prostate 39
5.3.2.a Open simple prostatectomy 39
5.3.2.b Bipolar transurethral enucleation of the prostate 40
5.3.2.c Holmium laser enucleation of the prostate 41
5.3.2.d Thulium:yttrium-aluminium-garnet laser enucleation of the prostate 43
5.3.2.e Diode laser enucleation of the prostate 44
5.3.2.f Alternative enucleation techniques 45
5.3.2.f.1 Laparoscopic/robotic simple prostatectomy (L/RASP) 45
5.3.2.f.2 532nm ('Greenlight') laser enucleation of the prostate (GreenLEP) 46
5.3.2.g Anatomical endoscopic enucleation of the prostate 46
5.3.3 Vaporisation of the prostate 46
5.3.3.a Bipolar transurethral vaporisation of the prostate 46
5.3.3.b 532 nm ('Greenlight') laser vaporisation of the prostate 47
5.3.3.c Vaporisation techniques under investigation 49
5.3.4 Alternative ablative techniques 49
5.3.4.a Aquablation - image-guided robotic waterjet ablation: AquaBeam 49
5.3.4.b Prostatic artery embolisation 51
5.3.4.c Alternative ablative techniques under investigation 53
5.3.4.c.1 Convective water vapour energy (WAVE) ablation: The water vapour thermal therapy system 53
5.3.4.c.2 Transperineal interstitial laser ablation of the prostate 54
5.3.5 Nonablative techniques 55
5.3.5.a Prostatic urethral lift 55
5.3.5.b Intra-prostatic injections 56
5.3.5.c Non-ablative techniques under investigation 56
5.3.5.c.1 (i)TIND 56
5.3.5.c.2 Paclitaxel-coated ballon dilatation of the prostate (Optilume) 57
5.4 Patient selection for LUTS/BPO treatment 57
5.5 Management of nocturia in men with lower urinary tract symptoms 60
5.5.1 Diagnostic assessment 60
5.5.2 Medical conditions and sleep disorders shared care pathway 61
5.5.3 Treatment for nocturia 62
5.5.3.a Antidiuretic therapy 62
5.5.3.b Medications to treat LUTD 64
5.5.3.c Other medications 64
5.6 Management of male urinary incontinence 65
5.6.1 Epidemiology and pathophysiology 65
5.6.2 Diagnostic evaluation 66
5.6.2.a Urodynamic testing 66
5.6.3 Conservative treatment 67
5.6.3.a Simple clinical interventions 67

5.6.3.a.1 Lifestyle interventions 67
5.6.3.a.2 Treatment of comorbidities 68
5.6.3.a.3 Constipation 68
5.6.3.a.4 Containment 68
5.6.3.b Behavioural and physical therapies 69
5.6.3.b.1 Prompted or timed voiding 69
5.6.3.b.2 Bladder training 69
5.6.3.b.3 Pelvic floor muscle training 69
5.6.3.b.4 Electrical stimulation 70
5.6.3.b.5 Posterior tibial nerve stimulation 70
5.6.4 Pharmacological management 71
56.6.4.a Drugs for urgency urinary incontinence (UUI) 71
5.6.4.b Drugs for stress urinary incontinence 71
5.6.5 Surgical treatment for stress urinary incontinence 71
5.6.5.a Bulking agents in men 71
5.6.5.b Male slings 72
5.6.5.b.1 Nonadjustable slings 72
5.6.5.b.2 Adjustable slings in males 73
5.6.5.b.3 Autologous slings 74
5.6.5.c Compression devices in males 74
5.6.5.c.1 Artificial urinary sphincter 74
5.6.5.c.2 Non-circumferential compression device (ProACT®) 75
5.6.6 Surgical treatment for urgency urinary incontinence 76
5.6.6.a Bladder wall injection of botulinum toxin-A 76
5.6.6.b Sacral neuromodulation (SNM) 78
5.6.6.c Cystoplasty/urinary diversion 78
5.7 Management of underactive bladder 80
5.7.1 Epidemiology and pathophysiology 80
5.7.2 Diagnostic evaluation 81
5.7.2.a Medical history and physical examination 81
5.7.2.b Questionnaires 81
5.7.2.c Uroflowmetry 82
5.7.2.d Ultrasound scan and post-void residual measurement 82
5.7.2.e Urodynamics 82
5.7.3 Conservative management 82
5.7.3.a Behavioural interventions 82
5.7.3.b Pelvic floor muscle relaxation training with biofeedback 83
5.7.3.c Intermittent catheterisation 83
5.7.3.d Indwelling catheters 83
5.7.3.e Intravesical electrical stimulation 83
5.7.3.f Extracorporeal shockwave therapy 83
5.7.4 Pharmacological management 84
5.7.4.a Parasympathomimetics 84
5.7.4.b Alpha-adrenergic blockers 84
5.7.4.c Prostaglandins 84
5.7.4.d Other drugs 84
5.7.5 Surgical treatment for underactive bladder 84
56.7.5.a Benign prostatic surgery in patients with UAB 85
5.7.5.b Sacral neuromodulation 86
5.7.6 Follow-up 86
5.8 Voiding dysfunction in young men 87
5.8.1 Diagnostic evaluation 87
5.8.1.a Medical history 87
5.8.1.b Questionnaires 87
5.8.1.b.1 Physical examination 87
5.8.1.c Uroflowmetry and PVR measurement 88
5.8.1.d Ultrasound scan 88
5.8.1.e VUDS and electromyography 88
5.8.1.f Magnetic resonance imaging 88
5.8.1.g Urethrocystoscopy 88

5.8.2 Treatment 89
5.8.2.a Conservative treatment 89
5.8.2.a.1 Observation 89
5.8.2.a.2 Behavioural modifications plus biofeedback 89
5.8.2.b Pharmacological treatment 89
5.8.2.b.1 Alpha-blockers 89
5.8.2.c Surgical treatment 89
5.8.2.d OnabotulinumtoxinA (BoNTA) injection therapy 90
5.8.2.e Intermittent catheterisation 90
5.8.2.f Sacral neurostimulation 90

6. FOLLOW-UP 91
6.1 Watchful waiting (behavioural) 91
6.2 Medical treatment 91
6.3 Surgical treatment 91

7. REFERENCES 92

8. CONFLICT OF INTEREST 139

9. CITATION INFORMATION 140

10. COPYRIGHT AND TERMS OF USE 140

1. INTRODUCTION

1.1 Aim and objectives

Lower urinary tract symptoms (LUTS) are common complaints in adult men that have a major impact on quality of life (QoL) and present a substantial economic burden. The present Guidelines focus on offering practical, evidence-based guidance on the assessment and treatment of men with various non-neurogenic, benign forms of LUTS. The understanding of the lower urinary tract (LUT) as a functional unit and the multifactorial aetiology of associated symptoms means that LUTS now constitute the main focus rather than the former emphasis on benign prostatic hyperplasia (BPH).

The term BPH (which is a histological diagnosis) is considered inappropriate because it is benign prostatic obstruction (BPO, a urodynamic diagnosis) that is treated if it is a cause of a man's LUTS. It must be emphasised that clinical guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients but rather help to focus decisions. Taking personal values and preferences/individual circumstances of patients into account is also important. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel composition

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

1.3 Available publications

A quick reference document, the Pocket Guidelines, is available in print and on the Uroweb website. These are abridged versions, which may require consultation together with the full text version. All documents are accessible through the EAU website Uroweb: https://uroweb.org/guidelines/management-of-non-neurogenic-male-luts.

1.4 Publication history

The Non-neurogenic MLUTS Guidelines were first published in 2000. All sections of the 2026 MLUTS Guidelines have been fully updated following a full literature search.

1.4.1 Summary of changes

All Chapters of the 2026 MLUTS Guidelines have been updated based on the 2024 version of the Guidelines. References have been added throughout the document and text updated accordingly. Other key changes incorporated in this publication include:

- Minor updates throughout Chapter 4 on diagnostic evaluation, including a new Section 4.15 discussing prostate cancer (PCa).
- Updates to the text in Section 5.1 on conservative treatment, including an update on the strength rating for β_3 agonists.
- Addition and deletion of subsections in Section 5.3 on the surgical treatment of BPO, with special attention to alternative enucleation techniques and alternative ablative techniques, as well as new Sections 5.3.5.c.2 and 5.3.5.c.3.
- Addition of recommendations for management of male urinary incontinence (UI), both for diagnosis and conservative treatment.
- New Figure 7 on the management of detrusor underactivity (DU).
- New Section 5.8 on voiding dysfunction in young men.

2. METHODS

2.1 Introduction

For the 2026 EAU Guidelines on Non-Neurogenic MLUTS, new and relevant evidence was identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Non-Neurogenic MLUTS Guidelines was performed. The search was limited to studies representing high levels of evidence, i.e. systematic reviews (SRs) with meta-analysis, randomised controlled trials (RCTs) and prospective non-randomised comparative studies, published in the English language. Databases searched included Medline, EMBASE and the Cochrane Libraries, covering a time frame between 1 May 2023 and 1 May 2025. A total of 2,036 unique records were identified, retrieved and screened for relevance.

Detailed search strategies for the 2026 Guidelines are available online:
https://uroweb.org/guidelines/management-of-non-neurogenic-male-luts/publications-appendices.

Recommendations within the Guidelines are developed by the Panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates) and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms that accompany each Guidelines recommendation, addresses several key elements:

1. the overall quality of the evidence that exists for the recommendation [1];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study-related factors);
4. the balance between desirable and undesirable outcomes; and
5. the impact and certainty of patient values and preferences on the intervention.

Strong recommendations typically indicate a high degree of evidence quality and/or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower-quality evidence and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional methodology information and a list of associations endorsing the EAU Guidelines can be found online: https://uroweb.org/eau-guidelines/methodology-policies.

2.2 Review

The 2026 Non-Neurogenic MLUTS Guidelines were peer reviewed prior to publication.

2.3 Patients to whom the Guidelines apply

Recommendations apply to men who seek professional help for LUTS in various non-neurogenic and nonmalignant conditions such as BPO, dysfunctional voiding (DV), detrusor overactivity (DO)/overactive bladder (OAB), UI and/or nocturnal polyuria (NP). Specific context usually requires a more extensive workup, for example, concomitant neurological diseases, young age, prior LUT disease or surgery, which is not covered in these Guidelines but may include several tests indicated in the following Sections. Guidelines on Neuro-Urology, Urological Infections, Urolithiasis or malignant diseases of the LUT have been developed by other EAU Guidelines Panels and are available online: www.uroweb.org/guidelines/.

3. EPIDEMIOLOGY, AETIOLOGY AND PATHOPHYSIOLOGY

Lower urinary tract symptoms can be divided into storage, voiding and post-micturition symptoms [3], and they are prevalent, cause bother and impair QoL [4-7]. An increasing awareness of LUTS, and storage symptoms in particular, is warranted to discuss management options that could improve QoL [8]. Lower urinary tract symptoms are strongly associated with ageing [4, 5], associated costs and burden are therefore likely to increase with future demographic changes [5, 9]. Lower urinary tract symptoms are also associated with a number of modifiable risk factors, suggesting potential targets for prevention (e.g. metabolic syndrome) [10]. In addition, men with moderate-to-severe LUTS may have an increased risk of major adverse cardiac events [11].

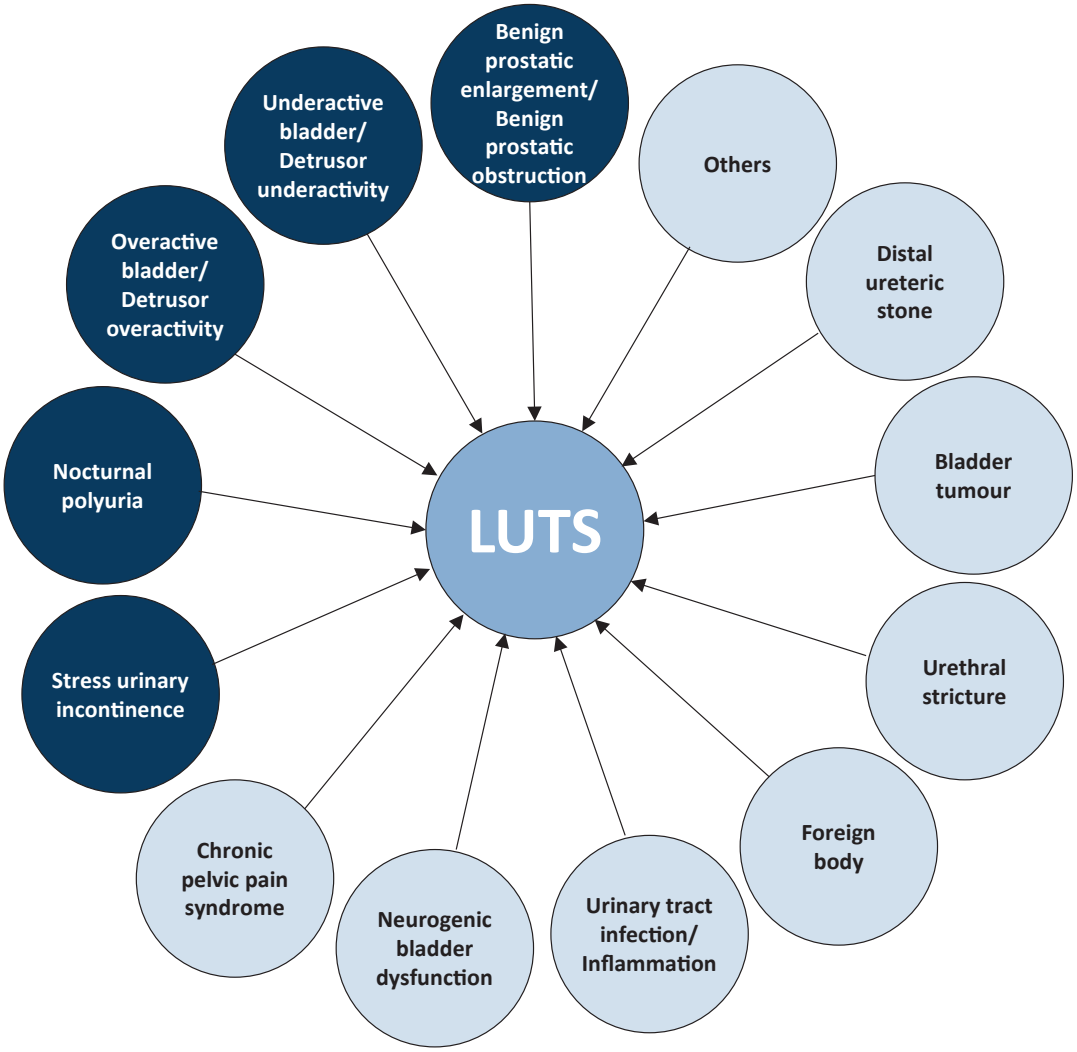
Most elderly men have at least one LUTS [5], however, symptoms are often mild or not very bothersome [7, 8, 12]. Lower urinary tract symptoms can progress dynamically: for some individuals, LUTS persist and progress over long time periods, while for others they remit [5]. Lower urinary tract symptoms have traditionally been related to bladder outlet obstruction (BOO), most frequently when histological BPH progresses through benign prostatic enlargement (BPE) to BPO [3, 6]. However, increasing numbers of studies have shown that LUTS are often unrelated to the prostate [5, 13]. Bladder dysfunction may also cause LUTS, including DO/OAB, DU/underactive bladder (UAB), as well as other structural or functional abnormalities of the urinary tract and its surrounding tissues [13]. Prostatic inflammation also appears to play a role in BPH pathogenesis and progression [14, 15]. In addition, many nonurological conditions also contribute to urinary symptoms, especially nocturia [5].

The following list provides definitions for some of the most common conditions related to MLUTS:

- Acute retention of urine: A painful, palpable or percussible bladder when the patient is unable to pass any urine [3].
- Chronic retention of urine: A nonpainful bladder that remains palpable or percussible after the patient has passed urine. Such patients may be incontinent [3].
- Bladder outlet obstruction: The generic term for obstruction during voiding. This conditions is characterised by increasing detrusor pressure and reduced urine flow rate. Bladder outlet obstruction is usually diagnosed by invasive pressure/flow studies [3].
- Benign prostatic obstruction: A form of BOO that may be diagnosed when the cause of outflow obstruction is known to be BPE [3]. In the Guidelines, the term BPO or BOO is used as reported by the original studies.
- Benign prostatic hyperplasia: A term used (and reserved) for the typical histological pattern, which defines the disease.
- Detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked [3]. DO is usually associated with OAB syndrome characterised by urinary urgency, with or without urge urinary incontinence (UUI), usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology [16].
- Detrusor underactivity during voiding is characterised by decreased detrusor voiding pressure leading to a reduced urine flow rate. Detrusor underactivity causes UAB syndrome which is characterised by voiding symptoms similar to those caused by BPO [17].

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

Figure 1: Causes of MLUTS



4. DIAGNOSTIC EVALUATION

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

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

4.1 Medical history

The importance of assessing the patient's history is well recognised [18-20]. A medical history aims to identify the potential causes and relevant comorbidities, including medical and neurological diseases. In addition, current medication, lifestyle habits, emotional and psychological factors must be reviewed. The Panel recognises the need to discuss LUTS and the therapeutic pathway from the patient's perspective. This includes reassuring the patient that there is no definite link between LUTS and PCa [21, 22].

As part of the urological/surgical history, a self-completed validated symptom questionnaire (see Section 4.2) should be obtained to objectify and quantify LUTS [18, 20]. Bladder diaries or frequency/volume charts (FVCs) are particularly beneficial (see Section 4.3) [23]. Sexual function should also be assessed, preferably with validated symptom questionnaires such as the International Index of Erectile Function (IIEF) and the Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [24, 25].

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

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

4.2 Symptom score questionnaires

All published guidelines for MLUTS recommend using validated symptom score questionnaires [18, 20]. Several questionnaires have been developed which are sensitive to symptom changes and can be used to monitor treatment [26-32]. Symptom scores are helpful in quantifying LUTS and in identifying which type of symptoms are predominant, however, they are not disease- or age-specific. An SR evaluating the diagnostic accuracy of individual symptoms and questionnaires, compared with urodynamic studies (the reference standard), for the diagnosis of BOO in males with LUTS found that individual symptoms and questionnaires for diagnosing BOO were not significantly associated with one another [33].

4.2.1 International Prostate Symptom Score

The International Prostate Symptom Score (IPSS) is an eight-item questionnaire, consisting of seven symptom questions and one QoL question [27]. The IPSS score is categorised as 'asymptomatic' (0 points), 'mildly symptomatic' (1-7 points), 'moderately symptomatic' (8-19 points) and 'severely symptomatic' (20-35 points). Limitations include lack of assessment of incontinence, post-micturition symptoms and bother caused by each separate symptom.

4.2.2 International Consultation on Incontinence Questionnaire for MLUTS

The International Consultation on Incontinence Questionnaire for MLUTS (ICIQ-MLUTS) was developed from the International Continence Society (ICS) male questionnaire. The ICIQ-MLUTS is a widely used and validated patient-completed questionnaire consisting of incontinence questions and bother for each symptom [28]. The questionnaire contains 13 items and is available in 24 languages [34]. The ICIQ-MLUTS more deeply explores the subtypes of MLUTS [35].

4.2.3 Danish Prostate Symptom Score

The Danish Prostate Symptom Score (DAN-PSS) [31] is a symptom score used mainly in Denmark and Finland. The DAN-PSS has 12 questions divided into parts A and B with questions on incontinence and measures the bother of each individual LUTS.

4.2.4 Symptoms of Lower Urinary Tract Dysfunction Research Network

The Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN-SI-10) correlates strongly with the IPSS but identifies additional important symptomatology including incontinence and bladder pain in men with LUTS [36].

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

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

4.3 Frequency volume charts and/or bladder diaries

The recording of the volume and time of each void by the patient is referred to as a FVC. Inclusion of additional information, such as fluid intake, use of pads, activities during recording, or that grades symptom severity and bladder sensation, is referred to as a bladder diary [3]. Parameters that can be derived from the FVC and bladder diary include daytime and night-time voiding frequency, total voided volume, the fraction of urine production during the night relative to the 24-hour urine volume (NP index) and volume of individual voids.

The mean 24-hour urine production is subject to considerable variation. Similarly, circumstantial influence and intraindividual variation cause FVC parameters to fluctuate, although comparatively little data is available to support this [37, 38]. The FVC/bladder diary is particularly relevant in nocturia, for which it underpins the categorisation of underlying mechanism(s) [39-41]. The use of FVCs may cause a 'bladder training (BT) effect' and influence the frequency of nocturnal voids [42].

The duration of the FVC/bladder diary needs to be long enough to avoid sampling errors, but short enough to avoid noncompliance [23]. An SR of the available literature recommended that FVCs should continue for at least three days [43]. No data is available as to whether the three days should be consecutive or scattered or whether it must be on weekdays or weekends, as long as it is representative. The ICIQ-Bladder diary (ICIQ-BD) is the only diary that has undergone full validation [44].

Summary of evidence	LE
Frequency/volume charts and/or bladder diaries provide real-time objective documentation of urinary symptoms and reduce recall bias.	3
Three-day FVCs provide reliable measurement of urinary symptoms in patients with LUTS similar to seven days and without losing the diagnostic accuracy.	2b

Recommendations	Strength rating
Use a bladder diary to assess male LUTS, particularly for nocturia.	Strong
Have the patient complete a bladder diary for at least three days.	Strong

4.4 Physical examination and digital rectal examination

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

4.4.1 Digital rectal examination and prostate size evaluation

Digital rectal examination (DRE) is the simplest way to assess prostate volume, but the correlation to prostate volume is poor. Quality-control procedures for DRE have been described [45]. Transrectal ultrasound (TRUS) is more accurate in determining prostate volume than DRE as a DRE underestimates prostate volume. The underestimation increases with increasing TRUS volume, particularly where the volume is > 30mL [46]. A model of visual aids has been developed to help urologists estimate prostate volume more accurately [47]. One study concluded that DRE was sufficient to discriminate between prostate volumes > or < 50mL [48].

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

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

4.5 Urinalysis

Urinalysis (dipstick or microscopy) must be included in the primary evaluation of any patient presenting with LUTS to identify conditions such as urinary tract infections (UTI), microhaematuria and diabetes mellitus. If abnormal findings are detected, further tests are recommended according to other EAU Guidelines, for example, Guidelines on Urinary Tract Cancers and Urological Infections [49-52].

In most Guidelines, urinalysis is recommended in the primary management of patients with LUTS [53, 54]. Limited evidence is available, but general expert consensus suggests that the benefits outweigh the costs [55]. The value of urinary dipstick/microscopy for diagnosing UTI in men with LUTS without acute frequency and dysuria has been questioned [56].

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

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

4.6 Prostate-specific antigen

4.6.1 Prostate-specific antigen and the prediction of prostatic volume

Pooled analysis of RCTs of men with LUTS and presumed BPO showed that prostate-specific antigen (PSA) has a good predictive value for assessing prostate volume, with areas under the curve (AUC) of 0.76-0.78 for various prostate volume thresholds (30mL, 40mL and 50mL). To achieve a specificity of 70% whilst maintaining a sensitivity of 65-70%, approximate age-specific criteria for detecting men with prostate glands exceeding 40mL are PSA > 1.6ng/mL, > 2.0ng/mL and > 2.3ng/mL for men with BPH in their 50s, 60s and 70s, respectively [57].

A strong association between PSA and prostate volume was found in a large community-based study in the Netherlands [58]. A PSA threshold value of 1.5ng/mL could best predict a prostate volume of > 30mL, with a positive predictive value (PPV) of 78%. The prediction of prostate volume can also be based on total and free PSA. Both PSA forms predict the TRUS prostate volume (± 20%) in > 90% of cases [59, 60].

4.6.2 Prostate-specific antigen and the probability of PCa

The EAU Guidelines on PCa present the role of PSA in the diagnosis of PCa [61]. The potential benefits and harms of using serum PSA testing to diagnose PCa in men with LUTS should be discussed with the patient.

4.6.3 Prostate-specific antigen and the prediction of BPO-related outcomes

Serum PSA is a stronger predictor of prostate growth than prostate volume [62]. In addition, an RCT showed that PSA also predicted the changes in symptoms, QoL/bother and maximum flowrate (Q_{max}) [63]. In a longitudinal study of men managed conservatively, PSA was a highly significant predictor of clinical progression to urinary retention [64, 65]. In the placebo arms of large double-blind studies, baseline serum PSA predicted the risk of AUR and BPO-related surgery [66, 67]. The Olmsted County Study also confirmed an equivalent link. The risk for treatment was higher in men with a baseline PSA of > 1.4ng/mL [68]. Patients with BPO appear to have a higher PSA level and larger prostate volumes. The PPV of PSA for the detection of BPO was recently shown to be 68% [69]. Moreover, in an epidemiological study, elevated free PSA levels could predict clinical BPE, independent of total PSA levels [70].

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

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

4.7 Renal function measurement

Renal function may be assessed by serum creatinine or estimated glomerular filtration rate (eGFR). Hydronephrosis, renal insufficiency or urinary retention are more prevalent in patients with signs or symptoms of BPO [71]. Although BPO may be responsible for these complications, no conclusive evidence is available on the mechanism [72].

One study reported that 11% of men with LUTS had renal insufficiency [71]. Neither symptom score nor QoL was associated with the serum creatinine level. Diabetes mellitus or hypertension were the most likely causes of the elevated creatinine concentration. Studies reported that non-neurogenic voiding dysfunction is not a risk factor for elevated creatinine levels [73]. It was concluded that only those with an elevated creatinine level or reduced eGFR require investigational ultrasound (US) of the kidney and bladder to assess post-void residual (PVR) [74].

In another study, a cross-sectional association was identified between signs and symptoms of BPO (although not prostate volume) and chronic kidney disease (CKD) [75]. In 2,741 consecutive patients who presented with LUTS, decreased maximum flow rate (Q_{max}), a history of hypertension and/or diabetes were associated with CKD [76]. Another study demonstrated a correlation between Q_{max} and eGFR in middle-aged men with moderate-to-severe LUTS [77]. Patients with renal insufficiency are at an increased risk of developing postoperative complications [78].

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

Recommendation	Strength rating
Assess renal function if renal impairment is suspected based on history and clinical examination, or in the presence of hydronephrosis, or when considering surgical treatment for male LUTS.	Strong

4.8 Post-void residual urine

Post-void residual urine can be assessed using transabdominal US, bladder scan or catheterisation. Post-void residual is not necessarily associated with BOO, since high PVR volumes can be a consequence of obstruction and/or poor detrusor function/DU [79, 80]. Using a PVR threshold of 50mL, the diagnostic accuracy of PVR measurement has a PPV of 63% and a negative predictive value (NPV) of 52% for the prediction of BOO [81]. A large PVR is not a contraindication to watchful waiting (WW) or medical therapy, although it may indicate a poor response to treatment and in particular to WW. In both the MTOPS and ALTESS studies, a high baseline PVR (PVR of ≥ 350mL) was associated with an increased risk of symptom progression [66, 67].

Monitoring of changes in PVR over time may allow for identification of patients at risk of AUR [82]. This is of importance for the treatment of patients using antimuscarinic medication. In contrast, baseline PVR has little prognostic value for the risk of BPO-related invasive therapy in patients on α1-blockers or WW [83]. However, due to large test-retest variability and lack of outcome studies, no PVR threshold for treatment decision has yet been established; this is a research priority.

Since the role of PVR in males with LUTS has given inconclusive data, bladder voiding efficiency (BVE) (voided volume/total bladder capacity × 100) has been introduced [84]. This parameter seems to be more reliable than PVR especially in patients with DU [85]. Together with BE, to overcome some limits of PVR, post-void residual urine ratio (PVR-R) was investigated. Post-void residual urine ratio represents the ratio of PVR to bladder volume (BV). This parameter indicates the non-functional bladder storage of urine after micturition and could be better related to voiding/emptying than the PVR *per se* and is defined as (PVR/total BV) × 100 [86].

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

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

4.9 Uroflowmetry

Urinary flow rate assessment is a widely used non-invasive urodynamic test. Key parameters are Q_{max}, voided volume, PVR and flow pattern. Uroflowmetry is best conducted with BVs > 150mL. Since Q_{max} is prone to within-subject variation [87, 88], and is affected by voided volumes, it is useful to repeat uroflowmetry measurements, especially if the voided volume is < 150mL, or Q_{max} or flow pattern is abnormal and not representative of the patient's normal voided volumes. Patients should also be asked whether the flow recorded during uroflowmetry reflects their usual voiding pattern at home, as this helps ensure that the results are interpreted in the right clinical context.

The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. A threshold Q_{max} of 10mL/s has a specificity of 70%, a PPV of 70% and a sensitivity of 47% for BOO. The specificity using a threshold Q_{max} of 15mL/s was 38%, the PPV 67% and the sensitivity 82% [89]. If Q_{max} is > 15mL/s, physiological compensatory processes mean that BOO cannot be excluded. Low Q_{max} can arise as a consequence of BOO [90], DU or an under-filled bladder [91]. Therefore, uroflowmetry is limited as a diagnostic test because it is unable to discriminate between the underlying mechanisms causing the low Q_{max}.

Uroflowmetry can be used for monitoring treatment outcomes [92] and correlating symptoms with objective findings [89, 93]. Recently, a deep-learning system for sound-based prediction of urinary flow has been proposed as a simple, home-based alternative to uroflowmetry with acceptable correlation to conventional test [94].

Summary of evidence	LE
The diagnostic accuracy of uroflowmetry for detecting BOO varies considerably and is substantially influenced by threshold values. Specificity can be improved by repeated flow rate testing.	2b

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

4.10 Imaging

4.10.1 Upper urinary tract

Men with LUTS are not at increased risk for upper tract malignancy or other abnormalities as compared to the overall population [74, 95-97]. Several arguments support the use of renal US in preference to urological computed tomography (UROCT). Ultrasound allows for better characterisation of renal masses, the possibility of investigating the liver and retroperitoneum, and simultaneous evaluation of the bladder, PVR and prostate, together with a lower cost, no radiation dose and less side effects [95]. Ultrasound can be used for the evaluation of men with large PVR, haematuria, or a history of urolithiasis.

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

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

4.10.2 Prostate

Imaging of the prostate can be performed by means of transabdominal US, TRUS, computed tomography (CT) and magnetic resonance imaging (MRI). However, in daily practice, prostate imaging is performed by transabdominal (suprapubic) US or TRUS [95].

4.10.2.a Prostate size and shape

Assessment of prostate size is important for the selection of interventional treatment, i.e. Open prostatectomy (OP), enucleation techniques, transurethral resection, transurethral incision of the prostate (TUIP) or minimally invasive therapies. Assessment of the prostate size is also important prior to treatment with 5α-reductase inhibitors (5-ARIs). Prostate volume predicts symptom progression and the risk of complications [97].

Transrectal US is superior to transabdominal volume measurement [98, 99]. The presence of a median lobe may guide treatment choice in patients scheduled for a minimally invasive approach, since median lobe presence can be a contraindication for some minimally invasive treatments (see Section 5.3).

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

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

4.10.3 Voiding cystourethrogram

Voiding cystourethrogram (VCUG) on its own is not recommended in the routine diagnostic workup of men with LUTS but may be useful for the detection of vesicoureteral reflux, bladder diverticula or urethral diseases and can be combined with urodynamics (UDS) in the form of Videourodynamics (VUDS). Retrograde urethrography may additionally be useful for the evaluation of suspected urethral strictures.

4.11 Urethrocystoscopy

Patients with a history of microscopic or gross haematuria, urethral stricture or bladder cancer who present with LUTS should undergo urethrocystoscopy during diagnostic evaluation. The evaluation of a prostatic middle lobe with urethrocystoscopy should be performed when considering interventional treatments for which the presence of middle lobe may affect the treatment offered.

A prospective study evaluated 122 patients with LUTS using uroflowmetry and urethrocystoscopy [100]. The preoperative Q_{max} was normal in 25% of 60 patients who had no bladder trabeculation, 21% of 73 patients with mild trabeculation, and 12% of 40 patients with marked trabeculation on cystoscopy. All 21 patients who presented with diverticula had a reduced Q_{max}.

Another study showed that there was no significant correlation between the degree of bladder trabeculation (graded from I to IV) and the preoperative Q_{max} value in 39 symptomatic men aged 53-83 years [101]. The largest study published on this issue examined the relation of urethroscopic findings to urodynamic studies in 492 elderly men with LUTS [102]. The authors noted a correlation between cystoscopic appearance (grade of bladder trabeculation and urethral occlusion) and urodynamic indices, DO and low compliance. It should be noted, however, that BOO was present in 15% of patients with normal cystoscopic findings, while 8% of patients had no obstruction, even in the presence of severe trabeculation [102].

Summary of evidence	LE
Men with a history of microscopic or visible haematuria, urethral stricture or bladder cancer who present with LUTS should undergo urethrocystoscopy during diagnostic evaluation.	3
No study clearly identified a strong association between the urethrocystoscopic and urodynamic findings.	3

Recommendation	Strength rating
Perform urethrocystoscopy in men with LUTS if the findings may change diagnosis or treatment.	Weak

4.12 Urodynamics

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

*4.12.1 **Diagnosing bladder outflow obstruction***

Pressure flow studies are used to diagnose and define the severity of BOO, which is characterised by increased detrusor pressure and decreased urinary flow rate during voiding. Bladder outflow obstruction/BPO must be differentiated from DU, which exhibits decreased detrusor pressure during voiding in combination with decreased urinary flow rate [3]. The bladder outlet obstruction index (BOOI) is calculated according to the equation detrusor pressure at a maximum flow rate ($p_{det}Q_{max}$-$2Q_{max}$) (BOO > 40 = obstructed; BOO 20-40 = equivocal; and BOO < 20 = unobstructed) [103], and to assess the contractility of the bladder, the blader contractility index (BCI) is calculated according to the equation $p_{det}Q_{max} + 5Q_{max}$ [104] (BCI > 150 = strong contractility, 100-150 = normal contractility, and < 100 = weak contractility) [84]. Deep learning algorithms can enhance diagnostic interpretation of urodynamic traces and even provide automated systems for accurately detecting and predicting between BOO and DU [104], however these are currently underdeveloped.

Urodynamic testing may also identify DO. Studies have described an association between BOO and DO [105, 106]. In men with LUTS attributed to BPO, DO was present in 61% and independently associated with BOO grade and ageing [105].

The prevalence of DU in men with LUTS is 11-40% [107, 108]. Detrusor contractility does not appear to decline in long-term BOO and surgical relief of BOO does not improve contractility [109, 110]. The UPSTREAM trial investigated whether UDS would reduce surgery without increasing urinary symptoms. The UPSTREAM trial was a non-inferiority RCT in men with bothersome LUTS, in whom surgery was an option, in 26 hospitals in England. In the UDS arm, 153/408 patients (38%) received surgery compared with 138/384 (36%) in the routine care (RC) arm. A total of 428 adverse events were recorded, with related events similar in both arms and 11 unrelated deaths. The UDS group was non-inferior to the RC group for IPSS, and UDS did not significantly reduce surgical rates. The authors concluded that routine use of UDS in the evaluation of uncomplicated LUTS has a limited role and should be used selectively [111]. However, in a prospective cohort study of urodynamically assessed patients prior to surgery, patients with DU alone with BCI < 100 and BOO index (BOOI) < 40 had significantly worse outcome with regard to postoperative maximum flow rate at 12 months than those with DU and BOO with BCI < 100 and BOOI ≥ 40, as well as patients with BOO alone with BCI ≥ 100 and BOOI ≥ 40 [112]. Nevertheless, if urodynamic investigation is performed, a rigorous quality control is mandatory [113, 114].

Exploratory findings from the UPSTREAM trial have characterised the basic diagnostic and urodynamic parameters to identify men who will benefit more from deobstructive surgery [114]. The investigators reported that surgery was more beneficial in those men with higher symptom scores (IPSS > 16), age < 74 years, poor urine flow (Q_{max} < 10mL/s), BOOI > 47.6 and BCI > 123.

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

Patients with neurological disease, including those with previous radical pelvic surgery, should be assessed according to the EAU Guidelines on Neuro-Urology [115].

*4.12.2 **Videourodynamics***

Videourodynamics provides additional anatomical and functional information and may be recommended if the clinician considers this necessary to understand the pathophysiological mechanism of an individual patient's LUTS. Only low-level evidence is available for the addition of imaging to UDS.

Summary of evidence	LE
Pressure-flow studies are not tests for routine use prior to prostate surgery for all patients.	3

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

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

4.13.1 Prostatic configuration/intravesical prostatic protrusion

Prostatic configuration can be evaluated with TRUS, using the concept of the presumed circle area ratio (PCAR) [116]. The PCAR evaluates how closely the transverse US image of the prostate approaches a circular shape. The ratio tends toward one as the prostate becomes more circular. The sensitivity of PCAR was 77% for diagnosing BPO when PCAR was > 0.8, with 75% specificity [116].

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

Intravesical prostatic protrusion correlates well with BOO, with a PPV of 94% and a NPV of 79% [117]. An SR examined the role of IPP in UDS determined BOO [118]. At cut-off > 10mm, the sensitivity was found to be 0.71 and the specificity 0.77. Intravesical prostatic protrusion may also correlate with prostate volume, DO, bladder compliance, detrusor pressure at maximum urinary flow, BOO index and PVR, and negatively correlates with Q_{max} [119]. Moreover, IPP also appears to successfully predict the outcome of a trial without catheter (TWOC) after AUR [120, 121]. Evidence from the above-mentioned SR showed that, at an IPP cut-off of > 10mm, the sensitivity and specificity to predict unsuccessful voiding TWOC was 0.51 and 0.79, respectively [118]. However, no information with regards to intra- or interobserver variability and learning curve is available as yet. Therefore, whilst IPP may be a feasible option to infer BPO in men with LUTS, the role of IPP as a non-invasive alternative to PFS in the assessment of MLUTS remains under evaluation.

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

For bladder wall thickness (BWT) assessment, the distance between the mucosa and the adventitia is measured. For detrusor wall thickness (DWT) assessment, the only measurement needed is the detrusor sandwiched between the mucosa and adventitia [122].

A correlation between BWT and UDS parameters has been reported. A threshold value of 5mm at the anterior bladder wall with a bladder filling of 150mL was best at differentiating between patients with or without BOO [123]. Detrusor wall thickness at the anterior bladder wall with a bladder filling > 250mL (threshold value for BOO > 2mm) has a PPV of 94% and a specificity of 95%, achieving 89% agreement with PFS [74]. Threshold values of 2.0, 2.5, or 2.9mm for DWT in patients with LUTS are able to identify 81%, 89% and 100% of patients with BOO, respectively [124]. A meta-analysis reported that DWT has high accuracy in diagnosing BOO with 71% sensitivity and 88% specificity [125].

All studies found that BWT or DWT measurements have a higher diagnostic accuracy for detecting BOO than Q_{max} or average flow rate (Q_{ave}) of free uroflowmetry, measurements of PVR, prostate volume or symptom severity. One study could not demonstrate any difference in BWT between patients with normal UDS, BOO or DO. However, the study did not use a specific bladder-filling volume for measuring BWT [126]. Disadvantages of the method include the lack of standardisation, and lack of evidence to indicate which measurement (BWT/DWT) is preferable [127]. Measurement of BWT/DWT is therefore not recommended for the diagnostic workup of men with LUTS.

Ultrasound-estimated bladder weight (UEBW) may identify BOO with a diagnostic accuracy of 86% at a cut-off value of 35g [128, 129]. Severe LUTS and a high UEBW (> 35g) are risk factors for prostate/BPO surgery in men on α-blockers [130].

4.13.3 Non-invasive pressure-flow testing

The penile cuff test (PCT), in which flow is interrupted to estimate isovolumetric bladder pressure, shows promising data, with good test repeatability [131] and interobserver agreement [132]. A nomogram has also been derived [133] whilst a method in which flow is not interrupted is also under investigation [134]. An SR and meta-analysis assessed the performance of PCT to recognise BOO, reported sensitivity 0.85, specificity 0.78, PPV 0.74 and NPV 0.87 [135]. However, there was marked heterogeneity among the included studies in the definition of obstruction.

The data generated with the external condom method [136] correlates with invasive PFS in a high proportion of patients [137]. Resistive index [138] and prostatic urethral angle [139] have also been proposed, but are still experimental.

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

An SR including 42 studies investigated the diagnostic performance of non-invasive tests in diagnosing BOO in men with LUTS compared with UDS/PFS [140]. The majority of the included studies were prospective cohorts, focusing on BOO and not specifically on BPO, and the diagnostic accuracy of the following non-invasive tests were assessed: PCT; uroflowmetry; DWT/BWT; bladder weight; external condom catheter method; IPP; Doppler US; prostate volume/height; and near-infrared spectroscopy. Overall, although the majority of studies have a low risk of bias, data regarding the diagnostic accuracy of these non-invasive tests is limited by the heterogeneity of the studies in terms of the threshold values used to define BOO, the various urodynamic definitions of BOO used across various studies and the small number of studies for each test. Specificity, sensitivity, PPV and NPV of the non-invasive tests were found to be highly variable. Therefore, even though several tests have shown promising results regarding non-invasive diagnosis of BOO, invasive UDS remains the modality of choice.

The diagnostic performance of non-invasive tests could theoretically be improved when two or more tests are combined along with clinical parameters, however, the evidence is still limited. Investigators have proposed a model and a clinical nomogram that uses BWT, prostate volume and PVR ratio to predict BOO with reported accuracy 0.82 [141].

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

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

4.14 Novel assessment

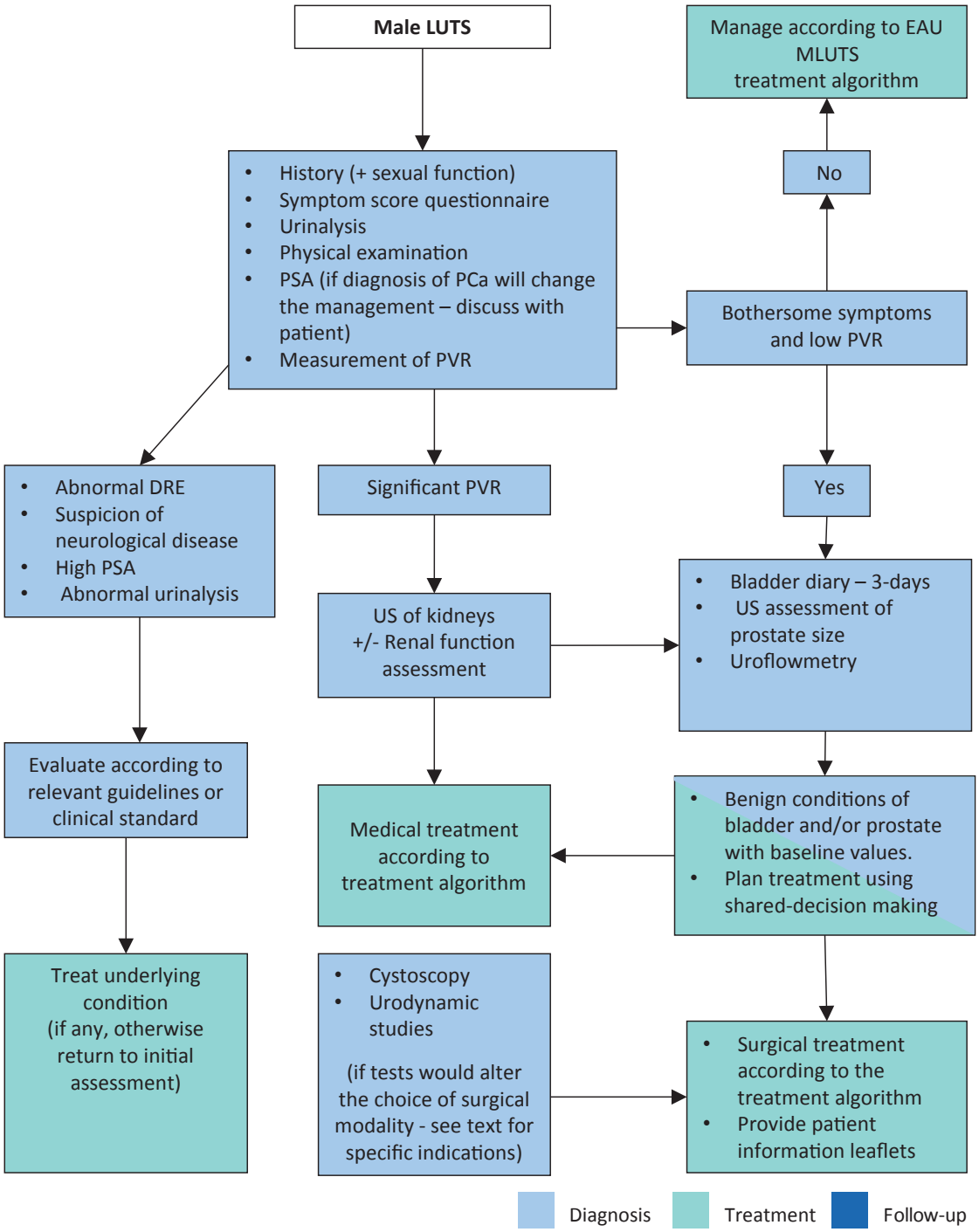
4.14.1 Visual prostate symptom score

A novel visual prostate symptom score (VPSS) has been prospectively tested versus the IPPS and correlated positively with the IPSS score [142, 143]. This visual score can be used as an option in men with limited literacy.

4.14.2 *MicroRNA*

The use of miR-221 has been shown to have the potential to be used as a biomarker and novel target in the early diagnosis and therapy of BPH [144].

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older



Readers are strongly recommended to read the full text that highlights the current position of each test in detail.

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

4.15 Prostate cancer

Incidental PCa is diagnosed in more than 5% of all patients undergoing surgery for BPO [145]. When identified, the possibility of extracapsular extension requires careful evaluation. Subsequent management should follow the recommendations outlined in the EAU Guidelines on Prostate Cancer [146].

5. DISEASE MANAGEMENT

5.1 Conservative treatment

5.1.1 Watchful waiting

Many men with LUTS are not troubled enough by their symptoms to require drug treatment or surgical intervention. All men with LUTS should be formally assessed prior to any allocation of treatment to establish symptom severity and to differentiate between men with uncomplicated (the majority) and complicated LUTS. Watchful waiting is a viable option for many men with non-bothersome LUTS, as few will progress to AUR and complications (e.g. renal insufficiency or stones) [147, 148], whilst others can remain stable for years [149]. In one study, approximately 85% of men with mild LUTS were stable on WW at one year [150].

A study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed the surgical group had improved bladder function (flow rates and PVR volumes), particularly in those with high levels of bother: 36% of WW patients crossed over to surgery within five years, leaving 64% doing well in the WW group [151, 152]. Increasing symptom bother and PVR volumes are the strongest predictors of WW failure. Men with mild-to-moderate uncomplicated LUTS who are not too troubled by their symptoms are suitable for WW.

5.1.2 Behavioural and dietary modifications

This type of management to includes the following components:

- education (regarding the patient's condition)
- reassurance (that cancer is not a cause of the urinary symptoms)
- periodic monitoring
- lifestyle advice [149, 150, 153, 154] concerning topics such as:
    - reduction of fluid intake at specific times aimed at reducing urinary frequency when most inconvenient (e.g. at night or when going out in public)
    - avoidance/moderation of intake of caffeine or alcohol, which may have a diuretic and bladder irritant effect, thereby increase fluid output and enhancing frequency, urgency and nocturia
    - use of relaxed and double-voiding techniques
    - urethral milking to prevent post-micturition dribble
    - distraction techniques, such as penile squeeze, breathing exercises, perineal pressure and mental tricks to take the mind off the bladder and toilet, to help control OAB symptoms
    - bladder retraining that encourages men to hold on when they have urgency to increase their bladder capacity and the time between voids
    - reviewing the medication and optimising the time of administration or substituting drugs for others that have fewer urinary effects (these recommendations apply in particular to diuretics)
    - providing necessary assistance when there is impairment of dexterity, mobility or mental state
    - treatment of constipation

Evidence exists showing that self-management as part of WW reduces both symptoms and progression [153, 154]. Men randomised to three self-care management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care only, for up to a year [153]. Two SRs and meta-analyses reported reasonable certainty in estimates that self-management interventions significantly reduced symptom severity in terms of IPSS at six months and improve QoL as compared to usual care [155, 156]. The reduction in IPSS score with self-management was similar to that achieved with drug therapy at six to twelve weeks. Self-management had a smaller, additional benefit at six weeks when added to drug therapy [155]. An RCT evaluating the addition of application-based therapeutic interventions (physical, psychological and behavioural) to standard medical care, reported significant improvements in IPSS, HRQoL, OAB-SF and overall QoL compared to medical care alone [157]. Providing patients with a standardised information booklet that offers guidance on conservative and lifestyle interventions has the potential to improve LUTS outcomes compared with usual care in the primary care setting, as supported by emerging evidence [158].

5.1.3 Practical considerations

The components of self-care management have not been individually studied. The above components of lifestyle advice have been derived from formal consensus methodology [159]. Further research in this area is required.

Summary of evidence	LE
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21% and 79% of patients were clinically stable.	1b
An additional study reported that 81% of patients were clinically stable on WW after a mean follow-up of 17 months.	2
Men randomised to three self-management sessions in addition to standard care had better symptom improvement and QoL than men treated with standard care alone at up to a year. Self-care management as part of WW reduces both symptoms and progression.	1b
Self-management achieved a clinically meaningful reduction in symptom severity at six months compared to usual care. There was also a small but significant additional benefit of adding self-management to drug therapy.	1b

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

5.2 Pharmacological treatment

5.2.1 α1-Adrenoceptor antagonists (α1-blockers)

Mechanism of action:

α1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and BOO [160]. However, α1-blockers have a small effect on urodynamically determined bladder outlet resistance [161], and treatment-associated improvement of LUTS correlates poorly with obstruction [162]. Therefore, other mechanisms of action may also be relevant.

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

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

Efficacy

All α1-blockers have a similar efficacy in appropriate doses [163] and the effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days [162].

Controlled studies show that α1-blockers typically reduce IPSS by approximately 30-40% and increase Q_{max} by approximately 20-25%. However, substantial improvements also occurred in the corresponding placebo arms [64, 164]. In open-label studies, an IPSS improvement of up to 50% and Q_{max} increase of up to 40% were documented [64, 164]. A SR and meta-analysis suggested that Q_{max} variation underestimates the real effect of α1-blockers on BPO, as small improvements in Q_{max} correspond to relevant improvements in BOO index in PFS [165].

An α1-blocker can reduce both storage and voiding LUTS. Prostate size does not affect α1-blocker efficacy in studies with follow-up periods of less than one year, but α1-blockers do appear to be more efficacious in patients with smaller prostates (< 40mL) in longer-term studies [66, 166-169]. The efficacy of α1-blockers is similar across age groups [164]. A pooled analysis of phase III and IV trials of silodosin 8mg demonstrated that improvements in total, storage, voiding and QoL IPSS scores were similar for the severe and not severe LUTS cohorts [170]. Reduction in IPPS and Q_{max} improvement during α1-blocker treatment appears to be maintained over at least four years [66]. In addition, α1-blockers neither reduce prostate size nor prevent AUR in long-term studies [167-169]. However, evidence suggests that the use of α1-blockers (alfuzosin, tamsulosin and silodosin) improves resolution of AUR [171, 172].

Tolerability and safety

Tissue distribution, subtype selectivity and pharmacokinetic profiles of certain formulations may contribute to the tolerability profile of specific drugs. The most frequent adverse events of α1-blockers are asthenia, dizziness and (orthostatic) hypotension. Vasodilating effects are most pronounced with doxazosin and terazosin and are less common with alfuzosin and tamsulosin [173]. Patients with cardiovascular comorbidity and/or vasoactive comedication may be susceptible to α1-blocker-induced vasodilatation [174]. In contrast, the frequency of hypotension with the α1A-selective blocker silodosin is comparable with placebo [175]. In a large retrospective cohort analysis of men aged > 66 years treated with α1-blockers, the risks of falling (odds ratio [OR] 1.14) and of sustaining a fracture (OR: 1.16) was increased, most likely as a result of induced hypotension [176]. In terms of cardiovascular risk, a large population-based study reported an increased risk of cardiac failure with long-term α-blocker use (hazard radio [HR]: 1.22), which was higher for non-selective α-blockers [177]. Whilst there has been concern about a possible risk of dementia with long-term use of α1-blockers, a large nationwide Finnish case-control study of 24,602 cases and 98,397 controls did not find evidence of a significant association [178].

An adverse ocular event termed intraoperative floppy iris syndrome (IFIS) was reported in 2005, affecting cataract surgery [179]. A meta-analysis on IFIS after alfuzosin, doxazosin, tamsulosin or terazosin exposure showed an increased risk for all α1-blockers [180]. However, the OR for IFIS was much higher for tamsulosin. It appears prudent not to initiate α1-blocker treatment prior to scheduled cataract surgery, and the ophthalmologist should be informed about α1-blocker use.

An SR concluded that α1-blockers do not adversely affect libido or erectile function but can cause abnormal ejaculation (OR: 7.53) [181]. Originally, abnormal ejaculation was thought to be retrograde, but more recent data demonstrate that abnormal ejaculation is due to a decrease or absence of seminal fluid during ejaculation, with young age being an apparent risk factor. In a meta-analysis, ejaculatory dysfunction (EjD) was significantly more common with α1-blockers than with placebo (OR: 5.88). In particular, EjD was significantly more commonly related with tamsulosin or silodosin (OR: 8.57 and 32.5) than placebo, while both doxazosin and terazosin (OR: 0.80 and 1.78) were associated with a low risk of EjD [182]. In the meta-regression, the occurrence of EjD was independently associated with the improvement of urinary symptoms and flow rate, suggesting that the more effective the α1-blocker is the greater the incidence of EjD.

Practical considerations

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

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

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

5.2.2 5α-reductase inhibitors

Mechanism of action

Androgen effects on the prostate are mediated by dihydrotestosterone (DHT), which is converted from testosterone by the enzyme 5α-reductase [183], and has two isoforms:

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

Two 5-ARIs are available for clinical use: dutasteride and finasteride. Finasteride inhibits only 5α-reductase type 2, whereas dutasteride inhibits both 5α-reductase types (dual 5-ARI). The 5-ARIs induce apoptosis of prostate epithelial cells [184] leading to prostate size reduction of approximately 18-28% and a decrease in circulating PSA levels of approximately 50% after six to twelve months of treatment [185]. Mean prostate volume and PSA reduction may be even more pronounced after long-term treatment. Continuous treatment reduces the serum DHT concentration by approximately 70% with finasteride and 95% with dutasteride. However, prostate DHT concentration is reduced to a similar level (85-90%) by both 5-ARIs.

Efficacy

Clinical effects relative to placebo are seen after treatment of at least six months. After two to four years of treatment, 5-ARIs improve IPSS by approximately 15-30%, decrease prostate volume by 18-28% and increase Q_{max} by 1.5-2.0mL/s in patients with LUTS due to BPE [66, 168, 169, 186-192]. An indirect comparison and one direct comparative trial (12 months duration) indicated that dutasteride and finasteride are equally effective in the treatment of LUTS [185, 193]. Symptom reduction depends on initial prostate size.

Finasteride may not be more efficacious than placebo in patients with prostates < 40mL [194]. However, dutasteride seems to reduce IPSS, prostate volume and the risk of AUR, and to increase Q_{max} even in patients with prostate volumes of between 30 and 40mL [195, 196]. A long-term trial with dutasteride in symptomatic men with prostate volumes > 30mL and increased risk for disease progression showed that dutasteride reduced LUTS at least as much as the α1-blocker tamsulosin [168, 192, 197]. The greater the baseline prostate volume (or serum PSA level), the faster and more pronounced the symptomatic benefit of dutasteride as compared to tamsulosin.

5α-reductase inhibitors, but not α1-blockers, reduce the long-term (> one year) risk of AUR or need for surgery [66, 190, 198]. In the PLESS study, finasteride reduced the relative risk of AUR by 57% and need for surgery by 55% (absolute risk reduction 4% and 7%, respectively) at four years compared with placebo [190]. In the MTOPS study, finasteride reduced the relative risk of AUR by 68% and need for surgery by 64% (absolute risk reduction 2% and 3%, respectively), also at four years [66]. A pooled analysis of three RCTs with two-year follow-up data reported that treatment with finasteride decreased the relative risk of AUR by 57% and surgical intervention by 34% (absolute risk reduction 2% for both) in patients with moderately symptomatic LUTS [199]. Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPO-related surgery. Open-label trials have demonstrated relevant changes in urodynamic parameters [200, 201]. A large Danish registry study reported that treatment with 5-ARI versus α-blocker monotherapy was associated with a reduced risk of BPO-related surgery and AUR for up to 15 years of follow-up, and the absolute risk reduction was 4% [202].

Additionally, finasteride might reduce blood loss during transurethral prostate surgery, probably due to its effects on prostatic vascularisation, although evidence for a clinically significant effect is mixed [203-205].

Tolerability and safety

The most common adverse events are reduced libido, ED and, less frequently, EjD such as retrograde ejaculation, ejaculation failure or decreased semen volume [66, 169, 185, 206]. Gynaecomastia (with breast or nipple tenderness) develops in 1-2% of patients. Two studies have suggested that treatment with 5-ARIs is associated with a higher incidence of high-grade cancers, although no causal relationship has been proven [207-209].

A long-standing debate has been ongoing regarding potential cardiovascular side effects of 5-ARIs, in particular dutasteride [210]. Population-based studies in Taiwan and Ontario did not find an association between the use of 5-ARIs and increased cardiovascular side effects [210, 211]. In a British-Taiwanese population-based cohort study, the risk of type II diabetes was higher in men with 5-ARIs than in men receiving tamsulosin, but did not differ between dutasteride and finasteride [212]. A large Swedish cohort study showed an increased risk of depression with both finasteride (HR 1.61) and dutasteride (HR 1.68), but no long-term association with dementia or suicide risk [213] . An SR found no association between 5-ARI use and depression or suicide risk [214]. However, the European Medicines Agency (EMA), based on an EU-wide review of available data, have issued a warning advising patients taking finasteride to stop treatment and seek medical advice if they experience depressed mood, depression or suicidal ideation [215].

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

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

5.2.3 Muscarinic receptor antagonists

Mechanism of action

The detrusor is innervated by parasympathetic nerves whose main neurotransmitter is acetylcholine, which stimulates muscarinic receptors (M-cholinoreceptors) on the smooth muscle cells. Muscarinic receptors are also present on other cell types, such as bladder urothelial cells and epithelial cells of the salivary glands. Five muscarinic receptor subtypes (M1-M5) have been described, of which M2 and M3 are predominant in the detrusor. The M2 subtype is more numerous, but the M3 subtype is functionally more important in bladder contractions [216, 217]. Antimuscarinic effects might also be induced or modulated through other cell types, such as the bladder urothelium or by the central nervous system [218, 219].

The following muscarinic receptor antagonists are licensed for treating OAB/storage symptoms: darifenacin hydrobromide (darifenacin); fesoterodine fumarate (fesoterodine); oxybutynin hydrochloride (oxybutynin); propiverine hydrochloride (propiverine); solifenacin succinate (solifenacin); tolterodine tartrate (tolterodine); and trospium chloride. Transdermal preparations of oxybutynin have been formulated and evaluated in clinical trials [220, 221].

Efficacy

A subanalysis of an open-label trial of OAB patients showed that age, but not gender, had an impact on urgency, frequency or urgency incontinence [222]. In a pooled analysis, which included a subanalysis of male patients, fesoterodine 8mg was superior to tolterodine extended release (ER) 4mg for the improvement of severe urgency episodes/24 hours and the OAB-q Symptom Bother score at week 12. The urinary retention rate was approximately 2% [223].

The efficacy of antimuscarinics as single agents in men with OAB in the absence of BOO have been tested [224-229]. Most trials lasted only 12 weeks. Four *post hoc* analyses of large RCTs on the treatment of OAB in women and men without presumed BOO were performed focusing only on the men [225, 230, 231]. Tolterodine can significantly reduce urgency incontinence, daytime or 24-hour frequency and urgency-related voiding whilst improving patient perception of treatment benefit [232]. Solifenacin significantly improved mean patient perception of bladder condition scores, mean OAB questionnaire scores and overall perception of bladder problems. Fesoterodine improved micturition frequency, urgency episodes and UUI episodes. In open-label trials with tolterodine, daytime frequency, nocturia, UUI and IPSS were significantly reduced compared with baseline values after 12 to 25 weeks [226, 229]. The TIMES RCT reported that tolterodine ER monotherapy significantly improved UUI episodes per 24 hours at week 12 compared to placebo. Tolterodine ER did not significantly improve urgency, IPSS total or QoL compared with placebo [228].

A further analysis showed that men with PSA levels of < 1.3ng/mL (smaller prostates) might benefit more from antimuscarinics [233]. Two other studies found a positive effect of antimuscarinics in patients with OAB and concomitant BPO [229, 234]. In a small RCT, propiverine improved frequency and urgency episodes [234].

Tolerability and safety

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

Increased PVR in men without BOO is minimal and similar to placebo. Nevertheless, fesoterodine 8mg showed higher PVRs (+20.2mL) than placebo (-0.6mL) or fesoterodine 4mg (+9.6mL) [226]. Incidence of urinary retention in men without BOO was similar to placebo for tolterodine (0-1.3% vs. 0-1.4%). With fesoterodine 8mg, 5.3% had symptoms, which was higher than placebo or fesoterodine 4mg (both 0.8%). These symptoms appeared during the first two weeks of treatment and mainly affected men aged 66 years or older.

Theoretically, antimuscarinics might decrease bladder strength, and hence might be associated with PVR or urinary retention. A 12 week safety study on men with mild-to-moderate BOO showed that tolterodine increased the PVR (49mL vs. 16mL) but not AUR (3% in both arms) [235]. The urodynamic effects included larger BVs at first detrusor contraction, higher maximum cystometric capacity and decreased BCI, Q_{max} was unchanged. This trial indicated that short-term treatment with antimuscarinics in men with BOO is safe [230].

Practical considerations

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

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

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

5.2.4 β_3 agonist

Mechanism of action

β_3 adrenoceptors are the predominant beta receptors expressed in the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. The mode of action of β_3 agonists is not fully elucidated [236].

Efficacy

Mirabegron 50mg is the first clinically available β_3 agonist with approval for use in adults with OAB. Mirabegron has undergone extensive evaluation in RCTs conducted in Europe, Australia, North America and Japan [237-241]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, including micturition frequency, urgency and UUI, and also patient perception of treatment benefit. These studies had a predominantly female study population. A meta-analysis of eight RCTs including 10,248 patients (27% male) found that mirabegron treatment resulted in reduced frequency, urgency and UUI rates, as well as an improved voided volume with a statistically significant improvement of nocturia compared with both placebo and tolterodine [242]. A meta-analysis of 28 RCTs of 27,481 patients also confirmed that mirabegron treatment resulted in reduced frequency, urgency and UUI rates when compared with placebo. Mirabegron 50mg significantly reduces micturition episodes per 24 hour compared with tolterodine [243].

Mirabegron has been evaluated in male patients with OAB in the context of LUTS either associated or not associated with BPO confirmed by UDS [244]. Mirabegron 25mg daily led to increased satisfaction and improved QoL, but symptoms assessed by validated questionnaires (IPSS and OAB-SS), only improved in non-obstructed patients. Mirabegron as an add-on therapy has been studied in OAB patients with incontinence despite antimuscarinic therapy [245], again in a predominantly female study population. An Asian study with a higher proportion of male subjects (approximately one third) reported superiority over placebo in reducing frequency of micturition but did not report the results separately for the genders [246].

In a study of more than 1,000 patients, of whom approximately 30% were male, combination therapy of mirabegron 25/50mg and solifenacin 5/10mg was associated with statistically significant improvements in patient outcomes and health-related QoL versus solifenacin 5mg and placebo, however, they did not separate out the effects in men and women [247]. In another study, in which 28% patients were male, mirabegron significantly improved patient-reported perception of their condition and QoL, whether patients were incontinent or not [248]. A phase IV study with a small proportion of male subjects reported addition of mirabegron in people with persisting urgency despite solifenacin in a Japanese population [249].

An RCT has suggested Mirabegron might lead improvement of urinary symptoms and sexual function in patients suffering from BPO and concurrent erectile dysfunction (ED) [250]. The study showed a significant improvement in the IIEF-15 total score and IPSS score in patients treated with Mirabegron + Doxazosin [250]. Nevertheless, further multicentre RCTs with large numbers of patients are required to consolidate these data.

Tolerability and safety

The most common treatment-related adverse events in the mirabegron groups were hypertension, UTI, headache and nasopharyngitis [237-240]. Mirabegron is contraindicated in patients with severe uncontrolled hypertension (systolic blood pressure ≥ 180mmHg or diastolic blood pressure ≥ 110mmHg or both). Blood pressure should be measured before starting treatment and should be monitored regularly during treatment. A combination of 13 clinical studies including 13,396 patients, 25% of whom were male, showed that OAB treatments (anticholinergics or mirabegron) were not associated with an increased risk of hypertension or cardiovascular events compared to placebo [251]. The proportion of patients with dry mouth and constipation in the mirabegron groups was notably lower than reported in RCTs of other OAB agents or of the active control tolterodine [237]. Evaluation of urodynamic parameters in men with combined BOO and OAB concluded that mirabegron did not adversely affect voiding urodynamic parameters compared to placebo in terms of Q_{max}, detrusor pressure at maximum flow and BCI [252]. The overall change in PVR with mirabegron is small [252].

A small prospective study (mainly focused on males) has shown that mirabegron 25mg is safe in patients aged 80 years and above with multiple comorbidities [253]. A pooled analysis of three trials, each of 12 weeks, and a one-year trial, showed a more favourable tolerability profile for mirabegron than antimuscarinics in patients aged > 65 years [254]. The PILLAR phase IV study also showed that, in a large population of 888 patients ≥ 65 years (approximately 30% of males), mirabegron 50mg was safe and effective [255]. In an 18-week study of 3,527 patients (23% male), the incidence of adverse events was higher in the combination (solifenacin 5mg plus mirabegron 25mg) group (40%) than the group prescribed mirabegron 25mg alone (32%). Events recorded as urinary retention were low (< 1%) but were reported slightly more frequently in the combined group when compared with the monotherapy and placebo groups. The PVR volume was slightly increased in the combined group compared with solifenacin 5mg and the mirabegron monotherapy and placebo groups. Combined therapy with solifenacin 5mg plus mirabegron 25mg and solifenacin 5mg plus mirabegron 50mg provided improvements in efficacy generally consistent with an additive effect [256].

In a retrospective analysis of persistence and adherence in 21,996 patients, 30% of whom were male, the median time to discontinuation was significantly longer for mirabegron (169 days) compared to tolterodine (56 days) and other antimuscarinics (30-78 days). There was no statistical difference between men and women [257].

The phase III EMPOWUR trial comparing vibegron to placebo and tolterodine showed once daily 75mg vibegron provided statistically significant reductions in micturitions, urgency episodes and UUI [258]. Treatment was well tolerated, with a favourable safety profile. However, the majority of the study population (85%) were female.

Practical considerations

Long-term studies on the efficacy and safety of mirabegron in men with LUTS are not yet available. Available studies on mirabegron in combination with antimuscarinics in OAB patients had a predominantly female study population, while further trials are still pending. Further evidence in male patients using vibegron is awaited.

Summary of evidence	LE
β_3 agonists improve storage LUTS, including urinary frequency, urgency and UUI.	2
Patients prescribed mirabegron remained on treatment longer than those prescribed antimuscarinics.	3

Recommendation	Strength rating
Use β_3 agonists in men with moderate-to-severe storage LUTS.	Weak

**Further evidence is awaited for vibegron.*

5.2.5 *Phosphodiesterase type 5 inhibitors*

Mechanism of action

Phosphodiesterase type 5 inhibitors (PDE5Is) increase intracellular cyclic guanosine monophosphate, thus reducing smooth muscle tone of the detrusor, prostate and urethra. Nitric oxide and PDE5Is might also alter reflex pathways in the spinal cord and neurotransmission in the urethra, prostate or bladder [259]. Moreover, chronic treatment with PDE5Is appears to increase blood perfusion and oxygenation in the LUT [260]. Phosphodiesterase type 5 inhibitors could also reduce chronic inflammation in the prostate and bladder [261]. The exact mechanism of PDE5Is on LUTS remains unclear.

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

Efficacy

Randomised controlled trials have demonstrated that PDE5Is reduce IPSS, storage and voiding LUTS and improve QoL. However, Q_{max} did not significantly differ from placebo in most trials [262]. A Cochrane review included a total of 16 RCTs that examined the effects of PDE5Is compared to placebo and other standard of care drugs (α1-blockers and 5-ARIs) in men with LUTS [263]. In the updated meta-analysis, PDE5Is led to a small reduction (mean difference [MD] 1.89 lower; 95% confidence interval [CI]: 2.27 to 1.50 lower; n = 4293) in IPSS compared to placebo [263]. There was no difference between PDE5Is and α1-blockers in IPSS [264]. Most evidence was limited to short-term treatment up to 12 weeks. In other meta-analyses, PDE5Is were also found to improve IPSS and IIEF score, but not always Q_{max} [265, 266]. A meta-regression suggested that younger men with low body mass index and more severe LUTS benefit the most from treatment with PDE5Is [265].

In a *post hoc* analysis of data pooled from four blinded trials of tadalafil 5mg versus placebo once daily, a minimum improvement of 25% in IPSS score was found in 60% in the tadalafil and in 44% in the placebo group [267]. The maximum trial duration was 52 weeks [268]. A subgroup analysis of pooled data from four RCTs demonstrated a significant reduction in LUTS, regardless of baseline severity, age, previous use of α-blockers or PDE5Is, total testosterone level or predicted prostate volume [269]. In a *post hoc* analysis of pooled data from four RCTs, tadalafil was shown to also be effective in men with cardiovascular risk factors/comorbidities, except for patients receiving more than one antihypertensive medication. Among sexually active men > 45 years, tadalafil improved both LUTS/BPH and ED [269].

An integrated data analyses from four placebo controlled clinical studies showed that total IPSS improvement was largely attributed to direct (92.5%) versus indirect (7.5%) treatment effects by means of IIEF-erectile function improvement [270]. Another analysis showed a small but significant increase in Q_{max} without any effect on PVR [271]. An integrated analysis of RCTs showed that tadalafil was not superior to placebo for IPSS improvement at 12 weeks in men ≥ 75 years (with varied effect size between studies), but was for men < 75 years [272]. An open label urodynamic study of 71 patients showed significant improvements in both voiding and storage symptoms, confirmed by improvements in BOO index (61.3 to 47.1), and resolution of DO in 15 (38%) of 38 patients. Flow rate improved from 7.1 to 9.1mL/s and mean IPSS from 18.2 to 13.4 [273].

A multicentre, double blind, placebo controlled RCT compared once daily tadalafil 20mg versus placebo during 12 weeks in men with LUTS with or without BOO. Urodynamic measures including detrusor pressure at maximum urinary flow rate, Q_{max}, maximum detrusor pressure, BOO or bladder capacity remained largely unchanged during the study with no statistically significant or clinically adverse event differences between tadalafil and placebo [274].

A study has shown that, in patients with OAB and LUT obstruction unresponsive to previous treatment, the simultaneous administration of solifenacin, tadalafil and dutasteride could be an effective and safe choice [275].

Tolerability and safety

Reported adverse effects in RCTs comparing the effect of all PDE5Is versus placebo in men with LUTS, include flushing, gastroesophageal reflux, headache, dyspepsia, back pain and nasal congestion [265].

Tadalafil is contraindicated in patients using nitrates or guanylate cyclase stimulators, such as Riociguat, and in men with cardiac disease for whom sexual activity is inadvisable [276]. Tadalafil is also contraindicated in patients with myocardial infarction within the last 90 days; patients with unstable angina or angina occurring during sexual intercourse; patients with New York Heart Association Class 2 or greater heart failure in the last six months; patients with uncontrolled arrhythmias, hypotension (< 90/50mm Hg), or uncontrolled hypertension; patients with a stroke within the last six months; or if anterior ischaemic optic neuropathy with sudden loss of vision is known or was reported after previous use of PDE5Is [276]. Detailed information regarding tolerability/safety of all available PDE5Is for the treatment of ED in men treated with α-blockers for LUTS are provided in the EAU Guidelines on Sexual and Reproductive Health [277].

Practical considerations

To date, only tadalafil 5mg once daily has been officially licensed for the treatment of MLUTS with or without ED. Long-term experience with tadalafil in men with LUTS is limited to one trial with a one-year follow-up [268], limiting conclusions about efficacy or tolerability greater than one year. There is limited information available on reduction of prostate size and no data on disease progression.

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

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

5.2.6 Plant extracts - phytotherapy

Potential mechanism of action

Herbal drug preparations are made of roots, seeds, pollen, bark or fruits. Single plant preparations (monopreparations) and preparations are available that combine two or more plants in one pill (combination preparations) [278].

Possible relevant compounds include phytosterols, ß-sitosterol, fatty acids and lectins [278]. *In vitro*, plant extracts can have anti-inflammatory, antiandrogenic and oestrogenic effects; decrease sexual hormone-binding globulin; inhibit aromatase, lipoxygenase, growth factor-stimulated proliferation of prostatic cells, α-adrenoceptors, 5 α-reductase, muscarinic acetylcholine receptors, dihydropyridine receptors and vanilloid receptors; and neutralise free radicals [273, 278, 279]. The *in vivo* effects of these compounds are uncertain, and the precise mechanisms of plant extracts remain unclear.

Efficacy

The extracts of the same plant produced by different companies do not necessarily have the same biological or clinical effects. Therefore, the effects of one brand cannot be extrapolated to others [280]. In addition, batches from the same producer may contain different concentrations of active ingredients [281]. A review of recent extraction techniques and their impact on the composition/biological activity of available Serenoa repens-based products showed that results from different clinical trials must be compared strictly according to the same validated extraction technique and/or content of active compounds [282], because the pharmacokinetic properties of the various preparations can vary significantly.

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

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

Table 1: European Union monographs for herbal medicinal products [283]

Herbal substance	HMPC evaluation	Therapeutic Indication by HMPC	Date of monograph
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: hexane [284]	Well-established use	Symptomatic treatment of BPH	14/01/2016 Addendum 1/9/21**
Serenoa repens, fructus (saw palmetto, fruit) Extraction solvent: ethanol [284]	Traditional use	LUTS related to BPH*	14/01/2016 Addendum 1/9/21**
Cucurbita pepo L, semen (pumpkin seed) Preparation as defined in the monograph [285]	Traditional use	LUTS related to BPH or related to an OAB*	25/03/2013 Call ended 30/4/21
Prunus africana (Hook f.) Kalkm., cortex (pygeum africanum bark) Preparation as defined in the monograph [286]	Traditional use	LUTS related to BPH*	01/09/2017 No call for update
Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix Preparation as defined in the monograph [287]	Traditional use	LUTS related to BPH*	05/11/2012 Call ended 30/6/21
Epilobium angustifolium L. and/or Epilobium parviflorum Schreb., herba (Willow herb) Preparation as defined in the monograph [288]	Traditional use	LUTS related to BPH*	13/01/2016 No call for update

**After serious conditions have been excluded by a medical doctor.*
***Addendum concluded that no revision was required.*

Panel interpretation

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

A large meta-analysis of 30 RCTs with 5,222 men and follow-up ranging from four to 60 weeks demonstrated no benefit of treatment with *S. repens* in comparison to placebo for the relief of LUTS [289]. It was concluded that *S. repens* was not superior to placebo, finasteride or tamsulosin with regard to IPSS improvement, Q_{max} or prostate size reduction. However, the similar improvement in IPSS or Q_{max} compared with finasteride or tamsulosin could be interpreted as treatment equivalence. Importantly, in the meta-analysis, various brands of *S. repens* were included regardless of the presence of HESr as the main ingredient in the extract.

Another SR focused on data from 12 RCTs on the efficacy and safety of HESr [290]. This review concluded that HESr was superior to placebo in terms of improvement of nocturia and Q_{max} in patients with enlarged prostates. Improvement in LUTS was similar to tamsulosin and short-term use of finasteride. An updated SR analysed 15 RCTs and also included 12 observational studies. The review confirmed the results of the previous SR on the efficacy of HESr [291]. Compared with placebo, HESr was associated with 0.64 (95% CI: 0.98-0.31) fewer voids/night and an additional mean increase in Q_{max} of 2.75mL/s (95% CI: 0.57-4.93); both were significant. When compared with α-blockers, HESr showed similar improvements in IPSS (WMD 0.57; 95% CI: 0.27-1.42) and a comparable increase in Q_{max} when compared to tamsulosin (WMD 0.02; 95% CI: 0.71-0.66). Efficacy assessed using IPSS was similar after six months of treatment between HESr and 5-ARIs. Analysis of all available published data for HESr showed a mean significant improvement in IPSS from baseline of 5.73 points (95% CI: 6.91-4.54) [291].

A network meta-analysis tried to compare the clinical efficacy of *S. repens* (HESr and non-HESr) against placebo and α1-blockers in men with LUTS. Interestingly, only two RCTs on HESr were included in the analysis. The results of the analysis showed that *S. repens* achieved no clinically meaningful improvement against placebo or α1-blockers in short-term follow-up. However, *S. repens* showed a clinical benefit after a prolonged period of treatment, and HESr demonstrated a greater improvement than non-HESr in terms of IPSS [292].

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

A cross-sectional study compared the combination of HESr with silodosin-to-silodosin monotherapy in patients treated for at least 12 months (mean duration 13.5 months) [293]. It was reported that 69.9% of the combination therapy patients achieved the predefined clinically meaningful improvement (improvement of more than three points in baseline IPSS) compared to 30.1% of patients treated with silodosin only. In addition, a greater than 25% improvement in IPSS was found in 68.8% and 31.2% of the patients in the combination and the monotherapy groups, respectively. These data suggest that a combination of an α1-blocker with HESr may result in greater clinically meaningful improvements in LUTS compared to α1-blocker monotherapy [293].

Practical considerations

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

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

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

5.2.7 Combination therapies

5.2.7.a α1-blockers + 5α-reductase inhibitors

Mechanism of action

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

Efficacy

Several studies have investigated the efficacy of combination therapy against an α1-blocker, 5-ARI or placebo alone. Initial studies with follow-up periods of six to twelve months demonstrated that the α1-blocker was superior to finasteride in symptom reduction, whereas combination therapy of both agents was not superior to α1-blocker monotherapy [187, 188, 294]. In studies with a placebo arm, the α1-blocker was consistently more effective than placebo, but finasteride was not. Data at one year in the MTOPS study showed similar results [66].

Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery [66, 168, 169].

The CombAT study demonstrated that combination treatment is superior to either monotherapy regarding symptoms and flow rate starting from month nine, and superior to α1-blocker for AUR and the need for surgery after eight months [169]. The differences in MTOPS may therefore reflect different inclusion and exclusion criteria and baseline patient characteristics.

Discontinuation of the α1-blocker after six to nine months of combination therapy was investigated in an RCT and an open-label multicentre trial [295, 296]. The first trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after six months [295], with nearly three quarters of patients reporting no worsening of symptoms. However, patients with severe symptoms (IPSS > 20) at baseline may benefit from longer combination therapy.

A trial evaluated the symptomatic outcome of finasteride monotherapy at three and nine months after discontinuation of nine-month combination therapy [296]. Lower urinary tract symptom improvement after combination therapy was sustained at three months (IPSS difference 1.24) and nine months (IPSS difference 0.4). The limitations of studies include short duration and short follow-up period after discontinuation.

In both the MTOPS and CombAT studies, combination therapy was superior to monotherapy in preventing clinical progression as defined by an IPSS increase of at least four points, AUR, UTI, incontinence or an increase in creatinine > 50%. The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy versus placebo and to a greater extent than with either finasteride or doxazosin monotherapy (34% and 39%, respectively) [66]. In addition, finasteride (alone or in combination), but not doxazosin alone, significantly reduced both the risks of AUR and the need for BPO-related surgery over the four-year study. In the CombAT study, combination therapy reduced the relative risks of AUR by 68%, BPO-related surgery by 71% and symptom deterioration by 41% compared with tamsulosin, after four years [297]. To prevent one case of urinary retention and/or surgical treatment, 13 patients need to be treated for four years with dutasteride and tamsulosin combination therapy compared to tamsulosin monotherapy, while the absolute risk reduction (risk difference) was 7.7%.

The CONDUCT study compared efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin to a WW approach with the potential initiation of tamsulosin (step-up approach) in a two-year RCT with a total of 742 patients. In both arms, detailed lifestyle advice was given. This fixed-dose combination resulted in a rapid and sustained improvement in men with moderate LUTS at risk of disease progression - the difference in IPSS at 24 months was 5.4 in the active arm and 3.6 in the placebo arm [298]. Moreover, tamsulosin plus dutasteride significantly reduced the relative risk of clinical progression (mainly characterised as a worsening in symptoms) by 43.1% when compared with WW, with an absolute risk reduction of 11.3% (number needed to treat [NNT] = 9).

The influence of baseline variables on changes in IPSS after combination therapy with dutasteride plus tamsulosin or either monotherapy was tested based on the four-year results of the CombAT study. Combination therapy provided consistent improvement of LUTS over tamsulosin across all analysed baseline variables at 48 months [299].

A combination of the 5-ARI finasteride and tadalafil 5mg was tested in a large-scale RCT against finasteride monotherapy. This study supports the concept of this novel combination therapy and is described in more detail in Section 5.2.5 [300].

Tolerability and safety

Adverse events for both drug classes have been reported with combination treatment [66, 168, 169]. The adverse events observed during combination treatment were typical of α1-blockers and 5-ARIs. The frequency of adverse events was significantly higher for combination therapy. The MTOPS study demonstrated that the incidence of treatment-related adverse events is higher during the first year of combined treatment between doxazosin and finasteride [301]. A meta-analysis measuring the impact of medical treatments for LUTS/BPH on ejaculatory function reported that combination therapy with α1-blockers and 5-ARIs resulted in a threefold increased risk of EjD compared with each monotherapy [182].

Practical considerations:

Compared with α1-blockers or 5-ARI monotherapy, combination therapy results in a greater improvement in LUTS and increase in Q_{max} and is superior in prevention of disease progression. However, combination therapy is also associated with a higher rate of adverse events. Combination therapy should therefore be prescribed primarily in men who have moderate-to-severe LUTS who are at risk of disease progression (higher prostate volume, higher PSA concentration, advanced age, higher PVR, lower Q_{max}, etc.). Combination therapy should only be used when long-term treatment (more than 12 months) is intended, and patients should be informed of this.

Summary of evidence	LE
Long-term data (four years) from the MTOPS and CombAT studies showed that combination treatment is superior to monotherapy for symptoms and Q_{max}, and superior to α1-blocker alone in reducing the risk of AUR or need for surgery.	1b
The MTOPS study found that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy versus placebo and to a greater extent than with either finasteride or doxazosin monotherapy.	1b
The CombAT study found that combination therapy reduced the relative risks of AUR by 68%, BPH-related surgery by 71% and symptom deterioration by 41% compared with tamsulosin after four years.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and 5-ARIs.	1b

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

5.2.7.b α1-blockers + muscarinic receptor antagonists

Mechanism of action

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

Efficacy

Several RCTs and prospective studies investigated combination therapy lasting four to twelve weeks, either as an initial treatment in men with OAB and presumed BPO or as a sequential treatment for storage symptoms persisting while on an α1-blocker [221, 232, 297, 302-306]. Combination treatment has marginal efficacy in reducing urgency, UUI, voiding frequency, nocturia or IPSS compared with α1-blockers or placebo alone and improves QoL [232, 306]. An SR and meta-analysis of RCTs (six studies of treatment-naïve patients and five studies of men with persistent storage LUTS, despite prior treatment with α-blockers) concluded that the addition of antimuscarinics to α-blockers marginally reduced the number of micturition episodes per day (standard MD -0.19) but did not have a significant impact on the number of urgency episodes, and had a higher side-effect profile [307]. Similar findings were also reported in a Cochrane review of RCTs of men with LUTS secondary to BPO, with a small improvement in IPSS (MD 2.04) and QoL (MD 0.71) with combination therapy compared to α-blocker monotherapy, although overall certainty of evidence (COE) was deemed moderate to very low [308].

Symptom improvement is higher regardless of PSA concentration with combination therapy, whereas tolterodine alone improved symptoms mainly in men with a serum PSA of < 1.3ng/mL [233].

In a meta-analysis of 16 studies with 3,548 patients with BPH/OAB, initial combination treatment of an α1-blocker with anticholinergic medication showed no difference in total IPSS and Q_{max} between the two group [309].

Effectiveness of therapy is evident primarily in those men with moderate-to-severe storage LUTS [310]. Long-term use of combination therapy has been reported in patients receiving treatment for up to one year, showing symptomatic response is maintained, with a low incidence of AUR [311]. In men with moderate-to-severe storage symptoms, voiding symptoms and PVR < 150mL, the reduction in symptoms using combination therapy is associated with patient-relevant improvements in health-related QoL compared with placebo and α1-blocker monotherapy [312].

Combined behavioural and drug therapy yielded greater improvements in OAB symptoms than drug therapy alone, but not behavioural therapy alone in an RCT evaluating the effectiveness of combined behavioural strategies and drug therapy for OAB symptoms in men [313].

Tolerability and safety

Adverse events of both drug classes are seen with combined treatment using α1-blockers and antimuscarinics. The most common side effect is dry mouth. Some side effects (e.g. dry mouth or ejaculation failure) may show increased incidence which cannot simply be explained by summing the incidence with the drugs used

separately. Increased PVR may be seen, but is usually not clinically significant, and risk of AUR is low up to one year of treatment [228, 314, 315]. Antimuscarinics do not cause evident deterioration in Q_{max} used in conjunction with an α1-blocker in men with OAB symptoms [306, 316].

An RCT investigated safety in terms of maximum detrusor pressure and Q_{max} for solifenacin (6mg or 9mg) with tamsulosin in men with LUTS and BOO compared with placebo [317]. The combination therapy was noninferior to placebo for the primary urodynamic variables and Q_{max} was increased versus placebo [317].

Practical considerations

Class effects are likely to underlie efficacy and QoL using an α1-blocker and antimuscarinic. Trials mainly used storage symptom endpoints, were of short duration, and included only men with low PVR volumes at baseline. Measuring PVR is therefore recommended during combination treatment.

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

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

5.2.7.c α1-blockers + Beta-3 agonist

Mechanism of action

Combination therapy consists of an α1-blocker (Section 5.2.1) together with a β_3-agonist (Section 5.2.4) as an add-on therapy in males receiving α1-blockers with persisting OAB symptoms.

Efficacy

The MATCH study explored the effect of the addition of mirabegron 50mg to tamsulosin 0.2mg compared to tamsulosin plus placebo in 544 patients [318]. A statistically significant difference of 0.52 voids per day was seen in favour of mirabegron. Total IPSS score also improved but was not significant between the groups. Another RCT evaluated add-on therapy with mirabegron for OAB symptoms persisting after treatment with tamsulosin 0.2mg daily in men with BPO [319]. Combination therapy was associated with greater improvements in OAB symptom score, in urinary urgency and daytime frequency, as well as the storage subscore of IPSS and QoL index compared to monotherapy with tamsulosin [320].

The PLUS phase IV trial [319] compared mirabegron and placebo in a population of males treated with a standard dose of tamsulosin 0.4mg. After a four-week run-in period of treatment with tamsulosin 0.4mg alone, 715 patients were randomised between placebo and mirabegron 25mg, upgraded to 50mg after one month. While mean number of micturition's was significantly reduced in the experimental arm, the effect size was deemed as low (mean adjusted difference of 0.39 voids per day). Similar results were seen for mean voided volume and urgency episodes, but total IPSS, IPSS subscores and OAB-q symptom score were not significantly different between the groups.

An RCT comparing the efficacy of mirabegron 50mg or fesoterodine 4mg add-on therapy to silodosin in LUTS patients with persisting OAB symptoms reported that, at three months, fesoterodine add-on therapy showed a significantly greater improvement than mirabegron add-on therapy in OAB symptom score and urgency score and IPSS-QoL [247]. Fesoterodine was also superior in alleviating DO.

An RCT (the COURAGE trial) comparing the efficacy of vibegron 75mg versus placebo as add-on therapy to an α1-blocker (initiated > three months before screening) with or without a 5 α-reductase inhibitor (initiated > six months before screening) in LUTS patients with persisting OAB symptoms, reported that vibegron add-on therapy showed a significantly greater improvement at 12 weeks than placebo in daily micturition's and urgency episodes. Vibegron was also associated with significant improvements versus placebo at week 12 in nocturia and UUI episodes, in IPSS storage score changes and volume voided [321].

Tolerability and safety

In the MATCH study, main adverse events were in line with previous trials, and cardiovascular events were uncommon in the studied populations [318]. The PLUS phase IV trial also reported adverse events similar to those seen in previous trials (hypertension, headache and nasopharyngitis being the most frequent) [319]. Six episodes of retention were recorded (1.7%), and overall, no clinically significant specific change was seen in Q_{max} and PVR. An open-label, randomised, two-arm, two-sequence study reported that the addition of mirabegron or tamsulosin to patients under tamsulosin or mirabegron monotherapy did not cause clinically relevant changes in cardiovascular safety or safety profiles [322].

Solifenacin and mirabegron were also compared in another RCT that has shown comparable efficacy, but a better safety profile for mirabegron [323].

In the COURAGE trial, adverse events, including hypertension and UTI, occurred at similar rates in vibegron and placebo arms. Urinary retention occurred in < 1% of patients in both arms [321].

Practical consideration

Add-on therapy with β_3 agonists in patients with remaining symptoms under α1-blocker therapy has been evaluated only in short-term clinical trials. The short-term benefit remains uncertain, with a low effect size in urinary frequency compared to placebo, and more studies with longer follow-up are required.

Summary of evidence	LE
Combination treatment with α1-blockers and β_3 agonists results in a slight decrease in number of voids and urgency episodes per day compared with α1-blockers alone.	1b
Adverse events of both drug classes are seen with combined treatment using α1-blockers and mirabegron.	1b

Recommendation	Strength rating
Use combination treatment of a α1-blocker with β_3 agonists in patients with persistent storage LUTS after treatment with α1-blocker monotherapy.	Weak

5.2.7.d α1-blockers + Phosphodiesterase type 5 inhibitors

Mechanism of action

Combination treatment consists of an α1-blocker together with a PDE5I (Section 5.2.5) with the intent to achieve better improvements in LUTS.

Efficacy

A meta-analysis of five RCTs (two studies with tadalafil 20mg daily, two with sildenafil 25mg, and one with vardenafil 20mg) showed that combination therapy significantly improved IPSS score (-1.8), IIEF score (+3.6) and Q_{max} (+1.5mL/s) compared with α-blockers alone [265]. Both an SR and Cochrane review found similar findings, and a network meta-analysis of 55 RCTs (excluding 5-ARIs) found that the combination of PDE5Is and α-blockers had greater IPSS improvement than monotherapy and any other combination therapy [263, 324, 325]. These results have been confirmed by recent prospective studies, which have shown an improvement in the IPSS QoL, IIEF-5 score and Q_{max} in patients taking PDE5Is and α-blockers [262, 326].

Tolerability and safety

No serious adverse events have been reported in the association of PDE5Is and α-blockers. In RCTs comparing α-blockers alone with combined therapy, adverse events occur with similar incidence across the two treatment arms, suggesting that the addition of PDE5Is to α-blockers is well tolerated [324].

Practical consideration

The combination of α-blockers and PDE5Is versus α-blockers monotherapy leads to greater improvements in LUTS, QoL, erectile function and Q_{max} without increase in adverse events.

Data from meta-analyses suggest that younger men with low body mass index and more severe LUTS may be the population that benefits most from this association [265]. However, further studies with large populations and longer follow-up are needed to confirm these findings.

Summary of evidence	LE
Combination of PDE5Is and α-blockers improves IPSS, but magnitude of effect is of low clinical significance.	1a

Recommendations	Strength rating
Use combination treatment of a α1-blockers + phosphodiesterase type 5 inhibitors in patients with bothersome LUTS, particularly in patients willing to improve their erectile function.	Weak
Inform the patients that the magnitude of the effect is modest.	Weak

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

5.3 Surgical treatment of benign prostatic obstruction

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

- Resection
- Enucleation
- Vaporisation
- Alternative ablative techniques
- Nonablative techniques

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

Based on Panel consensus, timeframes defining short-, mid- and long-term follow-up of patients submitted to surgical treatments are 12, 36 and over 36 months, respectively. The durability of a technique is reflected by the reoperation rate during follow-up, the failure to wean patients off medication, as well as the initiation of novel LUTS medication after surgery. However, for the majority of techniques, only the reoperation rate is reported, and clinicians should inform patients that long-term surgical RCTs are often lacking. Some patients value sexual function and perceive higher safety over maximum efficacy, and it is therefore not surprising that some patients consciously choose an alternative ablative or non-ablative technique despite the knowledge that it might not be their definitive treatment. In contrast, many urologists are critical about these procedures due to their inferior relief of BOO.

Recommendations on new devices or interventions will only be included in the Guidelines once supported by a minimum level of evidence. To clarify this, the Panel have published their position on CoE [327]. In summary, a device or technology is only included once supported by RCTs looking at both efficacy and safety, with adequate follow-up, and secondary studies to confirm the reproducibility and generalisability of the first pivotal studies [327]. Otherwise, there is a danger that a single pivotal study can be overexploited by device manufacturers. Studies that are needed include proof of concept, RCTs on efficacy and safety, as well as cohort studies with a broad range of inclusion and exclusion criteria to confirm both reproducibility and generalisability of the benefits and harms [327]. The Panel assesses the quality of all RCTs and, if they do not meet the standard required, the intervention will continue to have no recommendation, i.e. an RCT does not guarantee inclusion in the Guidelines.

In addition, the Guidelines continue to include techniques under investigation. These are devices or technologies that have shown promising results in initial studies, however, they do not yet meet the aforementioned criteria to provide a CoE that enables the Panel to regard these devices or technologies as recommended alternatives. To account for evolving evidence, recommendations for some techniques under investigation have been made, however, these techniques remain under investigation until further studies provide the recommended CoE.

Ultimately, shared decision-making and patient counselling should accompany all therapeutic choices, ensuring that patients have realistic expectations and are aware of potential risks, possible complications, need for reintervention, and expected outcomes.

5.3.1 Resection of the prostate

5.3.1.a Monopolar and bipolar transurethral resection of the prostate

Mechanism of action

Transurethral resection of the prostate is performed in either an M-TURP or bipolar TURP (B-TURP) fashion. Transurethral resection of the prostate removes tissue from the transition zone of the gland in various degrees, resulting in a volume and PSA reduction of 25-58%.

Contrary to M-TURP, in B-TURP systems, the energy does not travel through the body to reach a skin pad. Bipolar circuitry is completed locally. Rather, energy is confined between an active (resection loop) and a passive pole situated on the resectoscope tip ('true' bipolar systems) or the sheath ('quasi' bipolar systems) using normal saline for irrigation thereby eliminating TUR-syndrome [328, 329].

Efficacy

In a meta-analysis of 20 RCTs with a maximum follow-up of five years, M-TURP resulted in a substantial mean Q_{max} improvement (+162%), a significant reduction in IPSS (-70%), QoL (-69%) and PVR (-77%) [330]. Monopolar-TURP delivers durable outcomes, as shown by studies with a follow-up of eight to 22 years [331]. One study with a mean follow-up of 13 years reported a significant and sustained decrease in most symptoms and improvement in urodynamic parameters. Failures were associated with DUA rather than regrowth of BPH [110]. A secondary prostatic operation, usually re-TURP, has been reported at a constant annual rate of approximately 1-2%. An SR analysing 29 RCTs found a retreatment rate of 2.6% after a mean follow-up of 16 months [332]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed that the overall retreatment rates (re-TURP, urethrotomy and bladder neck incision) remained unchanged during the last decade (0.9%, 3.7%, 9.5% and 12.7%, at three months, one year, five years and eight years, respectively), and that the respective incidence of re-TURP was 0.8%, 2.4%, 6.1% and 8.3%, respectively [333, 334].

Bipolar TURP is the most widely investigated alternative to M-TURP. Pooled results from 59 RCTs have been reported to date [335]. Early pooled results at 12 months concluded that no clinically relevant differences exist in short-term efficacy (IPSS, QoL and Q_{max}) [335, 336]. Subsequent meta-analyses supported these conclusions, though trial quality was generally poor [330, 337-340]. The largest meta-analysis published to date confirmed that B-TURP compared to M-TURP results in little to no difference in urological symptoms and bother (IPSS and QoL) at 12 months [335]. Data from RCTs with mid- to long-term follow-up (up to 60 months) showed no differences in efficacy parameters [341-349]. A meta-analysis of RCTs comparing B-TURP versus M-TURP reported similar efficacy at 36 months in terms of IPSS and Q_{max} [350].

Tolerability and safety

Perioperative mortality and morbidity of M-TURP have decreased over time, but morbidity remains considerable (0.1% and 11.1%, respectively) [351]. Data from an Austrian nationwide study of two cohorts totalling 41,059 men submitted to M-TURP showed a 20% reduction in mortality rate over time to 0.1% at 30 days and 0.5% at 90 days [333, 334].

The risk of TUR-syndrome decreased to < 1.1% in M-TURP [332, 352]. Data from 10,654 M-TURPs reported bleeding requiring transfusion in 2.9% of cases [351]. Short- to mid-term complications reported in an analysis of RCTs using M-TURP as a comparator were: bleeding requiring transfusion 2% (0-9%), TUR-syndrome 0.8% (0-5%), AUR 4.5% (0-13.3%), clot retention 4.9% (0-39%) and UTI 4.1% (0-22%) [330]. Long-term complications of M-TURP include UI, urinary retention and UTIs, bladder neck contracture (BNC), urethral stricture, retrograde ejaculation and ED [332].

Early pooled results concluded that no differences exist in short-term urethral stricture/BNC rates, but B-TURP is preferable to M-TURP due to a more favourable perioperative safety profile (elimination of TUR-syndrome; lower clot retention/blood transfusion rates; and shorter irrigation, catheterisation and possibly hospitalisation times) [336]. Subsequent meta-analyses supported these conclusions [330, 337-340, 350], however, trial quality was relatively poor and limited follow-up might cause underreporting of late complications, such as urethral stricture/BNC [336]. The largest meta-analysis published to date concluded that B-TURP compared to M-TURP reduced TUR syndrome and blood transfusion events by 20, and 28 fewer events per 1,000 participants, respectively [335].

An RCT-based meta-analysis has shown that TUR in saline (TURis) reduces the risk of TUR syndrome and the need for blood transfusion compared to M-TURP [340]. The meta-analysis concluded that TURis is associated with improved perioperative safety, eliminating the risk of TUR syndrome, reducing the risk of blood transfusion/ clot retention and hospital stay. No significant difference was detected in urethral stricture rates.

Data from the vast majority of individual RCTs with mid- to long-term follow-up (up to 60 months) showed no differences between M-TURP and B-TURP in urethral stricture/BNC rates [341-349], in accordance with all published meta-analyses. However, two individual RCTs have shown opposing results [348, 353]. A significantly higher stricture (urethral stricture + BNC) rate was detected in the B-TURP arm performed using a 'quasi' bipolar system (TURis, Olympus Medical) in patients with a prostate volume > 70mL at 36-months follow-up [348]. In addition, a significantly higher BNC - but not urethral stricture- rate was detected in the B-TURP arm performed with a ' true' bipolar system (Gyrus PK SuperPulse, Olympus Medical) in 137 patients at 12-months follow-up [353].

Randomised controlled trials using the erectile function domain of the IIEF (IIEF-ED) and the ejaculatory domain of the male sexual-health questionnaire (Ej-MSHQ) showed that M-TURP and B-TURP have a similar effect on erectile and ejaculatory function [354, 355]. Comparative evaluations of the effects on overall sexual function, quantified with IIEF-15, showed no differences between B-TURP and M-TURP at 12-month follow-up (erection, orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction) [355, 356]. Moreover, the largest meta-analysis published to date showed that erectile function measured by IIEF-5 appears to be similar at 12-month follow-up after B-TURP and M-TURP [335].

A comparative study [357] evaluated the safety of B-TURP in patients taking therapeutic oral anticoagulation (phenprocoumon) or antiplatelet drug therapy (acetylsalicylic acid or clopidogrel), without stopping or bridging the medication. Outcomes under acetylsalicylic acid were comparable to the unmedicated control group. Under oral anticoagulation therapy catheterisation (median 41 hours vs. 24 hours) and hospitalisation time was longer (median four days vs. three days), AUR rate was higher (18% vs. 6%), but blood transfusion rates did not differ from the control group. Under antiplatelet therapy blood transfusion (19% vs. 1%) and rehospitalisation rates (19% vs. 3%) were higher. In a retrospective study, elderly patients > 80 years undergoing TURP showed a significantly higher rate of complications when compared to those undergoing holmium laser enucleation of the prostate (HoLEP), including total postoperative complications (44.7% vs. 22.0%), postoperative haematuria (9.2% vs. 1.2%) and transient urinary retention (21% vs. 9.8%) [358].

Practical considerations

Monopolar TURP is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice should be based primarily on prostate volume (30-80mL suitable for M-TURP). No studies on the optimal cut-off value exist, but the complication rates increase with prostate size [351]. The upper limit for M-TURP is suggested as 80mL (based on Panel consensus, under the assumption that this limit depends on the surgeon's experience, choice of resectoscope size and resection speed). As surgical duration increases, there is a significant increase in the rate of complications, and the procedure is safest when performed in under 90 minutes [359].

Bipolar TURP in patients with moderate-to-severe LUTS secondary to BPO has similar efficacy with M-TURP but lower perioperative morbidity. The duration of improvements with B-TURP were documented in several RCTs with midterm follow-up. Long-term results (up to five years) for B-TURP showed that safety and efficacy are comparable to M-TURP [341-349]. The choice of B-TURP should be based on equipment availability, surgeon's experience and patient's preference.

Summary of evidence	LE
Bipolar or M-TURP is the current standard surgical procedure for men with prostate sizes of 30-80mL and bothersome moderate-to-severe LUTS secondary of BPO.	1a
Bipolar TURP achieves short-, mid- and long-term results comparable with M-TURP, but B-TURP has a more favourable perioperative safety profile.	1a

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

5.3.1.b Holmium laser resection of the prostate

With the advent of HoLEP (Section 5.3.2.c) and the fact that no relevant publications on holmium laser resection of the prostate (HoLRP) have been published since 2004, HoLRP of the prostate does not play a role in contemporary treatment algorithms.

5.3.1.c Thulium:yttrium-aluminium-garnet laser vaporesection of the prostate

Mechanism of action

The *Thulium:yttrium-aluminium-garnet laser* (Tm:YAG) emits a wavelength of 2010 or 2,013nm in a pulsed or continuous wave (CW) mode. The laser is primarily used with bare-ended laser fibres [360]. Various applications, such as vaporesection (ThuVARP), have been published [361].

Efficacy

Several meta-analyses with pooled data from both RCTs and non-RCTs have evaluated ThuVARP versus M-TURP [362-364] and B-TURP [365-367]. The largest meta-analyses included nine RCTs and seven non-RCTs and reported no clinically relevant differences in efficacy (IPSS, QoL and Q_{max}) between ThuVARP and M-TURP or B-TURP at 12 months [366]. A multicentre RCT with 410 men reported that ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at 12-month follow-up [368]. The beneficial effect of TURP in terms of Q_{max} was strengthened in men aged < 70 years and in those diagnosed with LUTS rather than urinary retention. No differences in individual patient-reported urinary symptoms were seen between arms, with the exception of some evidence to indicate potential reduction in nocturia in the TURP arm. Data from one RCT with long-term follow-up showed no difference in efficacy and reoperation rates between ThuVARP and M-TURP (2.1% vs. 4.1%, respectively) [369]. A prospective multicentre study on ThuVARP including 2,216 patients showed durable postoperative improvement in IPSS, QoL, Q_{max} and PVR for the entire eight years of follow-up [370].

Tolerability and safety

Two meta-analyses showed longer operation times, shorter catheterisation/hospitalisation times and less blood loss without significant differences in transfusion rates or in any other short-term complication rates for ThuVARP compared to TURP [362-367]. A significantly higher transfusion rate was reported after M-TURP in two meta-analyses [364, 366]. However, overall RCT quality was relatively low with limited follow-up, potentially accounting for under-reporting of late complications such as urethral stricture/BNC [366]. A multicentre RCT with 410 men followed up for 12 months reported that ThuVARP and TURP show similar operation, catheterisation and hospitalisation times between arms with no difference in the frequency or severity of surgical complications or in blood transfusions rate or haemoglobin change [368, 371]. Patients with urinary retention had similarly positive outcomes to those with LUTS [368, 371]. Data from three RCTs with mid- to long-term follow-up (18 to 48 months) showed no differences in late complication rates between ThuVARP and TURP [369, 372, 373].

Haemoglobin drop was significantly higher in the bridging group in a retrospectively analysed case series of 103 patients who underwent ThuVARP and received either low molecular weight heparin bridging or continued antiplatelet/anticoagulant therapy [374].

Practical considerations

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

Summary of evidence	LE
Laser vaporesection of the prostate using Tm:YAG laser (ThuVARP) has similar operation, catheterisation and hospitalisation times compared to TURP. ThuVARP and TURP are equivalent in terms of IPSS but not Q_{max}, with TURP deemed superior at 12-month follow-up. ThuVARP and TURP show similar short-term safety. Mid- to long-term results on efficacy and safety compared to TURP are very limited.	1b

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

ThuVARP = Thulium:yttrium-aluminium-garnet laser vaporesection of the prostate

5.3.1.d Transurethral incision of the prostate

Mechanism of action

Transurethral incision of the prostate involves incising the bladder outlet without relevant tissue removal. Transurethral incision of the prostate is conventionally performed with a Collins knife using electrocautery. However, alternative energy sources such as holmium laser may be used [375]. The mainstay of this technique is in prostate sizes < 30mL without a middle lobe.

Efficacy

An RCT comparing conventional TUIP versus TUIP using holmium laser in prostates ≤ 30mL with a follow-up of 12 months found both procedures to be equally effective in relieving BOO with similarly low reoperation rates [375]. A meta-analysis of ten RCTs found similar LUTS improvements and lower but significant improvements in Q_{max} for TUIP [376]. In this meta-analysis, an upper limit of prostate size was reported as an entry criterion for eight studies with five < 30mL and three < 60mL. A meta-analysis of six trials showed that reoperation was more common after TUIP (18.4%) than after M-TURP (7.2%) [376].

Tolerability and safety

An RCT comparing conventional TUIP versus TUIP using holmium laser reported both procedures to be safe with low complication rates. However, the operation time and retrograde ejaculation rate was significantly lower in the conventional TUIP arm [375]. No cases of TUR-syndrome have been recorded after TUIP. The risk of bleeding after TUIP is small [376].

Practical considerations

Transurethral incision of the prostate is an effective treatment for moderate-to-severe LUTS secondary to BPO. The choice between M-TURP and TUIP should be based primarily on prostate volume (< 30mL TUIP) [376].

Summary of evidence	LE
Transurethral incision of the prostate shows similar efficacy and safety to M-TURP for treating moderate-to-severe LUTS secondary to BPO in men with prostates < 30mL.	1a
No case of TUR-syndrome has been recorded, the risk of bleeding requiring transfusion is negligible and retrograde ejaculation rate is significantly lower after TUIP, but the reoperation rate is higher compared to M-TURP.	1a
The choice between TUIP and TURP should be based primarily on prostate volume (< 30mL and 30-80mL suitable for TUIP and TURP, respectively).	4

Recommendation	Strength rating
Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30mL, without a middle lobe.	Strong

5.3.2 Enucleation of the prostate

5.3.2.a Open simple prostatectomy

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

Efficacy

Open prostatectomy reduces LUTS by 63-86% (12.5-23.3 IPSS points), improves QoL by 60-87%, increases mean Q_{max} by 375% (+ 16.5-20.2mL/s) and reduces PVR by 86-98%. Efficacy is maintained for up to six years [377-382]. Data from an Austrian nationwide study of 2,452 men submitted to OP showed that the endourological reintervention rates after primary OP were 0.9%, 3.0%, 6.0% and 8.8% at three months, one year, five years and eight years, respectively [333].

Two meta-analyses [383, 384] evaluated the overall efficacy of OP performed via a transvesical approach versus two transurethral enucleation techniques for treating patients with large glands, namely bipolar transurethral enucleation of the prostate (B-TUEP) and HoLEP. Five RCTs compared OP with B-TUEP [382, 385-388] and four RCTs compared OP with HoLEP [377, 378, 389, 390]. There were no significant differences in Q_{max} at three-, six-, 12- and 24-months follow-up [384]. Post-void residual, PSA, IPSS and QoL showed no significant differences during 12-month follow-up [384]. Open prostatectomy and HoLEP had similar improvements regarding Q_{max}, IPSS score and reoperation rates after five years in one RCT [377].

Tolerability and safety

Two meta-analyses evaluated the overall safety of OP performed via a transvesical approach versus B-TUEP and HoLEP [383, 384]. Operation time did not differ significantly between OP and B-TUEP but was significantly shorter for OP compared to HoLEP. Catheterisation and hospitalisation time were significantly longer for OP, which was also associated with more blood transfusions. There were no significant differences regarding other complications. There was no significant difference in IIEF-5 at three-, six-, 12- and 24-months follow-up.

Open prostatectomy mortality has decreased significantly during the past two decades (< 0.25%) [381, 391]. Data from a study of 1,286 men submitted to OP showed mortality rates of 0.2% at 30 days and 0.4% at 90 days [334].

The estimated transfusion rate was about 7-14% [377, 380, 381, 383]. Long-term complications include persistent incontinence, BNC and urethral stricture (about 6%) [377-379, 383, 392].

Practical considerations

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

Summary of evidence	LE
Open prostatectomy is an effective and durable procedure for the treatment of LUTS/BPO, but it is the most invasive surgical method.	1b
Open prostatectomy shows similar short- and mid-term efficacy to B-TUEP and HoLEP for treating moderate-to-severe LUTS secondary to BPO in patients with large prostates.	1a
Open prostatectomy has a less favourable perioperative safety profile compared to B-TUEP and HoLEP.	1a
The long-term functional results of OP are comparable to HoLEP.	1b

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

5.3.2.b Bipolar transurethral enucleation of the prostate

Mechanism of action

Following the principles of bipolar technology (Section 5.3.1.a), the obstructive adenoma is enucleated endoscopically by the transurethral approach. Currently, two technologies exist: plasmakinetic (PK) enucleation of the prostate (PKEP) and bipolar plasma enucleation of the prostate (BPEP) [388, 393, 394]. Bipolar transurethral enucleation of the prostate is followed by either morcellation [388, 395] or resection [393, 396-400] of the enucleated adenoma.

Efficacy

Two meta-analyses reported similar efficacy at 12 months in terms of IPSS, QoL and Q_{max} for B-TUEP (PKEP or BPEP) versus B-TURP [401, 402]. Another meta-analysis evaluating B-TUEP versus B-TURP reported similar efficacy at 36 months in terms of IPSS and Q_{max} [350]. One RCT evaluating PKEP versus M-TURP reported a significant improvement in IPSS, QoL and Q_{max}, with urodynamically proven de-obstruction favouring PKEP at 36-months follow-up [397]. One RCT evaluating PKEP versus B-TURP in patients with prostate volume > 80mL reported no clinically relevant differences in IPSS, QoL and Q_{max} at six-months follow up [403]. Another RCT evaluating BPEP versus B-TURP in patients with prostate volume > 80mL reported no clinically relevant differences in IPSS, QoL, Q_{max} and PVR at 24-months follow-up [404]. Two RCTs evaluated the mid-term efficacy of PKEP versus B-TURP at 36 months [398, 399] and one RCT evaluated long-term efficacy at 60 months [400]. Efficacy was significantly better for PKEP in patients with large prostates at 36, 48 and 60 months [398, 400]. Comparative data on efficacy for B-TUEP versus OP and the various forms of laser enucleation are presented in Section 5.3.2.a to 5.3.2.e, respectively.

Tolerability and safety

Two meta-analyses evaluating B-TUEP versus B-TURP reported similar operation, catheterisation and hospitalisation times; lower acute urine retention rates; significantly reduced haemoglobin drop and blood transfusion rates; no difference in ED; and no difference in all other reported complication rates, including urethral stricture/BNC rates for B-TUEP at 24-months follow-up [400, 401, 403].

A meta-analyses evaluating PKEP versus TURP reported that mid-term IIEF-5 scores were comparable [405]. Another meta-analysis reported less bleeding with B-TUEP compared to M-TURP but similar UI rates and AUR after catheter removal [350]. An RCT evaluating PKEP versus M-TURP in patients with prostate volume < 80mL and 36-month follow-up reported that PKEP is superior to M-TURP in terms of catheterisation and hospitalisation time [397]. No significant differences between the arms were reported in operation time, blood transfusion rates, sexual function or any other reported complications (TUR syndrome, clot retention, incontinence, retrograde ejaculation or urethral structures/BNC) [397]. One RCT evaluating PKEP versus B-TURP in patients' prostate volume > 80mL and six-months follow-up reported that PKEP is superior to B-TURP in terms of operation, catheterisation and hospitalisation time [403]. Significant differences were reported in blood transfusion, BNC and retrograde ejaculation rates favouring PKEP, but no differences in urethral stricture and ED rates were reported [403]. Another RCT evaluating BPEP versus B-TURP in patients with prostate volume > 80mL reported that BPEP had longer operative time but shorter catheterisation, hospitalisation time with no differences in blood transfusion, urethral stricture and UI rates at 24-months follow-up [404]. No difference in urethral stricture/BNC rates was reported at 60-months follow-up [400]. Comparative data on efficacy for B-TUEP versus OP and the various forms of laser enucleation are presented in Sections 5.3.2.a to 5.3.2.e, respectively.

Summary of evidence	LE
Bipolar transurethral PKEP shows favourable mid- to long-term efficacy compared to TURP.	1b
Bipolar transurethral PKEP has a favourable perioperative safety profile and demonstrates similar mid- to long-term safety compared to TURP.	1b

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

5.3.2.c Holmium laser enucleation of the prostate

Mechanism of action

The holmium:yttrium-aluminium garnet (Ho:YAG) laser (wavelength 2,140nm) is a pulsed solid-state laser that is absorbed by water and water-containing tissues. Tissue coagulation and necrosis are limited to 3-4mm, which is enough to obtain adequate haemostasis [406].

Efficacy

An initial meta-analysis reported no significant differences in short-term efficacy (Q_{max}) and reintervention rates (4.3% vs. 8.8%) between HoLEP and M-TURP [407]. However, subsequent meta-analyses reported favourable short-term efficacy (Q_{max} and IPSS) for HoLEP [330, 363, 401, 408]. Meta-analyses reported similar efficacy at 24-months in terms of IPSS, and Q_{max} [350]. Three meta-analyses evaluating HoLEP versus B-TURP showed no

significant differences in short-term efficacy (IPSS, QoL and Q_{max}) [350, 401, 409]. One RCT comparing HoLEP with B-TURP in patients with prostate volume < 80mL reported no significant difference in IPSS, QoL and Q_{max} at 24 months [410]. One RCT comparing HoLEP with M-TURP in a small number of patients with mean prostate volume < 80mL and a seven-year follow-up found that the functional long-term results were comparable [406]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80mL reported no significant difference in IPSS, QoL and Q_{max} at 36 months. However, the overall retreatment rate was significantly lower following HoLEP with fewer patients restarting α-blockers and fewer reoperations [411]. Section 5.3.2.a presents comparative efficacy data for HoLEP versus OP. One RCT evaluating HoLEP versus PKEP in patients with mean prostate volume < 80mL reported similar improvements in IPSS and Q_{max} at 12-month follow-up [395]. Another RCT comparing HoLEP with PkEP improvements of IPSS found that QoL, PVR and Q_{max} were stable at three-year follow-up without differences between the groups [412, 413].

An RCT comparing HoLEP versus B-TUEP reported no significant difference in IPSS, QoL, PVR and Q_{max} at one-, three- and 12-month follow-up [414].

An SR and meta-analysis based on retrospective series revealed a superior enucleation efficiency associated with *en-bloc* and the two-lobe techniques compared to the three-lobe technique, but no superiority on functional outcomes were reported [415].

Another SR and meta-analysis of 15 retrospective studies demonstrated the safety and efficacy of HoLEP in patients with recurrent or residual adenoma of the prostate [416].

Tolerability and safety

Several meta-analyses found that HoLEP has longer operation times, shorter catheterisation and hospitalisation times, reduced blood loss and fewer blood transfusions but no significant differences in urethral strictures (2.6% vs. 4.4%) and stress urinary incontinence (SUI) (1.5% vs. 1.5%) rates compared to M-TURP [363, 401, 407, 408, 417]. Another meta-analysis reported that HoLEP has shorter catheterisation times, fewer blood transfusions, urethral strictures and UTIs but no significant differences in clot retention rates and AUR after catheter removal compared to M-TURP [350]. Three meta-analyses evaluated HoLEP versus B-TURP [401, 409, 418]. One reported longer operation times for HoLEP, but no significant differences in hospitalisation time or complication rates [401], whilst another reported no significant differences in operation and catheterisation times or short-term complication rates [409]. Data from a large national database on perioperative outcomes of 2,869 laser enucleations of the prostate and 37,577 TURP procedures supports that laser enucleation of the prostate is associated with longer operation times, shorter hospitalisation times and similar complication rates (including transfusions and reoperations), but lower rates of infectious complications [419]. An SR reported that HoLEP has lower AUR rates after catheter removal but similar haemoglobin drop, UTI, urethral stricture and UI rates [350]. An RCT comparing HoLEP with B-TURP in patients with prostate volume < 80mL reported longer operation time, shorter catheterisation and hospitalisation times and a lower risk for haemorrhage for HoLEP with no significant differences in blood transfusion rates or other complication rates at 24 months [410]. Another RCT comparing HoLEP with B-TURP in patients with prostate volume > 80mL reported shorter operation, catheterisation and hospitalisation times and lower blood transfusion rates for HoLEP but no differences in complication rates, including UI and IIEF-5 score at 36 months [411]. Section 5.3.2.a presents comparative data on the safety of HoLEP versus OP. One RCT evaluating HoLEP versus PKEP in patients with mean prostate volume < 80mL reported significantly shorter operation times for HoLEP, but similar catheterisation and hospitalisation times and complication rates at 12-month follow-up [395]. Another RCT comparing HoLEP with PKEP found a higher haemoglobin drop and a prolonged haematuria in the PKEP group, but no clinically significant blood loss in either arm occurred [412, 413]. An RCT comparing HoLEP versus bipolar B-TUEP demonstrated shorter operation and hospitalisation times and earlier catheter removal for HoLEP [414].

Another RCT comparing high- (2J, 50Hz) with medium-power (2J, 30Hz) HoLEP demonstrated comparable perioperative safety and long-term durability [420]. These results were confirmed in another RCT comparing low (1.5 J, 25Hz) with high power (2.5J, 40Hz) HoLEP in prostates larger than 80mL [421].

An SR and meta-analysis of seven studies comparing pulse modulation use (Virtual basket) with standard HoLEP, shorter enucleation, better haemostasis and shorter total surgical time was found with pulse modulating HoLEP [422].

Laser enucleation of the prostate has been safely performed in patients using anticoagulant and/or antiplatelet medications. However, current limitations include:

- a lack of RCTs;
- studies with prostate volumes < 110mL;
- limited data on short- and mid-term complications and bridging therapy; and
- data presentation does not allow for separate interpretation of either antiplatelet or anticoagulant therapy [423].

A meta-analysis of seven RCTs evaluating HoLEP versus TURP reported that short- and mid-term IIEF-5 scores were comparable, whilst long-term scores were significantly better for HoLEP [424]. Two other meta-analyses detected no difference in mid-term retrograde ejaculation rates [425].

The impact on erectile function is comparable [426, 427]. Attempts to maintain ejaculatory function with modified template HoLEP have been reported to be successful in up to 77.8% of patients [428, 429]. Median Lobe-only enucleation achieved maintained antegrade ejaculation in 88%. However, reintervention rate was 14.5% at one year follow-up [430].

Practical considerations

The experience of the surgeon is the most important factor affecting the overall occurrence of complications in HoLEP [431, 432]. Mentorship programmes are advised improving surgical performance from both an institutional and personal learning curve perspective [433-435]. Pulse modulation use in HoLEP (Virtual basket) demonstrated statistically significantly improved outcomes related to haemostasis and operation times, however, clinical and health economic benefits remain to be determined [422].

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

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

5.3.2.d Thulium:yttrium-aluminium-garnet laser enucleation of the prostate

Mechanism of action

The Tm:YAG laser is described in Section 5.3.1.c. Enucleation using the Tm:YAG laser includes thulium vapoenucleation of the prostate (ThuVEP) and thulium laser enucleation of the prostate (ThuLEP) (blunt enucleation). Pulsed or CW thulium:yttrium-aluminium-garnet or thulium fibre lasers are used for laser enucleation of the prostate and are well absorbed by water and water-containing tissues.

Efficacy

Two meta-analyses evaluating ThuLEP versus M-TURP and B-TURP reported no clinically relevant differences in short-term efficacy (Q_{max}, IPSS and QoL) [350, 401]. An RCT with five-years follow-up comparing ThuLEP with B-TURP found no difference between the two procedures for Q_{max}, IPSS, PVR and QoL [436]. A meta-analysis [437] evaluating ThuLEP versus HoLEP showed no clinically relevant differences in IPSS, QoL and Q_{max} at 12 months in accordance with one RCT showing similar results at 18 months [438]. Moreover, ThuLEP and PKEP were compared in one RCT with 12-month follow-up with no difference with regard to efficacy [439]. Mainly prospective case studies have been carried out on ThuVEP showing a significant improvement in IPSS, Q_{max} and PVR after treatment [440-443]. In a retrospective comparative series, no differences were found between (super) pulsed and CW ThuLEP with regard to intraoperative and perioperative data and clinical efficacy (Q_{max}, IPSS, QoL) [444].

Tolerability and safety

Two meta-analyses evaluating ThuLEP versus M-TURP and B-TURP reported a longer operation time and shorter catheterisation time for ThuLEP compared to M-TURP and a shorter hospitalisation time for ThuLEP compared to B-TURP [350, 401]. Lower blood transfusion rates compared to M-TURP, lower clot retention rates compared to B-TURP, and no difference in the other complication rates were also reported for ThuLEP [350, 401]. One meta-analysis [437] evaluating ThuLEP versus HoLEP showed a significant difference in enucleation time favouring ThuLEP, but no significant differences in operation, catheterisation and hospitalisation times, and short-term complication rates.

Evaluating ThuLEP versus HoLEP showed a significant difference in enucleation time favouring ThuLEP, but no significant differences in operation, catheterisation and hospitalisation times, and short-term complication rates. One RCT showed no urethral and bladder neck strictures at 18 months after ThuLEP and HoLEP, respectively [438]. ThuLEP and PKEP were compared in one RCT with 12-month follow-up [439]. No significant difference in complication rates was detected, but haemoglobin level decrease and catheterisation time was significantly lower for ThuLEP. An RCT comparing ThuLEP with B-TURP reported a significant difference in IIEF-5 score favouring ThuLEP at 12 months [445].

In comparative studies, ThuVEP shows high intraoperative safety [446], including in case series of patients with large prostates [440] and anticoagulation or bleeding disorders [441, 442]. A study focusing on postoperative complications after ThuVEP reported adverse events in 31% of cases, with 6.6% complications greater than Clavien grade 2 [447]. One case control study on ThuVEP with 48-month follow-up reported long-term durability of voiding improvements and overall reoperation rates of 2.4% [442].

Practical considerations

ThuLEP appears to offer similar efficacy and safety when compared to TURP, bipolar enucleation and HoLEP, whereas, in an RCT comparing HoLEP with ThuVEP, no differences were found with regard to the occurrence of perioperative complications, micturition improvement, hospitalisation and catheterisation time, as well as operation time [448, 449].

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

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

ThuLEP = Thulium Laser Enucleation of the Prostate, ThuVEP = Thulium Vaporization Enucleation of the Prostate, Tm:YAG = Thulium: Yttrium-Aluminum-Garnet

5.3.2.e Diode laser enucleation of the prostate

Mechanism of action

For prostate surgery, diode lasers with a wavelength of 940, 980, 1,318 and 1,470nm (depending on the semiconductor used) are marketed for vaporisation and enucleation. Only a few have been evaluated in clinical trials [450]. Diode laser enucleation of the prostate does not play a role in contemporary treatment algorithms of LUTS/BPO.

Practical considerations

Diode laser enucleation of the prostate does not play a role in current clinical practice, and the Panel consensus was not to provide a recommendation.

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

5.3.2.f Alternative enucleation techniques

5.3.2.f.1 Laparoscopic/robotic simple prostatectomy (L/RASP)

Mechanism of action

The acronym L/RASP includes laparoscopic simple prostatectomy (LASP) and [451] multiport or single-port robot-assisted simple prostatectomy (RASP) [452, 453]. Both LASP and RASP are performed using various personalised techniques, based on the transcapsular (Millin) or transvesical (Freyer) approach (transperitoneally or extraperitoneally).

Efficacy

An SR and meta-analyses showed that, in 27 observational studies including 764 patients, mean increase in Q_{max} was 14.3mL/s, and the mean improvement in IPSS was 17.2 [454]. No differences were observed in improvements in Q_{max} and IPSS [454]. A meta-analysis comparing L/RASP versus OP reported no significant differences regarding functional and symptom parameters between the two techniques [455]. A multicentre RCT with median follow-up of 26 months did not demonstrate any significantly different functional or perioperative results between LASP, RASP and HoLEP [456]. An SR and meta-analysis of five non-randomised comparative trials comparing RASP with LASP demonstrated a shorter length of hospital stay after RASP as well as a higher postoperative Q_{max} [456, 457]. An RCT comparing HoLEP versus L/RASP for large volume (≥ 120mL) prostate glands resulted in longer catheterisation time in the LASP group than RASP and HoLEP groups (P = 0.002). Moreover, L/RASP resulted in longer hospitalisation and lower rate of patients with new onset of storage LUTS [456]. The efficacy of RASP was also demonstrated in 87 patients after prior endoscopic treatment of the prostate: no differences with regards to efficacy and perioperative complications were found compared to those patients with primary RASP (433 patients) [458].

Tolerability and safety

A meta-analysis comparing L/RASP versus OP demonstrated shorter hospital stay, as well as blood loss and transfusion rates for L/RASP [455, 459]. In comparative studies to OP, length of hospital stay, length of catheter use and estimated blood loss were significantly lower in the L/RASP group, while the duration of surgery was longer. There were no differences in perioperative complications between the two procedures [454]. In a multicentre RCT comparing LASP, RASP and HoLEP, LASP demonstrated significantly longer catheterisation times than RASP and HoLEP, whilst RASP and LASP showed longer hospitalisation times and lower rates of *de novo* bladder storage symptoms [456]. This was confirmed in an meta-analysis of six studies comparing RASP with laser enucleation of the prostate: operative time, catheterisation time, length of stay, haemoglobin loss, transfusion rate and the occurrence of > Clavien Dindo Grade 3 complications favoured laser enucleation of the prostate [460]. In a comparative analysis of robotic versus OP for large-volume prostates, a propensity score-matched analysis was performed with five covariates. Robotic compared with OP demonstrated a significantly shorter average length of hospital stay but longer mean operative time. The robotic approach was associated with a lower estimated blood loss. Improvements in Q_{max}, IPSS, QoL, PVR and postoperative PSA levels were similar for both groups. No difference in complications was observed between the groups [461].

In a small retrospective case series of patients with prostates > 200mL, RASP (n = 53) was compared to HoLEP (n = 22). Although median PV was higher in RASP (225mL) as in HoLEP (204.5mL), the amount of resected tissue was higher in the HoLEP group (180g vs. 134.5g). However, there were no differences in perioperative complications and micturition improvement. The PSA was significantly lower one month postoperatively after HoLEP compared to RASP (0.4 vs. 1.8ng/mL) [462].

A retrospective cohort study found no differences with regards to perioperative complications and short-term complications comparing open simple prostatectomy (OSP)-RASP with ThuLEP (mean specimen weight 74 vs. 42g) in medium-sized prostates. ThuLEP was, however, associated with shorter catheterisation time compared with SP-RASP, while postoperative SUI was higher after ThuLEP than after SP-RASP (0 vs. 18.8%) [463].

Practical considerations

Currently, most studies on L/RASP are retrospective in nature. Adequately powered RCT against reference options are needed to compare efficacy, safety, and hospitalisation times, learning curve and costs of L/RASP, and both OP and endoscopic methods. Despite the lack of level 1 evidence, minimally invasive simple prostatectomy is increasingly being used in clinical practice.

Summary of evidence	LE
Laparoscopic/robotic simple prostatectom is feasible in men with LUTS/BPO and prostate sizes > 80mL needing surgical treatment, however, RCTs are needed.	2a

5.3.2.f.2 532nm ('Greenlight') laser enucleation of the prostate (GreenLEP)

Two approaches for potassium titanyl phosphate (KTP) and the lithium triborate (LBO) laser-based enucleation technique are available [464]. GreenLEP is an anatomical enucleation technique following the principle of blunt dissection of the adenoma with the sheath and laser energy for incision as described for ThuLEP [465]. A variation is the *in-situ* vaporisation of apically enucleated tissue, also referred to as anatomic vaporisation-incision technique [465, 466]. To date, no high quality adequate RCTs evaluating enucleation using the KTP/LBO laser have been carried out [467, 468].

5.3.2.g *Anatomical endoscopic enucleation of the prostate*

As all transurethral enucleation procedures follow the same surgical principles, the acronym AEEP has been introduced. Anatomical endoscopic enucleation of the prostate - AEEP - describes the removal of the transition zone of the prostate regardless of the energy source used.

5.3.3 *Vaporisation of the prostate*

5.3.3.a Bipolar transurethral vaporisation of the prostate

Mechanism of action

Bipolar transurethral vaporisation of the prostate (B-TUVP) utilises a bipolar electrode and a high-frequency generator to create a plasma field (thin layer of highly ionised particles) to vaporise prostatic tissue [469]. Bipolar transurethral vaporisation of the prostate displays thinner (< 2mm) coagulation zones [470], compared to monopolar TUVP (up to 10mm) [471], potentially resulting in fewer irritative side effects and SUI [470, 472, 473].

Efficacy

Bipolar-TUVP has been compared to TURP in 13 RCTs, including a total of 1,244 men with a prostate size of < 80mL [344, 474-485]. Early RCTs evaluated the PK B-TUVP system [474-478], however, during the last decade, only the 'plasma' B-TUVP system with the 'mushroom- or button-like' electrode (Olympus, Medical) has been evaluated [344, 479-485]. Results have been pooled in three meta-analyses [330, 486, 487], and a narrative synthesis has been produced in two SRs [330, 488].

Follow-up in most RCTs is 12 months [474-477, 479-481, 483, 485] with the longest being 36 months in a small RCT (n = 40) and 18 months in a subsequent RCT (n = 340) evaluating PK [478] and plasma B-TUVP [344], respectively. Pooled results from meta-analyses concluded that no significant differences exist in short-term efficacy (IPSS, QoL , Q_{max} and PVR) between PK B-TUVP and TURP [330, 350, 487], and this was confirmed in a separate SR of seven RCTs [488]. However, the promising initial efficacy profile of PK B-TUVP may be compromised by inferior clinical outcomes (IPSS and Q_{max}) at mid-term. Higher quality RCTs with longer follow-up are necessary to draw definite conclusions on mid and long-term outcomes [330, 478].

Tolerability and safety

Early pooled results concluded that no statistically significant differences exist for intraoperative and short-term complications between PK B-TUVP and TURP, but perioperative complications are significantly fewer after B-TUVP [330]. However, the results of a statistical analysis comparing pooled specific complication rates were not directly reported in this meta-analysis [330]. Mid-term complications (urethral stricture, ED and retrograde ejaculation) are similar [478], but larger RCTs with longer follow-up are necessary to draw definite conclusions [330, 478]. An SR of seven RCTs comparing PK and plasma B-TUVP with TURP concluded that most RCTs demonstrated shorter catheterisation (42.5 vs. 77.5 hours) and hospitalisation times (3.1 vs. 4.4 days) with B-TUVP [488], but another SR concluded that heterogeneity of RCTs and methodological limitations do not permit firm conclusions [330]. A meta-analysis reported that B-TUVP has shorter and similar catheterisation time compared to M-TURP and B-TURP, respectively; significantly fewer clot retentions/blood transfusions compared to M-TURP but not B-TURP; and no difference in other complication rates compared to either TURP technique [350]. A meta-analysis of six RCTs specifically evaluating plasma B-TUVP versus TURP concluded

that no significant differences exist between the techniques in overall complication and transfusion rates [487]. However, a statistically significant difference was detected in major complication rates (Clavien 3, 4), including urethral stricture, severe bleeding necessitating reoperation and UI, and in the duration of catheterisation, favouring plasma B-TUVP.

Practical considerations

Bipolar-TUVP and PK TUVP have similar short-term efficacy to TURP, but with a favourable short-term safety profile. However, heterogeneity of RCTs, non-standardised techniques and methodological limitations do not permit firm conclusions, and multicentre, long-term RCTs are needed. A shared decision-making approach should be undertaken and cover expected recovery, possible retreatment rates and the importance of centre-specific outcomes when counselling patients.

Summary of evidence	LE
Bipolar-TUVP and TURP have similar short-term efficacy.	1a
Plasmakinetic B-TUVP has a favourable perioperative profile, similar mid-term safety but inferior mid-term efficacy compared to TURP.	1a
Plasma B-TUVP has a lower short-term major morbidity rate compared to TURP.	1a

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

5.3.3.b 532 nm ('Greenlight') laser vaporisation of the prostate

Mechanism of action

Potassium titanyl phosphate and LBO lasers are described in Section 5.3.2.f.2.

Efficacy

Meta-analyses of RCTs comparing photoselective vaporisation of the prostate (PVP) using the 80W and 120W lasers with TURP have reported no difference in Q_{max} and IPSS between 80W or 120W PVP and TURP [489, 490]. Another meta-analysis of four RCTs including 559 patients on the 120W laser demonstrated no significant difference in functional and symptomatic parameters at 24-month follow-up when compared to TURP [491]. A meta-analysis of two RCTs reported similar efficacy of 120W PVP compared to M-TURP at 36-months follow-up [350].

The only available RCT for the 180W laser reported non-inferiority to TURP in terms of IPSS, Q_{max}, PVR, prostate volume reduction, PSA decrease and QoL questionnaires. Efficacy outcomes were similar to TURP, with stable results at 24-months follow-up [492].

One RCT comparing HoLEP to PVP in patients with prostates > 60mL showed comparable symptom improvement but significantly higher flow rates and lower PVR volume after HoLEP at short-term follow-up. In addition, PVP showed a 22% conversion rate to TURP [493].

One RCT compared B-TUVP with PVP with the 180W XPS laser. Comparable improvement in IPSS and Q_{max} were reported at 24-months follow-up [494].

Tolerability and safety

A meta-analysis of RCTs comparing the 80W and 120W lasers with TURP showed shorter catheterisation time (MD 32 hours) and length of hospital stay (MD 1.85 days) after PVP [330]. Fewer blood transfusions and less was observed with PVP. No difference was noted in postoperative urinary retention, UTI, meatal stenosis, urethral stricture or bladder neck stenosis [330]. Similarly, a meta-analysis including trials with the 120W laser reported lower transfusion rates and shorter catheterisation time and duration of hospital stay compared to TURP. Reoperation rates and operation time favoured TURP. No significant differences were demonstrated for treatment for urethral stricture, BNC, incidence of incontinence and UTI [491]. A meta-analysis confirmed that PVP was superior to both M-TURP/B-TURP with regard to catheterisation and to M-TURP but not to B-TURP with regard to transfusion rate and clot retention [350]. In an RCT comparing the 120W HPS laser with TURP with a follow-up of 36-months, the reoperation rate was significantly higher after PVP (11% vs. 1.8%) [495].

180W Greenlight laser prostatectomy is noninferior to TURP in terms of perioperative complications. Reoperation-free survival during a 24-month follow-up was comparable between the TURP arm and the 180W XPS laser arm [492].

A retrospective feasibility study on 537 patients with a median follow-up of 31 months, 517 of whom were treated on an outpatient basis, showed that outpatient PVP with the 180W XPS laser can be performed safely with a low readmission and complication rate [496].

One retrospective long-term follow-up study on 21,869 patients treated in 20 centres in Finland compared short-term and long-term morbidity in patients undergoing M-TURP, B-TURP or any of the three generations of PVP [488]. Reoperations for bleeding were less frequent after PVP. Cumulative incidence for reoperation was higher after PVP (23.5%) than after TURP in long-term follow-up (17.8%) [497].

Based mostly on case series, the 80, 120 and 180W Greenlight laser appears to be safe in high-risk patients undergoing anticoagulation treatment [498-501]. However, patients under anticoagulation therapy were either excluded from, or represented a very small sample in, currently available RCTs. In one study, anticoagulated patients had significantly higher rates of bladder irrigation (17.2%) compared with those not taking anticoagulants (5.4%) [501]. In contrast, another retrospective study focusing on the 180W LBO laser did not find any significant differences between patients receiving or not receiving anticoagulants [502]. A retrospective study of a mixed cohort of patients treated with 80W KTP PVP and 120W LBO HPS revealed that delayed gross haematuria was common in patients (33.8%) during an average follow-up of 33 months [503]. A retrospective review of a database of patients undergoing 180W PVP without interruption of anticoagulation therapy had a 30.5% rate of perioperative adverse events with a significant occurrence of high-grade Clavien Dindo events [504].

Real-world data indicate roughly 8% of surgical reintervention at four years for both PVP (7.8%) and TURP (7.5%), thus highlighting the importance of centre-specific outcome auditing to inform patient counselling [505].

Safety in patients with urinary retention, impaired detrusor contractility, elderly patients or prostates > 80mL was shown in various prospective short-term non-randomised trials.

A retrospective study on 1,077 patients [506] with a median 18-months follow-up compared the functional results and the safety profile of PVP in patients younger and older than 75 years of age. The authors did not find any differences in terms of complications in older patients, with only 0.6% of Clavien III and an overall complication rate of 29.6%. Data on functional outcomes in the older group of patients, showed amelioration of all parameters from the baseline, with 111.7% of improvement of peak flow and 69.5% of IPSS reduction without statistical differences with the counterparts at 12 months. However, this similarity of results disappears when the study period is extended up to a median of 18 months, underlying the fact that younger patients maintain their improvement more than older patients, who nevertheless maintain a relevant improvement compared to their baseline [506].

No RCT including prostates > 100mL has been reported, therefore, comparison of retreatment rates between prostate volumes of different sizes is not possible [507-509].

A meta-analysis of five RCTs collectively comparing all three 'Greenlight' lasers with TURP detected no difference in retrograde ejaculation rates [425]. Additional studies have also reported no difference between OP/TURP and Greenlight PVP for erectile function [510, 511]. However, IIEF-5 scores were significantly decreased at six, 12 and 24 months in patients with preoperative IIEF-5 greater than 19 [512].

No significant difference with respect to perioperative and postoperative complications was reported in an RCT comparing B-TUVP and PVP with the 180W XPS Laser. Redo TURP for recurrent adenoma was required in 9.8% (B-TUVP) and 1.7% (PVP) of the patients during 24-months follow-up, respectively [494].

Practical considerations

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

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

Recommendations	Strength rating
Offer 80W 532nm potassium titanyl phosphate (KTP) laser vaporisation of the prostate to men with moderate-to-severe LUTS/benign prostatic obstruction (BPO) with a prostate volume of 30-80mL as an alternative to transurethral resection of the prostate (TURP).	Strong
Offer 120W 532nm lithium borate (LBO) laser vaporisation of the prostate to men with moderate-to-severe LUTS/BPO with a prostate volume of 30-80mL as an alternative to TURP.	Strong
Offer 180W 532nm LBO laser vaporisation of the prostate to men with moderate-to-severe LUTS/BPO with a prostate volume of 30-80mL as an alternative to TURP.	Strong
Offer laser vaporisation of the prostate using 80W KTP, 120 or 180W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80mL.	Weak

5.3.3.c Vaporisation techniques under investigation

Alternative vaporisation techniques have been investigated, but do not play a role in current clinical practice (e.g. ThuVAP, Ho:YAG, Blue-wavelength diode) and other emerging techniques, such as transperineal laser ablation (TPLA), as discussed in Section 5.3.4.c.2.

Refer to previous editions of the Guidelines for full rationale.

5.3.4 Alternative ablative techniques

5.3.4.a Aquablation - image-guided robotic waterjet ablation: AquaBeam

Mechanism of action

Aquablation uses the principle of hydrodissection to ablate prostatic parenchyma while sparing collagenous structures such as blood vessels and the surgical capsule. A targeted high-velocity saline stream ablates prostatic tissue without the generation of thermal energy under real-time transrectal US guidance. After completion of ablation, haemostasis is performed with a Foley balloon catheter on light traction or diathermy or low-powered laser if necessary [513]. Early catheter removal (< day two) is commonly achievable with this approach [514].

Efficacy

In a double-blind, multicentre, pivotal RCT, 181 patients with a prostate size of 30-80mL were randomised to TURP or Aquablation [515, 516]. Mean total operative time was similar for Aquablation and TURP (33 vs. 36 minutes), but resection time was significantly lower for Aquablation (4 vs. 27 minutes). At six months, patients treated with Aquablation and TURP experienced large IPSS improvements (-16.9 and -15.1, respectively), satisfying the noninferiority hypothesis. At one-year follow-up, mean IPSS reduction was 15.1 with a mean reduction in IPSS score of 67% for both groups. No significant difference in improvement of IPSS, QoL, Q_{max} and reduction of PVR was reported between the groups [517].

Improvements in IPSS and Q_{max} were maintained after five years in both groups [518]. Mean IPSS decrease was 16.9 and 15.1 points in the Aquablation and TURP groups, respectively. Similarly, five-year improvements in Q_{max} were 125% and 89% compared to baseline for Aquablation and TURP, respectively. Over five years, surgical retreatments were 5.1% and 1.5%, respectively [518].

Results of Aquablation in patients with large prostates (80-150mL) were evaluated in a cohort study of 101 men (WATER II) [515]. After 12 months, significant improvements were seen in IPSS (mean decrease of 17 points), Q_{max} (increase of 12.5cc/sec.) and PVR (a drop of 171cc in those with PVR > 100 at baseline). At five-years follow-up, 3% of patients required surgical retreatment [519].

The five-year follow-up of Aquablation therapy confirms sustained outcomes, minimal irreversible complications and low retreatment rates across prostate volumes ranging from 30-150mL. In pooled analysis of the WATER and WATER II cohorts, mean IPSS reduction was 15.1-15.9 points, Q_{max} increase was 8.7-9.2mL/s and QoL score reduction was 3.2-3.3 points, demonstrating durable efficacy across small and large glands [514].

In an SR and network meta-analysis including 23 studies comparing Aquablation and HoLEP, HoLEP provided greater objective improvements with a Q_{max} increase of +3.24mL/s (95% CI: 0.52-5.96) and PVR reduction of -23.03mL (95% CI: -39.39 to -6.66), whereas IPSS (-1.11 points) and QoL (-0.06 points) were similar between the two techniques [520].

Urodynamic studies of 66 patients enrolled in the WATER trial at six-months follow-up showed significant changes in $p_{det}Q_{max}$ (reductions of 35 and 34cm H_20, respectively) and large improvements in BOO index in both groups [521].

Tolerability and safety

Results for the WATER trial have shown comparable hospital stay and catheterisation duration (1.4 and 1 day, respectively) [515]. One case of blood transfusion was reported after Aquablation and none after TURP. In an SR of seven patient groups involving 446 patients treated by Aquablation, although there was a significant haemoglobin drop (2.06g/dL), this did not translate into increased transfusion rates. In WATER, fewer men in the Aquablation group had a persistent Clavien-Dindo grade 1 or 2 or higher adverse events compared to TURP (26% vs. 42%) at three months. Among sexually active men, the rate of anejaculation was lower in those treated with Aquablation compared to TURP (10% vs. 36%, respectively). There were no procedure-related adverse events after six months [517].

In patients with a prostate volume of 80-150mL (WATER II trial), bleeding-related events were observed in 14 patients (13.9%), eight of which (7.9%) occurred prior to discharge and six (5.9%) occurred within one month of discharge. Blood transfusions were required in eight patients, return to the theatre for fulguration in three patients and both transfusion and fulguration in two patients [522]. Maintenance of antegrade ejaculation was slightly lower in WATER II at 81% compared to 90% in the smaller prostates of WATER I [523]. In WATER II, there was a 2% *de novo* incontinence rate at 12 months [524].

In an analysis of procedural differences including data from WATER I and II, compared to a single pass of ablation, the use of two or more passes during Aquablation resulted in lower IPSS scores by four points, and lower IPSS QoL by 0.7 points at 24 and 36 months. Similarly, 36-month Q_{max} values were higher by 5mL/sec. in those with two or more passes than in those with one pass [525].

In a network meta-analysis comparing Aquablation and HoLEP, HoLEP was associated with a significantly higher risk of incontinence (RR: 4.48; 95% CI: 1.02 to 19.65) but a lower risk of blood transfusion (RR = 0.14; 95% CI: 0.00-4.21) [520].

According to long-term data from the WATER and WATER II trials [514], a five-year surgical retreatment-free survival of over 94% was reported following Aquablation with low rates of *de novo* incontinence (2%) and high preservation of antegrade ejaculation (81-90%). These findings support the favourable safety profile and functional preservation associated with Aquablation, including in large-volume prostates.

Practical considerations

During long-term follow-up, Aquablation provides noninferior functional outcomes compared to TURP in patients with LUTS and a prostate volume of 30-80mL. Management of bleeding and bladder neck cautery is often performed at the end of the procedure.

This is particularly suitable when preservation of ejaculatory function and early recovery are priorities. In gland volumes of 80-150mL (WATER II), symptom and flow improvements are sustained for up to five years [514, 526]. Short-term comparative studies against enucleation have shown similar efficacy and safety at six months and favourable results regarding ejaculatory function and SUI. Durability against enucleation remains to be established.

Summary of evidence	LE
Aquablation appears to be as effective as TURP, both subjectively and objectively.	1b
Aquablation appears to have a low incidence of EjD.	1b
Aquablation is feasible in prostates > 80mL, however, additional RCTs are needed.	2a

Recommendation	Strength rating
Offer Aquablation to patients with moderate-to-severe LUTS/benign prostatic obstruction and a prostate volume of 30-80mL as an alternative to transurethral resection of the prostate, particularly in patients interested in preserving ejaculatory function.	Strong

5.3.4.b Prostatic artery embolisation

Mechanism of action

Prostatic artery embolisation (PAE) can be performed as a day procedure under local anaesthesia with access through the femoral or radial arteries. Digital subtraction angiography displays arterial anatomy, and the appropriate prostatic arterial supply is selectively embolised to effect stasis in treated prostatic vessels. Various technical variations (including bead size) have been described for PAE, which requires specific training [527, 528].

Efficacy

Superior efficacy of PAE compared with a sham procedure was found in a six-month randomised, single-blind, sham-controlled trial in 80 patients with LUTS, refractory to medical treatment. The decrease in IPSS at six months was 5.03 +/- 8.13 in the sham group and 17.1 +/- 7.25 in the PAE group [529].

An SR and meta-analysis including RCTs and two non-RCTs comparative studies (n = 708 patients) showed that TURP achieved a significantly higher mean postoperative difference for IPSS and IPSS-QoL - 3.80 and 0.73 points, respectively - compared to PAE [530]. All of the functional outcomes assessed were significantly superior after TURP: 3.62mL/s for Q_{max}, 11.51mL for prostate volume, 11.86mL for PVR and 1.02ng/mL for PSA [530].

According to a Cochrane network meta-analysis, PAE may result in little to no difference in urologic symptoms scores as well as QoL compared to TURP at short-term follow-up of three to 12 months [531]. A network meta-analysis included outcome data at three- to six-months follow up and concluded that improvement of IPSS was similarly high after TURP and PUL.

A meta-analysis of 11 RCTs comparing TURP and PAE found no significant difference between TURP and PAE for patient-reported outcomes, including IPSS and QoL at 12 months. Prostatic artery embolisation was less effective regarding improvements in most functional outcomes such as maximum flow rate, PSA [532].

In a randomised, single-centre, non-inferiority trial with five-year follow-up, PAE was shown to result in inferior improvements in IPSS (−7.8 vs. −11.6), Q_{max} (+3.6 vs. +9.3mL/s) and PVR (-28 vs. -220mL) compared to TURP [533].

A SR confirmed that reintervention after PAE is higher than after TURP or enucleation techniques [534].

A Cochrane review reported that, compared to TURP, the impact on urological symptoms and QoL improvement as perceived by patients appears to be similar following PAE [535]. This review did reveal major uncertainty as to how major adverse events compare.

Tolerability and safety

Available RCTs as well as SR and meta-analyses show conflicting results about the comparative rate of adverse events after PAE or TURP depending on studies included, definition of adverse events and follow-up. In an SR of comparative studies, PAE resulted in significantly more adverse events than TURP/OP (41.6% vs. 30.4%). The frequency of AUR after the procedures was significantly higher in the PAE group (9.4% vs. 2.0%) [536]. In another compilation of studies, PAE was associated with significantly fewer overall adverse events but similar rates of severe side effects, as well as shorter hospitalisation times (MD = -1.94 days), but longer procedural times (MD = 51.43 min.) [537].

Another SR and meta-analysis of four studies (506 patients) comparing PAE and TURP found no significant difference in the postoperative complication rate between TURP and PAE [538].

According to a Cochrane network meta-analysis, PAE may also result in a larger reduction in major adverse events than TURP, but the confidence interval includes substantial benefits and harms [531]. In addition, uncertainty exists about the effect of PAE on retreatment compared to TURP at follow-up from 12 to 60 months. A meta-analysis did reveal major uncertainty as to how major adverse events compare between TURP and PAE [535].

According to a non-inferiority trial, 42% of patients who initially had PAE underwent TURP within five years [533].

Concerning sexual adverse events, the mean differences in IIEF-5 score were not significantly different between TURP and PAE in a meta-analysis [537]. Another meta-analysis of two RCTs detected no difference in retrograde ejaculation rates [425]. Postoperative erectile function measured by IIEF-5 was in favour of PAE with MD in change of 2.56 points. In another updated meta-analysis, PAE was consistently associated with lower sexual dysfunction than TURP (OR 0.24) [539].

According to a Cochrane network meta-analysis, uncertainty exists on the effect of PAE on erectile function and ejaculatory function as compared to TURP [531].

Concerns persist regarding non-target embolisation reported in earlier studies [540], however, more recent studies report fewer incidents [530, 541]. In the PROSTATE registry, periprocedural adverse events occurred in ±11.5% of patients, with most being self-limiting. No major non-target embolisations were reported [542]. An SR of 22 studies reporting radiation exposure during PAE with a 20-fold range of exposures estimated that the median risk for a 66-year-old patient of a cancer-related death was 0.117%, equivalent to a reduced life expectancy of 5.4 days. Radiation exposure therefore should be part of the counselling for patients considered for PAE. These data suggest there is potential for significant radiation reduction in some centres using appropriate protocols [543].

Practical considerations

A multidisciplinary team approach of urologists and radiologists is mandatory, and patient selection should be done by urologists and interventional radiologists. The investigation of patients with LUTS to indicate suitability for invasive techniques should be performed by urologists only. This technically demanding procedure should only be carried out by an interventional radiologist with specific mentored training and expertise in PAE [544]. There are data suggesting that larger prostates have a higher chance of a superior outcome with PAE in *post hoc* analysis of RCTs, but larger trials are required to clarify the most suitable patients for PAE [522, 545].

Recent long-term RCT and large registry data underline the importance of counselling patients on the higher probability of retreatment compared to TURP and on the radiation exposure inherent to PAE; centre-level expertise and optimised protocols can reduce these risks [533, 542].

Further data with medium- and long-term follow-up are still required, and comparison with other minimally invasive techniques would be valuable. However, current evidence of safety and efficacy of PAE appears adequate to support the use of this procedure for men with moderate-to-severe LUTS, provided proper arrangements for consent and audit are in place. Therefore, a recommendation has been given, but PAE remains under investigation.

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

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

** PAE remains under investigation*

5.3.4.c Alternative ablative techniques under investigation

5.3.4.c.1 Convective water vapour energy (WAVE) ablation: The water vapour thermal therapy system

Mechanism of action

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

Efficacy

In a multicentre RCT, 197 men were enrolled and randomised in a 2:1 ratio to treatment with water vapour energy ablation or sham treatment [546]. At three months, relief of symptoms (measured by a change in IPSS and Q_{max}) was significantly improved and maintained after WAVE therapy compared to the sham arm, although only the active treatment arm was followed up to 12 months. No relevant impact was observed on PVR. Quality of life outcome was significantly improved with a meaningful treatment response of 52% at 12 months. Further validated objective outcome measures, such as BPH impact index (BPHII), Overactive Bladder Questionnaire Short Form for OAB bother, and impact on QoL and ICS Male Item Short Form Survey for male incontinence, demonstrated improvements of symptoms at three months follow-up with sustained efficacy throughout the study period of 12 months. The reported two-year results in the WVTT cohort arm of the same study and the recently reported five-year results confirmed durability of the clinical outcome after convective water vapour energy ablation [547]. Surgical retreatment rate was 4.4% over five years.

Limited comparative data for WVTT versus reference treatments exists, however, a single-centre RCT with 24-month follow-up comparing WVTT with B-TURP reported greater improvements in IPSS, Q_{max}, PVR and prostate volume after B-TURP. However the WVTT arm achieved -55.3% improvement in IPSS, +62.5% in Q_{max}, -50% in PVR, and preserved antegrade ejaculation in 98% of patients at 12-months, with shorter operative time and hospital stay [548].

A Cochrane review found no studies comparing convective radiofrequency water vapour thermal therapy to any other active treatment form, such as TURP [549]. Another recent network meta-analysis included outcome data at three- to six-months follow-up and concluded that improvement of IPSS was similarly high after TURP and WAVE [550]. Objective outcomes (PVR and Q_{max}) were improved to the greatest extent after TURP, with moderate improvement after WAVE. Water vapour thermal therapy demonstrates a retreatment rate of 15.8% at four years, which includes both surgical reintervention and reinitiation of pharmacotherapy, underscoring the importance of mid-term follow-up and patient counselling [551].

Tolerability and safety

Safety profile was favourable with adverse events documented to be mild-to-moderate and resolving rapidly. Preservation of erectile and ejaculatory function after convective WVTT was demonstrated utilising validated outcome instruments such as the IIEF and the MSHQ-EjD [546]. In the 24-month RCT versus B-TURP, Rezūm (WVTT) showed a lower perioperative complication rate [548].

Practical considerations

There are two SRs of the WFTT cohort studies. One concludes that WFTT provides improvement in BPH symptoms that exceeds established minimal clinically important difference thresholds, preserves sexual function and is associated with low surgical retreatment rates over four years, therefore suggesting that it may be a valuable addition to the urological armamentarium to treat LUTS in men with BPH [552]. The other, a Cochrane review, reported that the CoE ranged from moderate to very low, with study limitations and imprecision being the most common reasons for downgrading of the evidence [549]. A Cochrane network meta-analysis reported uncertainty about the effects of WVTT on retreatment compared to sham treatment at three-months follow-up and the CoE is very low [531]. Evidence at up to 24 months supports the durability of symptom relief and functional improvement, particularly in men prioritising preservation of sexual function and outpatient recovery, although objective improvements are generally greater after TURP [548]. Randomised controlled trials against a reference technique are needed to confirm the first promising clinical results and to evaluate mid- and long-term efficacy and safety of water vapour energy treatment.

In an SR and meta-analysis evaluating WVTT in prostates volumes > 80mL (up to 150mL), favourable outcomes have resulted in an extension in indications in some countries [553].

5.3.4.c.2 Transperineal interstitial laser ablation of the prostate

Mechanism of action

Transperineal interstitial laser ablation (TPLA) uses a CW diode laser, commonly at 1,064nm, that is delivered through transperineal needles guided by US. The procedure results in localised thermal coagulative necrosis within the prostatic tissue, which decreases prostate volume and alleviates obstruction [554].

Efficacy

Transperineal interstitial laser ablation of the prostate has been compared to TURP in two RCTs. One study assigned 50 patients to either TPLA or TURP. After one year, the improvement in Q_{max} was better in the TURP group, while IIEF-5 score was similar between groups [555]. In another RCT, 51 patients were randomised to TPLA (26 patients) or TURP (25 patients). The primary endpoint was a change in ejaculatory function assessed by the Ej-MSHQ at one month after surgery. The distribution of ejaculatory function assessed remained unmodified after TPLA (P = 0.2), while a median 30% decrease in EJ-MSHQ score was observed after TURP (P = 0.01). The Q_{max} was more pronounced after TURP (mean 23.9mL/s improvement) versus 6.0mL/s after TPLA and IPSS showed a mean decrease of 11.6 after TURP versus 5.8 after TPLA with respect to baseline [556].

Tolerability and safety

TPLA is characterised by a low incidence of complications, predominantly minor in nature (Clavien-Dindo grades I-II). Adverse events include transient urinary retention, UTI and perineal pain, while major complications occur infrequently (< 5%). The procedure is generally well tolerated with local anaesthesia, and most patients are discharged within 24 hours [554, 557].

Across studies, > 85% of sexually active patients maintain antegrade ejaculation, and erectile function is generally preserved or improved. This contrasts favourably with TURP and other more invasive procedures, which are associated with higher rates of sexual dysfunction [557-559].

Practical consideration

Despite the encouraging data, adequately powered RCTs with longer follow-up comparing TPLA to a reference technique are required.

5.3.5 *Nonablative techniques*

5.3.5.a *Prostatic urethral lift*

Mechanism of action

Prostatic urethral lift (PUL) is a minimally invasive approach under local or general anaesthesia. Encroaching lateral lobes are compressed by small permanent suture-based implants delivered under cystoscopic guidance, resulting in an opening of the prostatic urethra leaving a continuous anterior channel through the prostatic fossa.

Efficacy

Several reports have shown that PUL achieves a significant improvement in IPSS (-39% to -52%), Q_{max} (+32% to +59%) and QoL (-48% to -53%) [560-565]. In a meta-analysis of retrospective and prospective trials, pooled estimates showed an overall improvement following PUL, including IPSS, Q_{max} and QoL [565]. A Cochrane review of the sham RCT and the RCT against TURP concluded that PUL appears less effective than TURP in improving urological symptoms (IPSS, Q_{max}) in both the short- and long-term, while QoL outcomes may be similar [566]. Prostatic urethral lift was evaluated versus sham in a multicentre study with one- [562], three- [567] and five-years [568] follow-up of the treated cohort. Improvements in IPSS, QoL and Q_{max} were durable with improvement rates of 36%, 50% and 44% at 60-month follow-up, respectively [568]. A network meta-analysis included outcome data at 3- to 6-months follow up and concluded that improvement of IPSS was similarly high after TURP and PUL. Objective outcomes (PVR and Q_{max}) were improved to the greatest extent after TURP, with less improvement after PUL [550].

A retrospective observational study of 1,413 consecutive patients from North America and Australia split patients into those still voiding (Group A) and those in retention (Group B). The results from Group A were comparable to the results from the clinical trials and of the 165 patients in Group B 69% were catheter-free after five days, 83% after one month and 89% by study's end [569].

A real-world analysis of over 50,000 patients undergoing LUTS/BPO procedures [505] found that UroLift was associated with higher long-term surgical reintervention rates, reaching 16.1% at four years, compared to 7.5% for TURP and 7.8% for PVP. The average annual increase in reintervention after year one was 3.6%, suggesting reduced procedural durability of UroLift relative to resective and ablative techniques [505].

Tolerability and safety

The most common complications reported postoperatively included haematuria (16-63%), dysuria (25-58%), pelvic pain (5-17.9%), urgency (7.1-10%), transient incontinence (3.6-16%) and UTI (2.9-11%) [562, 565, 567, 568]. Most symptoms were mild-to-moderate in severity and resolved within two to four weeks after the procedure. In an RCT comparing PUL to TURP, surgical recovery was measured using a validated instrument. They found that recovery from PUL is more rapid and more extensive in the first three to six months [570]. An SR and meta-analysis found that sexual function with regard to erectile and ejaculatory function remained stable or improved slightly during the 24-month follow-up [565, 566, 571].

In an RCT comparing PUL to TURP, PUL resulted in superior quality of recovery and ejaculatory function preservation. Ejaculatory function and bother scores did not change significantly in either treatment arm [570]. When counselling, clinicians should also discuss the comparatively higher mid-term reintervention likelihood after PUL as supported by real-world analyses and network meta-analytic evidence [505].

An SR of surgical reinterventions of 11 studies (2,016 patients), among which TURP/laser (51%), repeat PUL (32.7%) and device explant (19.6%) were most common, revealed an annual rate of surgical reintervention of 6% per year (95% CI: 3.0-8.9) [572]. The retreatment rate was 13.6% over five years in a multicentre study comparing PUL versus sham [568].

Practical considerations

Only limited data is available on treating patients with an obstructed/protruding middle lobe [573]. The effectiveness in large prostate glands has not yet been shown. Long-term studies are needed to evaluate the duration of the effect in comparison to other techniques. Current real-world and network-level evidence reinforces shared decision-making about durability, balancing the advantages of quicker recovery and ejaculatory preservation against a higher probability of reintervention versus TURP/PVP at ± four years [505].

Summary of evidence	LE
Prostatic urethral lift improves IPSS, Q_{max} and QoL. These improvements are inferior to TURP at 24 months.	1b
Prostatic urethral lift has a low incidence of sexual side effects.	1b
Patients should be informed that risk of retreatment has been shown to be higher than after TURP.	3

Recommendation	Strength rating
Offer Prostatic urethral lift (Urolift®) to men with LUTS/benign prostatic obstruction interested in preserving ejaculatory function, with prostates < 70mL and no middle lobe.	Strong
Advise patients that retreatment rates are higher after PUL compared to transurethral resection of the prostate.	Weak

5.3.5.b Intra-prostatic injections

Botulinum toxin-A (BoNT-A), fexapotide triflutate (NX-1207) and PRX302 techniques have been investigated and have been proven to have no benefit in MLUTS/BPO management.

Recommendation	Strength rating
Do not offer intraprostatic injection treatment to patients with LUTS//benign prostatic obstruction.*	Strong

** Refer to previous editions of the Guidelines for full rationale.*

5.3.5.c Non-ablative techniques under investigation

5.3.5.c.1 (i)TIND

Practical considerations

The iTIND is a nitinol device composed of three elongated struts and an anchoring leaflet. Under direct visualisation, iTIND is deployed inside the prostate in expanded configuration. The intended mode of action is to compress obstructive tissue by the expanded device, thereby exerting radial force leading to ischaemic necrosis resulting in a Turner Warwick like incision. The iTIND device is left in position for five days and removed in an outpatient setting by standard urethroscopy.

Efficacy

A single-arm, prospective study of 32 patients with a three-year follow-up was conducted to evaluate feasibility and safety of the procedure [574]. The change from baseline in IPSS, QoL and Q_{max} was significant at every follow-up [575]. In a multicentre RCT, 175 men were randomised 2:1 between iTIND and sham procedures. Patients were assessed at baseline, 45 days, three and 12 months postoperatively. A total of 78.6% of patients in the iTIND arm showed a reduction of ≥ 3 points in IPSS, versus 60% of patients in the control arm at three months. At 12-month follow-up, the iTIND group reported a mean decrease of 9.25 in IPSS and 1.9 points in QoL, and a 3.52mL/s increase in Q_{max} compared to baseline [576]. In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. At twelve-month follow-up, mean IPSS decreased from 22.5 to 8.8 and Q_{max} at one month and increased from 7.3 to 14.7mL/s at 12-month [577].

Another recent network meta-analysis included outcome data at three- to six-months follow up and concluded that IPSS improvement was lower after iTIND compared to TURP. Improvements in objective outcomes (PVR and Q_{max}) were also lower after iTIND [550].

iTIND is associated with a retreatment rate of 5% at three years [551].

Tolerability and safety

The device was reported as well-tolerated by all patients. Four early complications (12.5%) were recorded, including one case of urinary retention (3.1%), one case of transient incontinence due to device displacement (3.1%) and two cases of infection (6.2%). No further complications were recorded during the 36-month follow-up period [575]. In the RCT against sham study, adverse events were typically mild and transient. Most were Clavien-Dindo grade 1 or 2, with 38.1% in the iTIND arm and 17.5% in the control arm [576]. No new EjD or ED has been reported [576, 577].

In a prospective multicentre study, 81 patients were enrolled and treated with a second generation iTIND device. During the 12-month period, two patients required medical therapy, two patients required TURP and ten patients were lost to follow-up [577].

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

5.3.5.c.2 Paclitaxel-coated ballon dilatation of the prostate (Optilume)

Mechanism of action
Optilume represents a minimally invasive therapeutic option for BPO and urethral strictures, integrating mechanical dilation with targeted drug delivery. This system employs a drug-eluting balloon, which serves both to mechanically dilate the affected segment and deliver medication. The balloon is inflated within the prostatic urethra to perform an anterior commissurotomy. Its surface is coated with paclitaxel, facilitating localised drug administration that suppresses smooth muscle cell proliferation and minimises scar tissue formation at the treatment site [578].

Efficacy
Optilume demonstrates rapid and sustained improvements in LUTS, as measured by IPSS. Studies report a ≥ 40% improvement in IPSS in 75-81% of patients at three months, with benefits persisting through one and even four years. The Q_{max} doubled post-treatment, with improvements maintained long-term (e.g. from 10.9 to 18.4mL/s at one year; +5.6mL/s at four years) [578-580].

Tolerability and safety
Most complications observed are mild and transient in nature, such as haematuria, UTI, dysuria and urinary retention. Serious adverse events related to the device or procedure are uncommon. Notably, larger balloon diameters have been associated with increased incidences of bleeding and incontinence [578-580].

Practical consideration
Randomised controlled trials comparing Optilume to a reference technique are required.

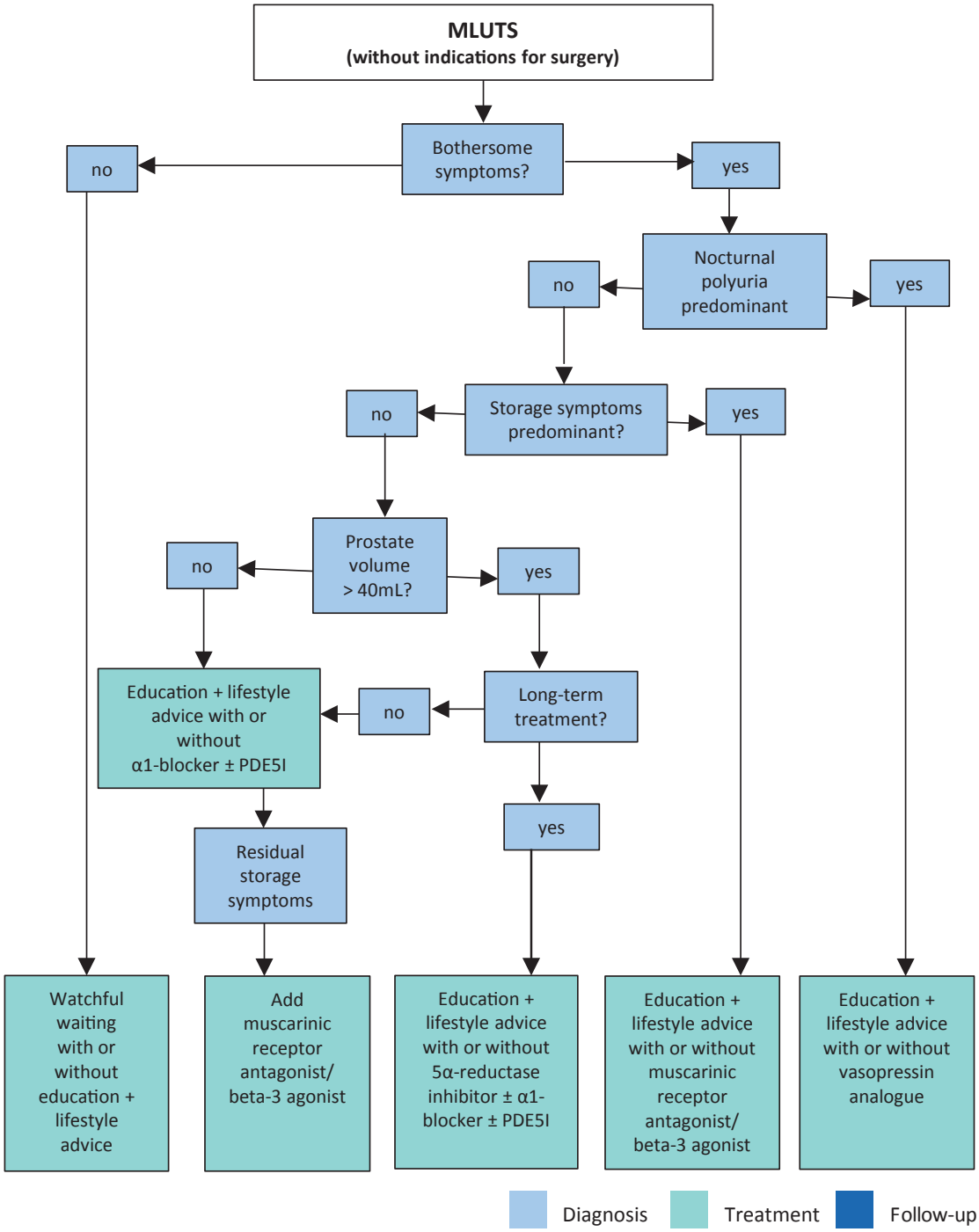
5.4 Patient selection for LUTS/BPO treatment

The choice of treatment depends on the assessed findings of patient evaluation, ability of the treatment to change the findings, treatment preferences of the individual patient, and the expectations to be met in terms of speed of onset, efficacy, side effects, QoL and disease progression.

Behavioural modifications, with or without medical treatments, are usually the first choice of therapy. Figure 3 provides a flow chart illustrating treatment choice according to evidence-based medicine and patient profiles. Surgical treatment is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent UTIs, bladder stones or diverticula, treatment-resistant macroscopic haematuria due to BPH/BPE, or dilatation of the upper urinary tract due to BPO, with or without renal insufficiency (absolute operation indications, need for surgery).

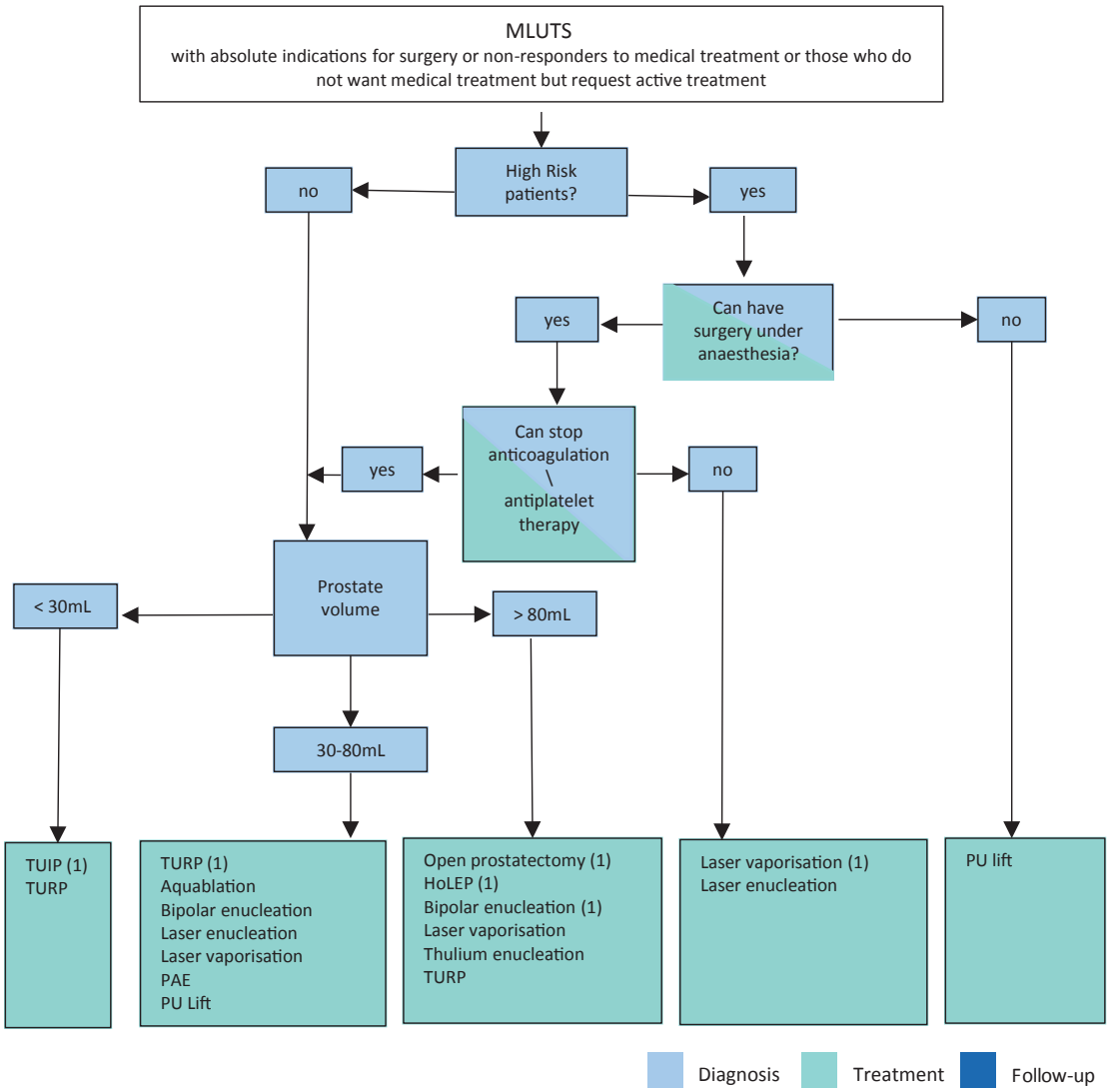
Additionally, surgery is usually needed when patients have not obtained adequate relief from LUTS or PVR using conservative or medical treatments (relative operation indications). The choice of surgical technique depends on prostate size, comorbidities of the patient, ability to have anaesthesia, patients'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

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options



Treatment decisions depend on results assessed during initial evaluation.
Note that patients' preferences may result in different treatment decisions.
α1-blocker = alpha-1 adrenergic receptor blocker; 5α-reductase inhibitor = 5-alpha-reductase inhibitor; LUTS = lower urinary tract symptoms; MLUTS = male lower urinary tract symptoms; PDE5I = phosphodiesterase type 5 inhibitor.

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications



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

The flowchart is stratified by the patient's ability to have anaesthesia, cardiovascular risk and prostate size [416, 421]

5.5 Management of nocturia in men with lower urinary tract symptoms

The following section reports an SR of therapy for the management of nocturia in men with LUTS. It also emphasises the need to consider the wide range of possible causes of nocturia [581].

Nocturia has been defined as the complaint of waking at night to void [3]. The ICS Standardisation Steering Committee has introduced the concept of main sleep period, defined as 'the period from the time of falling asleep to the time of intending to rise for the next day' [582].

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

Table 2: Categories of nocturia

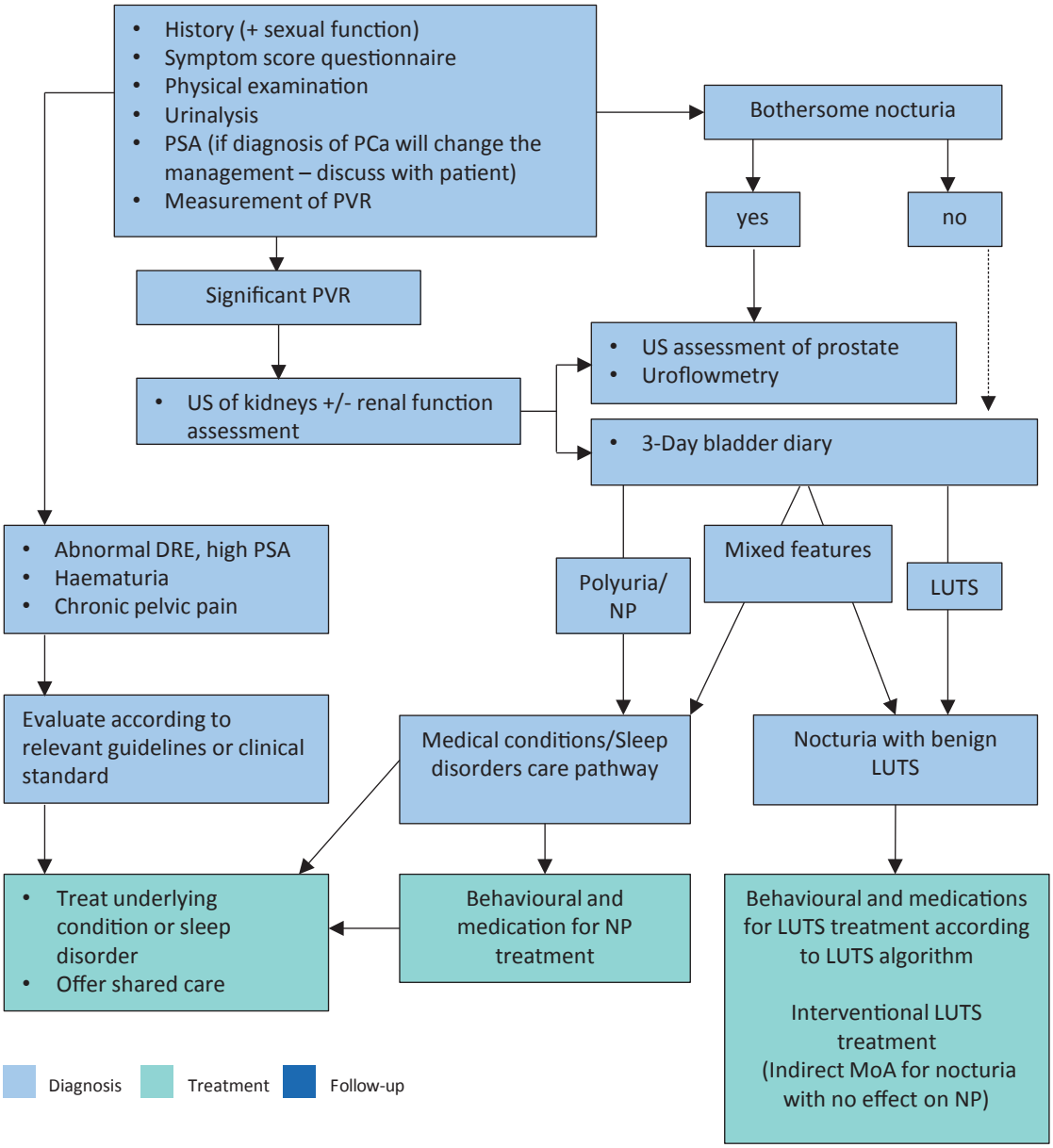
CATEGORY	Disproportionate urine production (at all times or during sleep)	Low volume of each void (at all times or overnight)
Behavioural	Inappropriate fluid intake	'Bladder awareness' due to secondary sleep disturbance
Systemic	Water, salt and metabolite output	
Sleep disorder	Variable water and salt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

5.5.1 Diagnostic assessment

Evaluation is outlined in Figure 5.

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

Figure 5: Evaluation of Nocturia in non-neurogenic MLUTS



Assessment must establish whether the patient has 24-hour (global) polyuria, LUTS, a sleep disorder or a combination of these. Therapy may be driven by the bother it causes, but non bothersome nocturia may warrant assessment with a FVC (indicated by the dotted line) depending on history and clinical examination since potential presence of a serious underlying medical condition must be considered.
DRE = digital rectal examination; FVC = frequency volume chart; LUTS = lower urinary tract symptoms; MLUTS = male lower urinary tract symptoms; MoA = mechanism of action; NP = nocturnal polyuria; PCa = prostate cancer; PVR = post-void residual; PSA = prostate-specific antigen; US = ultrasound.

5.5.2 ***Medical conditions and sleep disorders shared care pathway***

Causative categories for nocturia comprise [583]:

- Bladder storage problems
- 24-hour polyuria (> 40mL/kg urine output over a 24-hour period)
- Nocturnal polyuria (defined as excessive production of urine during the individual's main sleep period, i.e. nocturnal output exceeding 20% of 24-hour urine output in young people, or 33% of urine output in people > 65 years [3], or > 90mL/min. in men [584])
- Sleep disorders
- Mixed aetiology

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

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

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

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

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

IC = intermittent catheterisation; LUTD = Lower urinary tract dysfunction; LUTS = lower urinary tract symptoms; NP = nocturnal polyuria.

5.5.3 Treatment for nocturia

5.5.3.a Antidiuretic therapy

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

Desmopressin is a synthetic analogue of AVP with high V2 receptor affinity and no relevant V1 receptor affinity. Desmopressin has been investigated for treating nocturia [585], with specific doses, titrated dosing, differing formulations and options for route of administration. Most studies have short follow-up. Global interpretation of existing studies is difficult due to the limitations, imprecision, heterogeneity and inconsistencies of the studies.

An SR of randomised or quasi-randomised trials in men with nocturia found that desmopressin may decrease the number of nocturnal voids by -0.46 compared to placebo over short-term follow-up (up to three months). Over intermediate-term follow-up (three to 12 months), there was a change of -0.85 in nocturnal voids in a substantial number of participants without increase in major adverse events [586].

Another SR of comparative trials of men with nocturia as the primary presentation and LUTS including nocturia or NP found that antidiuretic therapy using dose titration was more effective than placebo in relation to nocturnal voiding frequency and duration of undisturbed sleep [581]. Adverse events include headache, hyponatremia, insomnia, dry mouth, hypertension, abdominal pain, peripheral oedema and nausea. Three studies evaluating titrated-dose desmopressin in which men were included reported seven serious adverse events in 530 patients (1.3%) with one death. There were 17 cases of hyponatraemia (3.2%) and seven of hypertension (1.3%). Headache was reported in 53 patients (10%) and nausea in 15 (2.8%) [581].

Hyponatremia is the most important concern, especially in patients > 65 years of age, with potentially life-threatening consequences. Baseline values of sodium over 130mmol/L have been used as inclusion criteria in some research protocols. Assessment of sodium levels must be undertaken at baseline after initiation of treatment or dose titration and during treatment. Desmopressin is not recommended in high-risk groups [581].

Desmopressin oral disintegrating tablets (ODT) have been studied separately in the sex-specific pivotal trials CS41 and CS40 in patients with nocturia [587, 588]. Nearly 87% of included patients had NP and approximately 48% of the patients were > 65 years. The coprimary endpoints in both trials were change in number of nocturia episodes per night from baseline and at least a 33% decrease in the mean number of nocturnal voids from baseline during three months of treatment. The mean change in nocturia episodes from baseline was greater with desmopressin ODT compared to placebo (difference: women = -0.3 [95% CI: -0.5 to -0.1]; men = -0.4 [95% CI: -0.6 to -0.2]). The 33% responder rate was also greater with desmopressin ODT compared to placebo (women: 78% vs. 62%; men: 67% vs. 50%).

Analysis of three published placebo-controlled trials of desmopressin ODT for nocturia showed that clinically significant hyponatraemia was more frequent in patients aged ≥ 65 years than in those aged < 65 years in all dosage groups, including those receiving the minimum effective dose for desmopressin (11% of men aged ≥ 65 years vs. 0% of men aged < 65 years receiving 50mcg; 4% of women ≥ 65 aged years vs. 2% of women aged < 65 years receiving 25mcg). Severe hyponatraemia, defined as ≤ 125mmol/L serum sodium, was rare, affecting 22 of 1,431 (2%) patients overall [589]. In a recent cases series including men aged of more than 60 treated with 50mcg ODT, only 12/80 men had hyponatremia (no severe) after one week. Hyponatraemia persistence was noted in 4/12 cases after reduction to 25mcg [590].

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

Desmopressin acetate nasal spray is a new low-dose formulation of desmopressin and differs from other types of desmopressin formulation due to its bioavailability and route of administration. Desmopressin acetate nasal spray has been investigated in two RCTs including men and women with nocturia (over two episodes per night) and a mean age of 66 years. The average benefit of treatment relative to placebo was statistically significant but low: -0.3 and -0.2 for the 1.5mcg and 0.75mcg doses of desmopressin acetate, respectively. The number of patients with a reduction of more than 50% of nocturia episodes was 48.5% and 37.9%, respectively, compared with 30% in the placebo group [591]. The reported adverse event rate of the studies was rather low, and the risk of hyponatremia was 1.2% and 0.9% for desmopressin acetate 1.5mcg and 0.75mcg, respectively. Desmopressin acetate nasal spray was approved by the FDA in 2017 for the treatment of nocturia due to NP, but it is not available in Europe.

Practical considerations

A complete medical assessment should be made, to exclude potentially non-urological underlying causes, for example, sleep apnoea, before prescribing desmopressin in men with nocturia due to NP. The optimal dose differs between patients, in men < 65 years desmopressin treatment should be initiated at a low dose (0.1mg/day) and may be gradually increased up to a dosage of 0.4mg/day every week until maximum efficacy is reached. Desmopressin is taken once daily before sleeping. Patients should avoid drinking fluids at least one

hour before and for eight hours after dosing. Low dose desmopressin may be prescribed in patients > 65 years. In men ≥ 65 years or older, low dose desmopressin should not be used if the serum sodium concentration is below normal: all patients should be monitored for hyponatremia. Urologists should be cautious when prescribing low-dose desmopressin in patients under-represented in trials (e.g. patients > 75 years) who may have an increased risk of hyponatraemia.

5.5.3.b Medications to treat LUTD

Where LUTD is diagnosed and considered causative of nocturia, relevant medications for storage (and voiding), LUTS may be considered. Applicable medications include; selective α1-adrenergic antagonists [592], antimuscarinics [593-595], 5-ARIs [596] and PDE5Is [597]. However, effect size of these medications is generally small, or not significantly different from placebo when used to treat nocturia [581]. Data on OAB medications (antimuscarinics, beta-3 agonist) generally had a female-predominant population. No studies specifically addressing the impact of OAB medications on nocturia in men were identified [581]. Benefits with combination therapies were not consistently observed.

5.5.3.c Other medications

Agents to promote sleep [598], diuretics [599], non-steroidal anti-inflammatory agents (NSAIDs) [600] and phytotherapy [601] were reported as being associated with response or QoL improvement [581]. Effect size of these medications in nocturia is generally small, or not significantly different from placebo. Larger responses have been reported for some medications, but larger scale confirmatory RCTs are lacking. One recent RCT has compared melatonin + tamsulosin compared to placebo + tamsulosin and found no difference on IPSS change [602]. Agents to promote sleep do not appear to reduce nocturnal voiding frequency but may help patients return to sleep.

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

Recommendations	**Strength rating**
Treat underlying causes of nocturia, including behavioural, systemic condition(s), sleep disorders (e.g. obstructive sleep apnoea), lower urinary tract dysfunction, or a combination of factors.	Strong
Discuss behavioural changes with the patient to reduce nocturnal urine volume and episodes of nocturia and improve sleep quality.	Strong
Offer desmopressin to decrease nocturia due to nocturnal polyuria in men < 65 years of age.	Weak
Screen for hyponatraemia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatraemia.	Strong
Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age.	Strong

Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with voiding LUTS.	Weak
Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder.	Weak
Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40mL).	Weak
Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia.	Weak

5.6 Management of male urinary incontinence

The aim of the following Section is to provide evidence-based recommendations for the management of male UI.

5.6.1 Epidemiology and pathophysiology

Urinary incontinence is defined as an unintentional loss of urine and is reported to have a prevalence of 11% in men aged 60-64 years old to 31% in men ≥ 85 years and to affect up to 32% of men with LUTS [603-605]. Urinary incontinence can be further classified into three types: SUI, UUI and mixed urinary incontinence (MUI). Overflow urinary incontinence, post-micturition dribble, nocturnal enuresis and total incontinence are specific forms of UI that are outside the current scope of these Guidelines. Table 4 provides an overview of the epidemiology and pathophysiology of male UI.

Table 4: Epidemiology and pathophysiology overview of male UI [589-593]

Type	Definition	Causes and associated factors	Pathophysiology	Clinical presentation
Stress UI: prevalence < 10%	Urine loss during movement, on effort or in general during increased abdominal pressure.	• Benign prostatic obstruction surgery • Neurogenic condition • Pelvic surgery • Radical prostatectomy • Urethral surgery • Pelvic radiation	Sphincter deficiency	**Symptoms:** UI during physical activity, exercises, e.g. during coughing, sneezing, no leakage during sleep Voiding diary/pad test: with activity **Voiding diary/Pad test:** with activity **Cough stress test:** leakage can coincide with coughing
Urgency UI: prevalence 40-80%	Urine loss concomitant or immediately following an urgency episode.	• Ageing process • Anorectal dysfunction/GI disorders • Behavioural factors (fluid intake and caffeine consumption) • BPO • Intrinsic bladder diseases (cystitis, fibrosis, interstitial cystitis) • Metabolic syndrome [610] • Neurogenic conditions • UTIs • Causes of both SUI and UUI	• Detrusor overactivity (neurogenic or not) • Urothelial irritation • Increased afferent signalling • Others (pelvic organ cross talk, bladder wall ischemia, etc.)	**Symptoms:** urgency, usually associated with, increased frequency and nocturia **Voiding diary:** urgency, frequency and nocturia, incontinence

Mixed UI: prevalence 10-30%	Any combination of SUI and UUI.	Causes of both SIU and UUI	Combination of SUI and UUI	**Symptoms:** UI on effort and with a sense of urgency **Voiding diary:** variable **Cough stress test:** may show leakage with coughing

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

5.6.2 Diagnostic evaluation

Medical history and physical examination of males with UI is the same as for MLUTS (Figure 2) and should allow UI to be categorised into SUI, UUI or MUI and to identify other types of UI (overflow UI, nocturnal enuresis), or those who need rapid referral to an appropriate specialist (e.g. pelvic diseases, neurological conditions).

Specific validated questionnaires, such as the ICIQ-UI-SF, can help to quantify UI severity. However, a detailed description of the various urinary symptoms questionnaires and Patient-Reported Outcome Measures is beyond the scope of these Guidelines. For more information on available questionnaires, see the 7th ICI review on patient reported outcomes assessment [611].

Voiding diaries are a standardised method of objectively assessing symptom severity, including frequency and extent of UI episodes, voided volume and 24-hour or nocturnal total urine volume [44].

Pad tests can be used to quantify severity of UI and to monitor patient's response to treatment although the usefulness of these tests in differentiating between the different types of incontinence or predicting outcome of treatment is uncertain. Despite this, early postoperative testing with pad tests may predict future continence in men after radical prostatectomy [612, 613].

5.6.2.a Urodynamic testing

Urodynamic testing

Urodynamic studies allow for an objective characterisation of the type of UI and the identification of additional storage and/or voiding dysfunctions [614].

UDS in patients with UI following BPO surgery

Sphincter injury is the most common finding in incontinent men after BPO surgery in some published urodynamic series [615]. However, data coming mostly from case series and reviews, show that besides sphincter incompetence, other LUTD, assessed via UDS, play an incidental role in post BPO surgery incontinence.

Urodynamics has been performed in a retrospective study on 125 patients with incontinence after surgery for BPO. Sphincter injury was the most common finding (66.7% and 79.6% of patients who underwent TURP and OP, respectively [615]). However, decreased detrusor compliance and DO have also emerged as a cause of incontinence on urodynamic examination. Interestingly, both impaired detrusor contraction and DO alone were responsible for UI in 4 to 14% of patients [615].

UDS in patients with UI following radical prostatectomy

Also in this case, UI is mainly due to sphincter deficiency. However, an SR on UDS findings in UI patients following radical prostatectomy showed that while intrinsic urethral sphincter deficiency was reported as the sole cause of UI following radical prostatectomy in 8-71% of cases, it was variably associated with detrusor dysfunction in 0-88% of cases. In details, sphincter weakness was associated with DO in 0-100% of patients, with reduced bladder compliance in 18-58% and with both DO and reduced bladder compliance in 4-64%. Interestingly, incontinent patients who did not complain of sphincter impairment showed detrusor dysfunction as follows: DO in 0%-4%, reduced bladder compliance in 1-12%, and DO plus impairment of bladder compliance in 1-7% [616].

UDS in patients with storage symptoms

In a retrospective evaluation of 668 UDS studies involving men with symptoms of urgency with or without urgency UI, DO was documented in 258 patients (38.6%) and 293 patients (43.9%) had evidence of BOO during PFS. The symptom UI correlated with the presence of DO [617].

The aforementioned evidence emphasises how urodynamic examination serves to clarify the origin of incontinence and the presence of any other associated LUTS. The level of the evidence for the impact of UDS in the evaluation/management/outcome prediction of male patients with UI remains low due to lack of studies [618] and does not allow the Panel to produce any recommendations.

Therefore, UDS should be considered in selected patients with UI or persistent/*de novo* LUTS/UI after surgery, mainly when invasive treatments are considered.

Post-void residual volume measurement can be applied with caution to men with non-neurogenic UI, because the prevalence, severity and clinical application of PVR in men with UI is uncertain. However, a high PVR measurement may indicate further testing is required, like invasive UDS or renal US [619].

Urethrocystoscopy can be performed in selected patients to exclude urethral or bladder neck strictures. Some tests have been proposed to evaluate any sphincter function, for example, repositioning tests, but with poor reliability. The examination of the bladder helps to exclude tumours, stones and diverticula that may exacerbate UI [620].

Imaging (US, MRI, CT scan) can improve the understanding of the anatomical and functional abnormalities that may cause UI and thus help its management [621].

Urinalysis: Reagent strip ('dipstick') urinalysis may indicate UTI, proteinuria, haematuria, or glycosuria, requiring further tests as recommended according to other EAU Guidelines, for example, Guidelines on urinary tract cancers and urological infections [49-52].

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

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

5.6.3 Conservative treatment

5.6.3.a Simple clinical interventions

5.6.3.a.1 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity, and diet. Modification of these factors may improve UI, but most of the evidence for these interventions come from studies with predominately female study populations. As many of these interventions are now generalised public health measures, their recommendation is in line with general medical practice [622-624]. Current evidence does not allow adequate personalisation of lifestyle interventions according to the type of UI.

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with UI to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that low or high 24-hour urine output should be investigated [622, 625, 626]. A cross-sectional population survey found no statistical association between caffeine intake and UI [627]. Conversely, an RCT showed that reduction of caffeine intake, associated with behavioural therapy, resulted in reduced urgency but not UI compared to behavioural therapy alone [628].

5.6.3.a.2 ***Treatment of comorbidities***

Urinary incontinence, especially in the elderly, has been associated with multiple comorbid conditions [629]. Improvement of associated disease may reduce the severity of urinary symptoms, however, this is often difficult to assess as patients frequently suffer from more than one condition. Interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's UI.

In patients with existing UI, particularly the elderly, it may be difficult or impossible to distinguish between the effects of medication, comorbidities or ageing on UI. Although changing drug regimens for underlying diseases may be considered as a possible early intervention, there is limited evidence of benefit [630]. There is also a risk that stopping or altering medication may result in greater harm than benefit.

5.6.3.a.3 ***Constipation***

One RCT with a majority female population found that a multimodal intervention in elderly patients involving assisted toileting, fluid intake and so on reduced the occurrence of UI and constipation, while behavioural therapy appeared to improve both [631]. However, there is no evidence to show whether treating constipation improves UI, although both constipation and UI appear to be improved by certain behavioural interventions.

5.6.3.a.4 ***Containment***

Containment methods include the use of absorbent pads, urinary catheters, external collection devices and penile clamps. An SR of six RCTs comparing various types of pads found that pads filled with super absorbent material were better than standard pads [632]. For men with light UI, a randomised crossover trial found that a leaf-shaped type of pad was preferred to rectangular pads [633].

A Cochrane review compared various types of long-term indwelling and intermittent [634] catheters and found no evidence that one catheter material or type of catheter was superior to another [635]. An SR of non-randomised studies found no differences in UTI outcome or upper urinary tract changes between the use of suprapubic or urethral catheter drainage. However, patients with suprapubic catheters were less likely to have urethral complications [636].

An RCT in 56 men with post-prostatectomy incontinence (PPI) compared sheath drainage system, body-worn urinal, penile clamp and absorbent pads. The results showed that the three devices and absorbent pads have different strengths and limitations that make them more (or less) suitable for particular activities. Most men prefer to use a combination of devices and pads to meet their lifestyle needs. A hinge-type penile clamp was effective for brief, vigorous activities, because it was the most secure, least likely to leak and most discreet, although almost all men described it as uncomfortable or painful [637].

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

Recommendations	**Strength rating**
Inform the patient that lifestyle modifications may improve urinary incontinence (UI); however, patients should be informed that the evidence for these interventions is lacking.	Strong
Review medical conditions and medication associated with the development or worsening of UI.	Strong
Discuss containment options (pads, sheaths, clamps) as a palliative option for the management of UI in a shared decision-making process.	Strong

5.6.3.b Behavioural and physical therapies

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

5.6.3.b.1 Prompted or timed voiding

With prompted voiding, carers rather than the patient initiate the decision to void. Two SRs confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [638, 639]. Timed voiding is defined as fixed, predetermined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding, included two RCTs, found inconsistent improvement in continence compared with standard care in cognitively impaired adults [640].

5.6.3.b.2 Bladder training

Bladder training goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes, and restore patient confidence in controlling bladder function. The ideal form or intensity of a BT program for UI is unclear. It is also unclear whether BT can prevent the development of UI. The addition of BT to anticholinergic therapy did not improve UI compared to antimuscarinics alone, but it did improve frequency and nocturia [641]. In seven RCTs, BT was compared to drug therapy alone and showed only a benefit for oxybutynin in cure and improvement of UI [641].

5.6.3.b.3 Pelvic floor muscle training

A Cochrane review concluded that there was no overall benefit at 12 months post-surgery for men who received postoperative pelvic floor muscle training (PFMT) for the treatment of PPI and that the benefits of conservative treatment of PPI remain uncertain [642]. However, a subsequent SR and meta-analysis showed that PFMT either alone or in combination with biofeedback and/or electrical stimulation was effective for treating PPI, significantly reducing the time to continence recovery [643]. A further meta-analysis demonstrated that the addition of guided programs using biofeedback and/or pelvic floor muscle electric stimulation significantly improved continence recovery rates at one- and three-month intervals post-surgery compared to PFMT alone [644].

Two subsequent SRs in patients who underwent robotic-assisted radical prostatectomy (RARP) demonstrated that the addition of PFMT to the postoperative management plan shortened the time to continence recovery [645, 646].

Other RCTs demonstrated that, like PFMT, increased pelvic floor muscle strength and quicker return to continence may be achieved with the pilates method [647], the oscillating rod [648], a combination of biofeedback with electrostimulation [649] and whole-body vibration training [650]. Moreover, quicker return to continence and improved QoL may be achieved, even with extended and continuing nursing care [651].

The role of supervised PFMT remains controversial.

Pelvic floor muscle training is commonly started as soon as possible after surgery (i.e. between seven and ten days after the withdrawal of the urethral catheter) [652]. However, one RCT found that PFMT was helpful in men who had been incontinent for at least one year after prostatectomy and who had had no previous therapy [653].

Two RCTs have shown that written instructions alone offer similar levels of improvement to supervised PFMT [654, 655]. An RCT comparing the outcomes of an eight-week home-based PFMT with action and cue observation ($n = 46$) and without (control, $n = 46$) in patients with UI after RP revealed significantly larger improvements in 24-hour pad test in the active treatment group (MD: 106.1g; 95% CI: 13.4g, 199.1g, $p = 0.037$) [656].

An RCT compared supervised PFMT with a physiotherapist (started two months before RARP and continued for 12 months after) versus verbal instructions plus a brochure about PFMT plus lifestyle advice. Significantly higher UI improvements were observed following supervised PFMT in terms of 24-hour pad weight at three months (5.0g vs. 21.0g; effect size: 0.34). A significant improvement was also seen in the intervention group in terms of continence rates (no pad use) at 12 months after surgery (65.2% vs. 31.6%) [657].

An RCT showed that adding comprehensive lifestyle recommendations + Knack manoeuvre to conventional PFMT provides greatest improvement in terms of subjective severity and impact of UI, objective severity of UI, health-related QoL and patient global impression of severity and improvement at eight weeks [658].

One RCT compared PFMT to no treatment in men undergoing TURP. No demonstrable difference was observed in the incidence of postoperative incontinence up to 12 months [659]. On the other hand, an RCT in men who underwent HoLEP demonstrated that PFMT, when started preoperatively, promoted early recovery of continence [660].

The role of preoperative PFMT role remains to be established.

5.6.3.b.4 ***Electrical stimulation***

Electromagnetic stimulation has been promoted as a treatment for UI, but only weak evidence of the short- and long-term effects has been reported in SRs [661, 662].

An SR found insufficient evidence to suggest that electrical stimulation is beneficial for male patients with PPI [663].

An RCT of 70 PPI men receiving surface or intra-anal electrostimulation reported a significant reduction in UI in terms of grams of urine loss and a significant improvement in QoL from baseline, but no statistically significant difference between treatment arms [664].

A Cochrane review of six RCTs on electrical stimulation in men with UI concluded that there was some evidence that electrical stimulation enhanced the effect of PFMT in the short-term but not after six months. Electrical stimulation was also more effective than sham stimulation at six, but not 12 months; however, there were more adverse effects including pain and discomfort with electrical stimulation [665].

5.6.3.b.5 ***Posterior tibial nerve stimulation***

Posterior tibial nerve stimulation (PTNS) has been studied as a treatment of UI, especially UUI. Electrical stimulation of the posterior tibial nerve delivers electrical stimuli to the sacral micturition centre via the S2-S4 sacral nerve plexus. Stimulation is done either percutaneously using a fine, 34-G needle inserted just above the medial aspect of the ankle (P-PTNS) or transcutaneously using surface electrodes (T-PTNS). Percutaneous-PTNS treatment cycles typically consist of 12 weekly treatments of 30 minutes, and T-PTNS treatment cycles typically consists of self-administered 20-minute daily sessions after adequate education.

A female-predominant, sham-controlled RCT assessed the effectiveness of P-PTNS in OAB population. The treatment and sham arms included 22.8% and 20% males, respectively [666]. Overactive bladder symptoms improved significantly in 54.5% of patients in the P-PTNS arm compared to 20.9% in the sham arm. A noninferiority RCT comparing T-PTNS to P-PTNS reported significant improvements in daytime frequency, urgency and UUI episodes without significant difference between treatment arms after 12 weeks of therapy [667]. An SR on T-PTNS in idiopathic and neurogenic female-predominant (males < 10%) population, reported significant improvement in OAB symptoms in 48-93% of patients and cure of UUI episodes in 25-45% [668].

For T-PTNS, mild pain and discomfort at the puncture site is the most common adverse event [669]. Small hematomas, swelling, leg tingling and vasovagal reaction to needle placement have also been reported [666]. Treatment adherence is generally high at 89.7% [667]. Contraindications include a cardiac pacemaker and skin disease at the site of stimulation.

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

Summary of evidence	**LE**
Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
The combination of BT with antimuscarinic drugs does not result in greater improvement of UI but may improve frequency and nocturia.	1b
There is conflicting evidence on whether the addition of BT, electrostimulation or biofeedback increases the effectiveness of PFMT alone.	1b

Preoperative PFMT does not confer additional benefit to men undergoing radical prostatectomy.	1b
Electrical stimulation may add benefit to PFMT up to six months.	2
There is limited evidence for the effectiveness of PTNS in male population.	2
There is no evidence that PTNS cures UUI in male population.	2

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

5.6.4 Pharmacological management

5.6.4.a Drugs for urgency urinary incontinence (UUI)

Muscarinic receptor antagonists [670-673] and beta-3 agonists [318-320, 674-677] are currently the first-line pharmacological treatments for UUI. The mechanism of action, efficacy and safety and tolerability profiles of both classes of drugs are discussed in detail in Sections 5.2.3 and 5.2.4, respectively.

5.6.4.b Drugs for stress urinary incontinence

An SR of eight studies evaluating the efficacy of duloxetine in postprostatectomy SUI reported that duloxetine resulted in a mean dry rate of 58% (25-89%), mean improvement in pad number of 61% (12-100%), and mean improvement in one-hour pad weight of 68% (53-90%) at short-term follow-up (mean one to nine months) [678]. However, mean adverse event rates were high, and treatment was discontinued in 38% of cases. The most common adverse events included fatigue, somnolence and nausea, and were reported in 18% of patients [678]. The overall certainty of evidence was low due to study heterogeneity and methodological limitations. Further RCTs with long-term follow-up are required.

Duloxetine is currently prescribed in an off-label setting in men with SUI.

Summary of evidence	LE
Antimuscarinic monotherapy can significantly improve urgency, UUI and increased daytime frequency.	1b
Beta-3 agonist is superior to placebo and as efficacious as antimuscarinics for improvement of UUI.	1b
Duloxetine led to a short-term improvement in postprostatectomy SUI symptoms and QoL improvement, however, a considerable proportion of men discontinued treatment.	1b

Recommendations	Strength rating
Offer antimuscarinic drugs or beta-3 agonists* to adults with urgency urinary incontinence who failed conservative treatment.	Strong
Offer duloxetine to men with stress urinary incontinence.	Weak
Inform patients about the possible adverse events of duloxetine and that its use is off-label for this indication in Europe.	Strong

**Further evidence is awaited for Vibegron.*

5.6.5 Surgical treatment for stress urinary incontinence

5.6.5.a Bulking agents in men

Mechanism of action

Urethral bulking agents work by adding bulk and improving the coaptation of a damaged sphincter zone. They represent a treatment option for men with either small volume leak or for those unfit for more invasive treatment options [679].

Efficacy

A Cochrane review on surgical treatment of PPI identified only one RCT that fulfilled the inclusion criteria. This trial randomised 45 men to Macroplastique injection or artificial urinary sphincter (AUS) implantation and compared their outcomes at 48 months [679]. Significant improvement was reported in both groups for men with minimal incontinence, but in men with total incontinence there was a significant difference in continence rates favouring AUS implantation (72% vs. 23%) [680]. An SR of eight studies (n = 142) in men using

Macroplastique, Opsys, Durasphere and Urolastic showed short-term improvement and reported dry rates between 0 and 83% [679]. A propensity score-matched analysis of 104 men with post-prostatectomy stress urinary incontinence (PP-SUI), compared submucosal injection of Macroplastique to transobturator male sling (TiLOOP male) [681]. At 12-month follow-up, the reported failure free rates were 15.4% and 76.9%, the daily use of zero to one pads was 21.2%, and 67.3% and the satisfaction rate was 3.8% and 71.2%, respectively. Several small cohort studies of several different bulking agents have not shown any benefit.

A narrative review including data from 25 articles reported a success rate with all bulking procedures of 54.3%, with a 37.5% symptoms improvement and nearly 30% of dryness [682].

In an SR and meta-analysis, three studies addressed bulking agents. Two of them, involving a total of 384 participants, showed a pooled short-term cure rate of 26.1%, and a single study on 68 subjects reported a 10.3% long term cure rate. Short- and long-term reoperation rates were not described [683].

Tolerability and safety

Bulking agent-associated dysuria and haematuria are frequently reported to be transient and self-resolving [679]. The risk of urinary retention requiring intermittent catheterisation (IC), or long-term catheter use is minimal [684]. However, they may provoke allergic reactions [685] and carry a potential risk for migration [686] to proximal and distal lymph nodes [687]. Overall, post-procedural urinary retention rates range between 3 and 17% with rare need for temporary catheterisation, while postoperative UTIs ranged from 6 to 7% [682].

Practical considerations

Bulking agents have shown low cure rates but remain an option for men unfit for more invasive treatment options. They currently do not play a role in clinical practice. Further clinical trials are warranted.

Summary of evidence	LE
There is very limited evidence that bulking agents are effective for the treatment of PP-SUI.	2

5.6.5.b Male slings

Male slings are used to treat mild-to-moderate PP-SUI [688]. However, the definitions of mild and moderate UI are unclear. Most studies define cure as 'no pad use' or 'one security pad per 24 hours.' Some authors used stricter criteria, such as 'urine loss of less than 2g per 24-hour pad test' [689].

5.6.5.b.1 Nonadjustable slings

Nonadjustable male slings are positioned under the urethra and fixed by means of a retropubic or transobturator approach. The tension is adjusted during the surgery and cannot be readjusted postoperatively. Synthetic slings restore continence in males either by urethral compression and/or by repositioning the bulb of urethra [690, 691].

Efficacy

An SR and meta-analysis involving 33 prospective cohorts and one RCT comparing sling to AUS reported that both options are effective in improving UI and QoL [692]. Following sling insertion, the overall cure rate was 60% (95% CI: 0.51-0.67) and 56% (95% CI: 0.44-0.68) for sling and AUS, respectively. The 24-hour pad use was -3.33 (95% CI: -4.33 to -2.34) and -3.75 (95% CI: -4.56 to -2.93) for slings and AUS, respectively. Similar findings were reported by a network meta-analysis that showed comparable efficacy between slings and AUS [693].

The MASTER trial, a non-inferiority RCT comparing the outcomes of continence surgery in men with bothersome urodynamic SUI, using a very strict definition of UI after prostate surgery reported that, at 12 months, incontinence rates were 87% for male sling versus 84.2% for AUS (95% CI: -11.6-4.6; $P_{NI} = 0.003$), confirming non-inferiority [694]. The subgroup analysis suggested that male sling is inferior to AUS for men with greater incontinence at baseline (pad weight > 250g), however, the difference did not reach statistical significance.

For the repositioning sling (AdVance™ and AdVanceXP©), a mean subjective cure rate of 49% (8.6-73.7%) after mean follow-up of three years has been reported for 136 patients [688]. A prospective multicentre cohort study with 60-month follow-up in men with AdVanceXP demonstrated a constant continence outcome over time with a 57.6% cure rate, 25.4% improvement rate and 16.9% failure rate. These findings were verified in an additional study which reported cure rates of 66.7% and 71.7%, improvement rates of 26.5% and 24.4%, and failures rates of 6.9% and 13.3% at 24 and 48 months, respectively [695]. A retrospective comparative study showed that both options are safe and effective in the treatment of male SUI [696].

With the transobturator compressive I-Stop TOMS male sling, 38% of men were dry at 12 months, but this dropped to 23% and 15% after four and five years, respectively [697].

Tolerability and safety

An SR and meta-analysis of 1,170 men with SUI and male sling reported that the predictors of failure are prior radiation, severity of incontinence and previous surgeries [698]. Pelvic radiotherapy has also been reported in other studies as a negative prognostic factor [699]. A comparison among radiated versus nonradiated men who had AdVanceXP reported a greater degree of postoperative improvement in the nonradiated group (49.6% vs. 22.2%), as well as greater satisfaction rates (95% vs. 64%) [700]. The most common complication with male slings is pain and local superficial wound infection [701]. Chronic pain has been observed in 1.3% of men who had nonadjustable slings [701]. Postoperative transient voiding dysfunction occurred in 4.3-10.3%, mostly as *de novo* urgency or urinary retention, while erosions and chronic pain were uncommon (0-0.4%), as was explantation [688, 695, 702-704].

Practical considerations

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

5.6.5.b.2 Adjustable slings in males

Mechanism of action

Adjustable slings in males are those for which the tension of the sling can be adjusted postoperatively. Three main systems have been used in men: Remeex® [705], Argus® [706] and ATOMS® [707].

Efficacy

One small RCT was carried out for adjustable slings in males [708]. Most studies consist of prospective or retrospective case series with variable follow-up and various definitions of success [705, 707-711]. An SR reported objective cure rates varying between 17 and 92% after adjustable sling implantation [701].

For the Remeex® system, only two studies with conflicting findings have been published. One study followed 19 patients for nearly seven years and reported 70% success, with no explants, infections or erosions [705]. The second study followed 14 patients for 25 months. Only 36% of patients were satisfied and multiple readjustments were needed. Mechanical failure was reported in 21% [709].

Data on the Argus® system has been reported for 404 men, but only a few series have reported on more than 40 patients, with the longest follow-up being 35-months. Success rates varied between 17-93%, with a mean of 73.0% reporting subjective cure [710, 711]. A head-to-head comparison between the two Argus® systems reported similar efficacy outcomes at 44 months, but Argus T® was associated with a higher inguinal pain and explantation rate [712]. A small study of 22 men with PPI randomised to AdVance® or Argus T® reported superior 24-hour pad test results and of patient satisfaction levels for Argus T at 18-month follow-up [708].

An SR of the ATOMS® system reported the pooled evidence from 1,393 patients with 67% dryness, 90% improvement after adjustment and 16.4% complication rate [707]. The expulsion rate was 5.75%. Another SR and meta-analysis with 3,059 patients reported that ATOMS® was superior to ProACT® in mean dryness rate (68% vs. 55%), overall improvement (91% vs. 80%), satisfaction rate (87% vs. 56%), mean number of filing adjustments (2.4 vs. 3.5) and postoperative pad use per day (1.1 vs. 2.1) [713].

Tolerability and safety

The most frequent complications in adjustable male slings are pain, erosions and infections [701]. Pain at the implant site was usually only temporary, but chronic pain has been reported in 1.5% of men [710, 711]. The number of implants requiring readjustment is reported between 8 and 38.6% [711, 714, 715]. Explantation (partial or total) rates range from 10 to 15.8% and the erosion rate is estimated at approximately 10% [698]. The most common reasons for explantation are device infection (4.1-8%), erosions (4-12%) and urethral perforations (2.7-16%). An SR reported a device explantation rate of 5% versus 25% and a major complication rate of 4.2% versus 10.4% for ATOMS® and ProACT®, respectively [713].

Practical considerations

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

5.6.5.b.3 *Autologous slings*

The strategy of intraoperative placement of an autologous vas deferens sling below the vesicourethral anastomosis during RARP has been explored with the intention to improve early return of continence. Two comparative studies [716, 717] showed an advantage of sling versus no sling at one-month follow-up, and another study [718] showed an advantage of a six-branch versus a two-branch sling at one-month follow-up. However, a larger RCT (n = 195) showed that continence rate and near-continence rate were similar between groups at six months with 66% versus 65% and 86% versus 88%, respectively [719].

Summary of evidence	LE
There is limited short-, medium- and long-term evidence that fixed transobturator male slings cure or improve PP-SUI in patients with mild-to-moderate SUI.	1b
Men with severe incontinence, previous radiotherapy or transurethral surgery may have less benefit from fixed transobturator male slings.	2
There is limited evidence that adjustable male slings can cure or improve SUI in men.	3
There is no evidence that adjustability offers additional benefit over other types of slings.	3
Explantation rate of adjustable male slings seems higher than fixed male sling.	4

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

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

5.6.5.c Compression devices in males

5.6.5.c.1 *Artificial urinary sphincter*

Mechanism of action

The AUS is the standard treatment for moderate-to-severe male SUI. The AMS 800 three-component system with inflatable cuff, control pump and pressure regulating balloon is the device with the longest follow-up and the greatest level of evidence [720]. The ZSI 375 is a two-component device, inflatable cuff and control pump, allowing an easier implantation process [721]. Other AUS devices have been launched, for example, the Victo, UroActive® and Br-SL-AS 904 systems, but robust evidence regarding their efficacy and safety is pending [722].

Efficacy

A meta-analysis of 33 cohort studies and one RCT reported significant improvement after AUS implantation in overall cure rates (56%) and reductions in pad use per 24-hours (-3.75) [692]. Several observational studies reported on functional outcomes after AMS 800. Social continence rates (zero to one pads used daily) ranged from 55 to 76.8% [723-725]. A 77.2% continence rate and 89.5% subjective satisfaction rate have been reported after a median follow-up of > 15 years in 57 men who had undergone AUS placement [726]. A prospective cohort study of 40 patients with a mean follow-up of 53 months showed that, of all urodynamic parameters, only low bladder compliance had a negative impact on outcome [727].

However, another retrospective study showed that no urodynamic factors adversely altered the outcome of AUS implantation [728].

Some recent multicentre studies have confirmed older statements that surgeon experience and higher surgical volume is associated with better outcomes and a lower revision rate after AUS implantation [729, 730].

The data regarding ZSI 375 are limited. A retrospective, non-randomised trial across several centres in Europe, reported an 84.4% success rate (19.3% dry rate and 65.1% improved zero to one pads per day) after 43 months [721]. A 72% success rate was reported at seven years' follow-up for 45 patients who underwent placement of the ZSI 375 device in France [731].

A retrospective study of 168 patients receiving AUS (AMS 800 AUS system) placements carried out by a single surgeon from 2008 to 2016 at a high-volume academic institution evaluated the causes of AUS failure at a median follow-up from initial placement of 2.7 years. Overall, 63 patients (37.5%) experienced AUS failure

requiring device explant/revision. Pressure-regulating balloon malfunction, cuff malfunction, pump malfunction, urethral atrophy, urethral erosion and infection occurred in 36.5%, 7.9%, 6.3%, 22.2%, 19.0% and 12.7% of all AUS failures, respectively. History of previous pelvic radiotherapy, urethral stricture, urethral sling placement and coronary artery disease were independent predictors of all-cause AUS failure [732].

A retrospective review of all cases of AUS implantation performed between 2005 and 2020 in 16 different French centres, including patients with primary implantation whose indication was moderate-to-severe SUI after radical prostatectomy (n = 417) or BPO surgery (n = 50) found similar social continence rates (zero or one pad per day) at three months between the groups (79% vs. 72%) [733].

Tolerability and safety

Artificial urinary sphincter complications include device infection/erosion (8.5%), mechanical failure (6.2%) and urethral atrophy (7.9%) [734]. In multivariate analysis, radiation therapy was independently associated with risk of urethral atrophy [725]. Urethral erosion is associated with previous irradiation and penoscrotal approach [735]. The reported revision rates at three years for any reason were 10-29.1% [723, 735-737]. The risk of urethral erosion after ZSI 375 AUS is 8.2-13.3% and risk of mechanical failure is 2.2-2.5% [721].

A retrospective database comparison found that significantly higher complication rates in patients have been reported to be significantly higher in patients undergoing AUS implantation due to UI following BPO surgery compared to patients with post-prostatectomy UI (8% vs. 18%; p = 0.044). The same was found for the Clavien-Dindo type 2 complication rate (20.6% vs. 44.4%; p = 0.026) [733].

A retrospective chart review of 1,020 patients who underwent AUS implantation in 16 centres showed an estimated five-year and ten-year overall revision-free survival of 60% and 40%, respectively. Reasons for revision were mechanical failures (27.6%), nonmechanical failures (56.5%) and other causes (15.9%). In multivariable analysis, larger cuff size was the only predictor of overall revisions (HR = 1.04 [1.01-1.07]; p = 0.01) and revision for nonmechanical failure (HR = 1.05 [1.02-1.09]; p = 0.004) [738].

A population-based retrospective cohort study including 8,475 men who underwent a first-ever AUS implantation for male SUI after prostate cancer or BPH treatment in France found reintervention-free survival rates of 71%, 57% and 40% at two, five and ten years, respectively. Reintervention-free survival was lower after BPH surgery, after radiotherapy combined with RP and in centres performing fewer implantations. Removal-free survival rates were 83%, 75% and 66% at two, five and ten years, respectively [739].

Practical considerations

Artificial urinary sphincter is efficacious and improves the QoL of men with PP-SUI. To minimise complications, it is advised to refer patients to specialised centres experienced in AUS implementation. Men considering insertion of an AUS should be fully informed that the success of the intervention relies on their ability to operate the pump. Treating physicians should bear in mind that operating the AUS may become difficult in men who develop cognitive impairment or lose manual dexterity. Artificial urinary sphincter has a limited lifespan and 'maintenance' reoperations are common in the long-term. These reinterventions should not be classified as complications [720].

The European prospective multicentre SATURN registry was developed to analyse surgical devices for male SUI. One-year self-reported cure rates (zero to one pads/die) by device were as follows: Advance-XP, 73%; other sling, 37%; ProACT®, 50%; AMS800, 76%; other AUS, 11%; and overall group, 68%. Overall, 132 patients had at least one revision (n = 122 for 110 patients with an AUS; n = 29 for 22 patients with a sling or ProACT®) [740].

5.6.5.c.2 Non-circumferential compression device (ProACT®)

Mechanism of action

The ProACT® system consists of two devices. Each device includes the balloon, the bilumen tubing and the volume-adjustment port. The devices are introduced by a trocar by means of two small perineal incisions and are placed under fluoroscopic guidance on each side of the bladder neck, close to the vesicourethral anastomotic site. The balloons can be filled and their volume can be adjusted postoperatively using a hypodermic needle injected through the intra-scrotal port.

Efficacy

An SR and meta-analysis of 19 studies including 1,264 patients reported a 60.2% dry rate, significant reduction in number of pads used per day (-3.1) and greatly improved QoL for ProACT® [741]. However, the level of heterogeneity among the included studies was high. A comparison between ATOMS® and ProACT® showed that the former is associated with higher improvement and satisfaction rates and fewer complications [713]. A quasi-randomised trial comparing ProACT® with bone-anchored male slings found that both resulted in similar improvements in SUI (68% vs. 65%, respectively) [742]. A questionnaire study showed that 50% of patients were still significantly bothered by persistent incontinence following ProACT® [743]. A subgroup analysis of radiotherapy patients reported worst outcomes as compared to patients not receiving radiotherapy (46% vs. 68% success rate) as well as a higher percentage of urethral erosion for ProACT® [744].

An updated SR and meta-analysis (18 studies involving 1,570 patients suffering from mild-to-moderate [60.7%] and severe [40.4%] post-RP SUI) showed an overall dryness rate (zero to one pads/day) of 55.1% at a mean follow-up of: 34.7 months [745].

Tolerability and safety

The most common intra-operative complication during ProACT® implantation is perforation of the bladder and/or urethra. A meta-analysis estimated a perforation rate of 5.3% [741]. The estimated overall revision rate is 22.2%, and the main causes are erosion (3.8%), device leaking (4.1%) and migration (6.5%) [741]. Other prospective series have shown that adverse events were frequent, leading to an explantation rate of 11-58% [742, 743, 746-748].

A meta-analysis reported a mean overall complication rate of 31.2%, an explantation rate of 26.5%, and a reoperation rate of 22.7% at a mean follow-up of 34.7 months [745].

Practical considerations

ProACT® has a satisfactory rate of success and appears to be a reasonable alternative for the treatment of male UI. However, it is associated with high complication rates.

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

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

5.6.6 Surgical treatment for urgency urinary incontinence

5.6.6.a Bladder wall injection of botulinum toxin-A

Mechanism of action

The primary mechanism of action of BoNT-A is through the inhibition of neurotransmitter release from cholinergic neurons [749]. OnabotulinumtoxinA (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory non-neurogenic UUI in adults [750, 751].

Efficacy

An RCT of OAB-wet patients whose symptoms were not adequately managed with anticholinergics and who receive either bladder wall injections of onabotA (100 U) or saline reported a 50% reduction in UUI episodes/day, whilst the number of micturitions/day reduced by more than two in patients receiving onabotA [752]. A total of 22.9% of the patients in the onabotA arm were fully dry versus 6.5% in the saline arm.

An SR and meta-analysis comparing the efficacy of onabotA, mirabegron and anticholinergics in adults with idiopathic OAB reported that patients who received onabotA (100 U) achieved greater reduction in UUI episodes, micturition frequency and the highest odds of achieving dryness, as well as > 50% reduction from baseline UUI episodes per day [753].

A randomised, placebo-controlled pilot study assessing the effect of onabotA for the treatment of refractory OAB symptoms after prostatectomy reported significantly improved QoL and ICIQ scores and improvements in daily frequency in patients receiving onabotA compared to placebo [754]. A retrospective trial assessed onabotA efficacy in 65 non-obstructed men with refractory OAB and reported significant improvement in UDI-6 score (-4.2) and IIQ-7 (-6.0) scores compared to baseline [755].

In a retrospective, single-centre cohort study of 120 patients treated with onabotA for OAB, lower IC rates were reported in male patients with prior de-obstructive surgery compared with surgery-naïve patients (28.6% IC in the group without prior surgery, 7.5% in the TURP subgroup, and 4.2% in the radical prostatectomy subgroup) [756].

A phase IIIb trial of randomised solifenacin-naïve patients (10% males) with refractory OAB to onabotA, solifenacin or placebo showed that patients receiving onabotA had significantly greater changes in UUI episodes (-3.19) compared to solifenacin (-2.6) and placebo (-1.33) [757].

A network meta-analysis (male population range 9.8-40.2%) that compared onabotA to mirabegron demonstrated that onabotA was associated with improved outcomes in frequency episodes per day (-0.43; [-1.22-0.37]) and in UUI episodes per day (-0.46, [-1.46-0.53]) [758].

Tolerability and safety

Urinary retention and UTIs are the two most common adverse events after onabotA injection. Other reported adverse events include haematuria, dysuria and post-treatment pain [759]. Compared to mirabegron, onabotA is associated with higher risk for UTI and treatment emergent adverse events [758]. A retrospective analysis compared the use of IC after onabotA injection among men who had previous prostatectomy versus those without prior surgery [756]. A 7.5% catheterisation rate after TURP, 4.2% rate after radical prostatectomy and 28.6% rate in men without prior prostate surgery was reported.

Practical considerations

BoNT-A injection is a treatment option for men with refractory UUI. Despite the lack of a universally accepted injection protocol, gender-specific studies and absence of studies in BPO patients, BoNT-A seems superior to medical therapy. BoNT-A is associated with higher UTIs and urinary retention risk coupled with the need for repeated injections. A dedicated series in male population focused on treatment persistence has shown a high discontinuation rate (68.8%) [760]. Patients treated for OAB with onabotA treatment that have not undergone prior de-obstruction are more likely to develop retention and subsequent IC.

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

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

5.6.6.b Sacral neuromodulation (SNM)

Mechanism of action

Sacral neuromodulation (SNM) delivers low amplitude electrical impulses to the sacral nerve roots via an electrode implanted adjacent to the third sacral nerve root and connected to an attached pulse generator implanted in the buttock. Sacral neuromodulation work by modulating neural activity, thus stabilising bladder electrical activity through an unknown mechanism. It is a two-stage process: in the first stage, a percutaneous nerve evaluation lead or tined lead electrode is placed percutaneously near the S3 (or if not found, near the S4) root and linked to an external stimulator to assess the response. If symptoms reduced by at least 50%, patients are candidates for the second stage, which is the full implant.

Efficacy

Several trials assess the clinical effectiveness of SNM. All RCTs suffer from the limitation that patients and assessors cannot be blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. In addition, the percentage of male population in these trials is approximately 10%. A meta-analysis compared the effectiveness of SNM to onabotA and reported no significant difference in successfully treated cases at six-months follow-up (RR 0.93; 95% CI: 0.63-1.39) [761].

Tolerability and safety

The main complications after SNM are pain at the implant site (13-42%), lead migration (4.0-21%), leg or back pain (3.0-18%) and wound infection (5.7-6.7%). Surgical revision is required in 29-33% of patients due to device malfunction, battery or device replacement or lead migration [762].

Practical considerations

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

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

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

5.6.6.c Cystoplasty/urinary diversion

Mechanism of action

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

Efficacy

There are no RCTs comparing bladder augmentation to other treatments for patients with refractory OAB/UUI. In a large study with three-years follow-up, augmentation cystoplasty resulted in a postoperative continence rate of 93% in idiopathic DO patients, 78% in neurogenic overactivity and up to 90% when an AUS was implanted, respectively [763]. The largest case series of bladder augmentation in an idiopathic population included only women [764]. At an average follow up of 75.4 months only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. A small prospective mixed gender trial reported high patient satisfaction rates with augmentation cystoplasty versus onabotA therapy [765]. A small study comparing ileal with colonic conduits concluded that there were no differences in the relative risks of upper urinary tract infection and uretero-intestinal stenosis [766]. However, there are no studies that have specifically examined these techniques in the treatment of intractable OAB/UUI [766]. Therefore, careful consideration on which operation is undertaken will depend on thorough preoperative counselling, access to stoma/continence nurses as well as patient factors to allow for fully informed patient choice.

Tolerability and safety

Cystoplasty and urinary diversion are major urological operations. The early postoperative complications include infection, bowel obstruction, bleeding and cardiorespiratory complications. Long-term complications include metabolic disturbances (hyperchloraemic metabolic acidosis if ileum is used), change in bowel habits, increased mucus production, stone formation, bladder perforation and rarely bladder cancer [767]. Following augmentation cystoplasty or diversion, the majority of patients will depend on self-catheterisation for bladder emptying. Patients with urinary conduit will depend on lifelong urine bags.

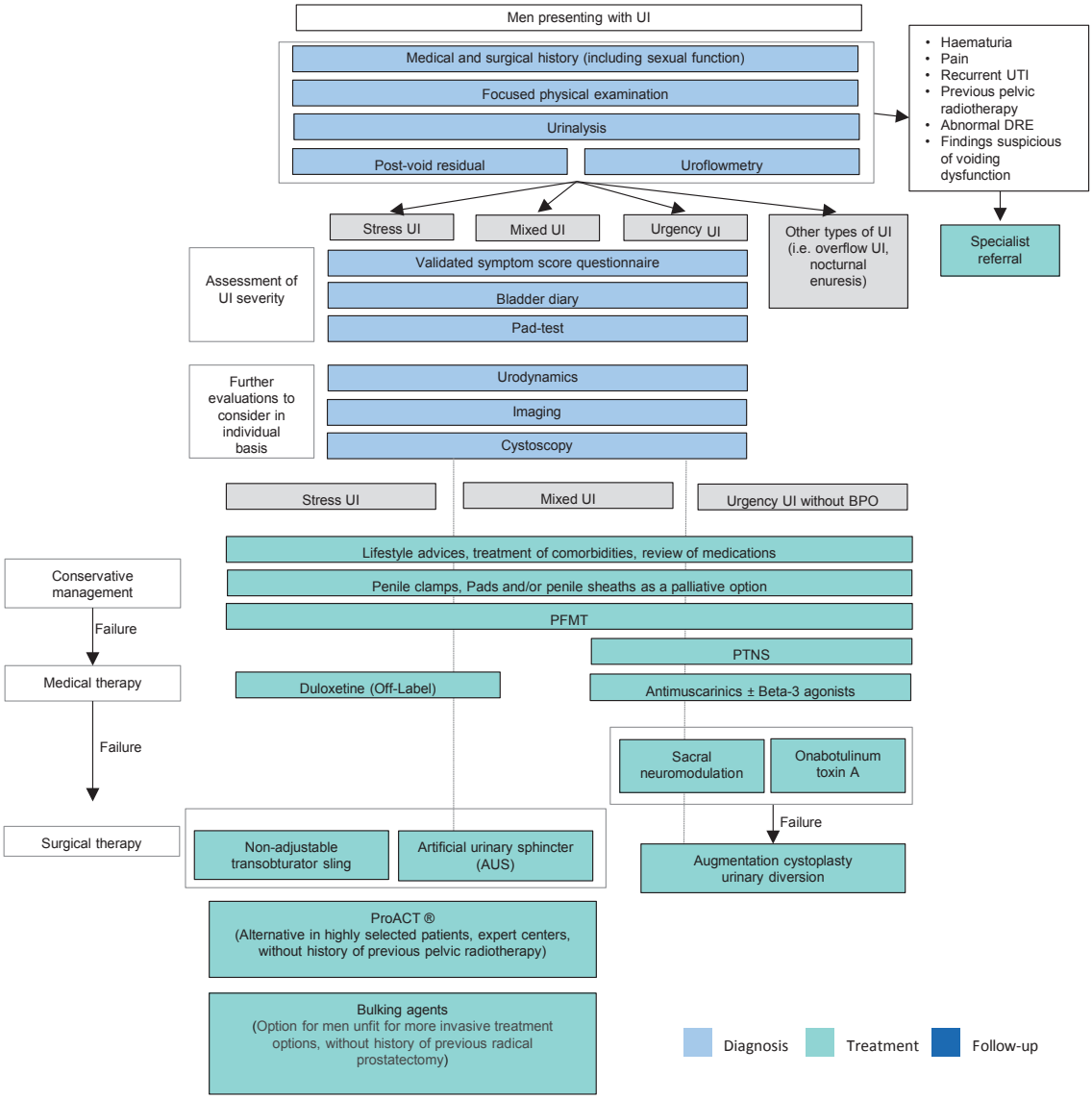
Practical considerations

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

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

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

Figure 6: Evaluation and management of urinary incontinence in non-neurogenic MLUTS



BPO = benign prostatic obstruction; DRE = digital rectal examination; LUTS = lower urinary tract symptoms; PFMT = pelvic floor muscle training; PTNS = posterior tibial nerve stimulation; UI = urinary incontinence; UTI = urinary tract infection.

5.7 Management of underactive bladder

5.7.1 Epidemiology and pathophysiology

Various definitions of UAB and DU can be identified in the current literature. Detrusor underactivity appears as the most consistent concept, is based on UDS, and is defined by the International Continence Society as: 'a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span' [17]. Underactive bladder is a terminology that should be reserved for describing symptoms and clinical features related to DU. A tentative definition has been proposed as 'a symptom complex suggestive of DU and usually characterized by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream' [768].

The prevalence of DU in the general population is unknown, because men with DU are either asymptomatic or have nonspecific LUTS. In clinical studies of men with non-neurogenic LUTS referred for VUDS, the prevalence of DU has been reported to be 10% [769, 770] ranging up to 48% in the elderly (≥ 70 years) [771]. Detrusor underactivity is a chronic condition, but its natural history in untreated men has shown a plateau-like course with few symptomatic and urodynamic changes over time [772].

Healthy voluntary bladder muscle contraction requires a functional detrusor muscle, intact efferent and afferent innervation and integrated central neural control mechanisms. Dysfunction of any of these essential components can lead to DU, which may be the consequence of various pathological processes, suggesting a multifactorial pathophysiology.

Neurogenic

Neurogenic DU may be the consequence of peripheral or central nervous system disease. This etiology is covered in the EAU Guidelines on Neuro-Urology [773].

Myogenic

Several conditions can affect the myocytes or their extracellular matrix, resulting in attenuated detrusor contraction. Bladder outflow obstruction and diabetic cystopathy are common causes of myogenic DU. However, many aspects of the pathophysiology of myogenic DU that relate to BOO and diabetic cystopathy are mainly based on animal studies and the clinical picture in any individual patient is probably multifactorial in nature [774, 775]. Some SRs have addressed the role of chronic BOO on bladder dysfunction in humans. Aside from the impact on smooth muscle cells, multiple other consequences were identified including modifications on the extracellular matrix, and damage to the urothelium, suburothelium and bladder innervation. To date, BOO-related DU pathophysiology remains poorly understood [776].

Iatrogenic

Patients may experience DU following pelvic surgery (e.g. radical prostatectomy or extended rectal surgery) and/or radiation therapy [774]. Pharmacological treatments (e.g. drugs with anticholinergic effects or opioids) may also be involved in the impairment of detrusor contractility [774].

Idiopathic

Given the higher prevalence of DU in the elderly, it has been hypothesised that ageing would be a major contributor. However, available data do not provide strong evidence to support the assertion that detrusor contractile function declines with common ageing [774].

5.7.2 Diagnostic evaluation

5.7.2.a Medical history and physical examination

A review of medical history, including comorbidities and current medications, can identify potential causes of UAB. The history should also include a thorough evaluation of LUTS, which should be classified into storage, voiding and post-micturition symptoms. There is no pivotal symptom to identify patients with UAB. The clinical presentation ranges from asymptomatic cases to symptomatic chronic urinary retention. Since UAB is a disorder of the voiding phase, voiding symptoms are the predominant symptoms, but they may be associated with storage symptoms, particularly in case of incomplete bladder emptying or other concomitant bladder dysfunctions [777].

Clinical diagnosis is even more difficult when patients have other conditions that may affect the presentation of LUTS, such as known or suspected BOO/BPO. In this setting, no validated tool is available to ascertain the respective roles of DU and BOO on voiding symptoms.

The Bristol group was the first to attempt to identify systematically which of the LUTS are most closely related to UAB [778]. Men with UAB reported a statistically significantly higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, feeling of incomplete bowel emptying, absent and/or decreased sensation and always straining to void compared with men with normal PFS. Several authors have proposed predictive models based on the patient's LUTS to distinguish individuals with an UAB from patients with normal PFS or BOO [779, 780]. However, there is no conclusive evidence that one prognostic model is more accurate than another, and there is no published external validation of these models.

5.7.2.b Questionnaires

There is no specific validated questionnaire for the diagnosis of UAB. Physicians can refer to validated questionnaires for MLUTS, but their clinical benefit to monitor symptom changes and treatment in patients with UAB is uncertain [781].

5.7.2.c Uroflowmetry

Some authors have proposed to distinguish UAB from BOO based on uroflowmetry parameters, not only on Q_{max}, but on flow patterns and combinations of scores [782, 783]. The diagnostic accuracy of the developed models remains to be established, and external validation is lacking.

5.7.2.d Ultrasound scan and post-void residual measurement

Ultrasound findings have been evaluated as noninvasive predictors of DU. In a single-centre prospective study including 143 adult males with LUTS, DWT ≤ 1.23mm and bladder capacity > 445mL was associated with urodynamically proven DU, with sensitivity and specificity of 42% and 100%, respectively [784].

Detrusor underactivity is often associated with prolonged bladder emptying time and/or PVR urine. However, while high PVR value have been associated with presence of DU, no consensus cut-off has been identified to diagnose DU and it is unlikely that one will ever exist [785].

5.7.2.e Urodynamics

Underactive bladder is a clinical diagnosis based on sign and symptoms, and DU is a term that should be reserved for a urodynamic diagnosis [786]. Invasive UDS is the only widely accepted method for diagnosing DU [777]. However, current data do not allow for a consensus definition of the urodynamic criteria to be used for the diagnosis of DU. Three algorithms, which are all based on computer-urodynamic investigation and quantification of detrusor pressure during voiding, have been suggested to quantify detrusor power [785]:

- Griffiths' Watt factor: quantification of detrusor power with a formula consisting of detrusor pressure during voiding, contraction speed, and BV at each point of micturition, expressed as W/m^2. Detrusor power varies during voiding, single calculations are usually offered on urodynamic evaluation sheets, for example, maximum detrusor power (W_{max}) or detrusor power at maximum flow (WQ_{max}). However, it remains controversial which of the calculations and what threshold value should be used. Expert opinion suggested using a W_{max} threshold value of $7.0W/m^2$ [785].
- Schafer's detrusor-adjusted mean PURR factor (DAMPF): detrusor power can be quantified as very weak, weak, normal or strong if linearised passive urethral resistance (linPURR) is drawn into the Schafer nomogram. The length of linPURR determines detrusor strength.
- Bladder contractility index: quantification of detrusor power/contractility can be derived from Schafer's linPURR lines and calculated by the formula: $BCI = p_{det}Q_{max} + 5Q_{max}$. BCI>150 describes strong contractility, 100-150 normal contractility, and < 100 weak contractility. The BCI is currently the most widely used in the literature and clinical trials.

None of these models are validated and their concordance for the diagnosis of DU is uncertain [787, 788], preventing a consensus to be reached on the optimal method for diagnosing DU. Moreover, detrusor contraction strength is only one aspect of voiding efficiency, and future models will need to encompass several aspects of assessing detrusor contraction (e.g. strength, durability) as well as how the bladder empties.

5.7.3 Conservative management

In general, the treatment of UAB should focus on symptom relief, avoiding complications (such as infections) and improving or at least maintaining QoL. It involves a pragmatic approach ensuring timely bladder drainage by trying to improve bladder contraction and/or decrease urethral resistance [785].

5.7.3.a *Behavioural interventions*

There are no randomised studies or large, high-quality studies available investigating the effect of behavioural interventions in male patients with UAB. The main goal is to reduce bothersome symptoms and prevent complications of incomplete bladder emptying (such as recurrent UTI) while avoiding invasive treatments. Asymptomatic patients at risk of UAB should be informed of this (like diabetes mellitus or after pelvic surgery/radiotherapy), because diagnosis is delayed due to loss in bladder sensation and enlarged bladder capacity. In patients with sensory impairment, timed or scheduled voiding schemes can be recommended. In patients with bothersome frequency, double or triple voiding, as well as Valsalva or the Credé manoeuver can reduce PVR and may improve their symptoms, however, no clinical trial has proven efficacy or harm of these measures in the non-neurogenic male population.

A descriptive cohort investigated male patients with DU started on conservative treatment (not further defined) and the need for intermittent catheterization (IC) after five years. They concluded that male patients with non-neurological DU can remain stable without the need to initiate IC. No urodynamic risk factors for IC were detected [789].

5.7.3.b Pelvic floor muscle relaxation training with biofeedback

Successful voiding is initiated by relaxation of the pelvic floor and urinary sphincter. A failure of at least one of these mechanisms can result in voiding dysfunction, as well as inhibition of detrusor contraction, which is called the guarding reflex [790]. Therefore, physiotherapy with pelvic floor muscle relaxation is usually a first line therapy for voiding dysfunction, but no RCT in male adults investigates its effect on UAB. Evidence is derived mostly from paediatric studies. One RCT in children compared the effect of standard urotherapy (diet, adapted fluid intake and timed voiding + toilet training) with animated biofeedback therapy versus urotherapy alone in children with proven DU. Improvement was seen in PVR, recurrent UTI and urodynamic parameters, such as flow curve and maximum flow rate, in both treatment groups, but improvement was significantly better at all stages in children receiving biofeedback [791].

5.7.3.c Intermittent catheterisation

In patients with persistently elevated PVR, IC is the preferred method for complete and timely bladder drainage. No data exist on the maximum accepted PVR, but after 300ml, the risk of UTIs increases [792]. Intermittent catheterisation is preferred over indwelling catheters, as it might reduce the risk of complications, such as UTI, bacterial colonisation, bladder stones and overflow incontinence. However, this technique demands a certain level of manual dexterity and cognition if performed by individuals themselves or it can be performed by a caregiver or second person, for example, a partner. More details are provided in Section 5.6.3.a.4.

5.7.3.d Indwelling catheters

Indwelling catheters should be avoided in the long-term unless other treatment options are not indicated, and the patient is unwilling or unable to perform IC, and there is no one else that can perform it for them. In this case, suprapubic catheters are preferred over urethral catheters due to the risk of traumatic hypospadias [636]. For further details, see Section 5.6.3.a.4.

5.7.3.e Intravesical electrical stimulation

Intravesical electrotherapy (IVES) is an electrical stimulation technique that stimulates the A-delta mechanoreceptor afferents thereby reinforcing bladder contractions. Therapy consists of daily sessions of stimulation with 10-15 sessions considered as a trial period. Afferent circuits should be intact together with a healthy detrusor muscle. An RCT in a mixed-gender population with neurogenic predominant UAB, reported improvement at four weeks after IVES compared to sham in PVR (-97ml vs. -10.5ml, $p<0.01$), in BVE (+13.3 vs. 0.0, $p<0.01$) and in Q_{max} (+1.3 vs. +0.2, $p<0.04$) [793]. One small retrospective study with a mixed population (11 women and 5 men) showed some improvement in voiding after IVES in two-third of the study population [794]. Other evidence is mainly derived from small studies in children [777].

5.7.3.f Extracorporeal shockwave therapy

Extracorporeal shockwave therapy (ESWT) improves neovascularisation and tissue regeneration and theoretically could improve detrusor contractility. A small placebo-controlled RCT reported significant improvements in PVR and UAB-Q scores at week 4 but not at week 12 of follow-up [795, 796].

Summary of evidence	LE
Behavioural interventions can be attempted in men with UAB and high PVR. Avoid increasing intrabdominal pressure with Valsalva or Credé in those with poorly compliant bladders.	3
Pelvic floor muscle relaxation techniques can help with voiding dysfunction.	4
Intermittent catheterisation is first-line therapy in men with UAB and high PVR over 300ml.	3
Indwelling catheters (urethral or suprapubic) are associated with a range of complications as well as an enhanced risk of UTI.	3
If indwelling catheters are the treatment choice, the suprapubic route is favoured over urethral due to risk of traumatic hypospadias.	3

Recommendations	Strength rating
Initiate intermittent catheterisation if there is a risk of upper tract damage or PVR is > 300mL.	Weak
Offer indwelling transurethral catheterisation or suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak

5.7.4 Pharmacological management

5.7.4.a Parasympathomimetics

For the mechanism of action of parasympathomimetics, see Section 5.2.3.

An SR and meta-analysis were performed in both male and female patients with UAB, evaluating 12 RCTs on the use of both subgroups (muscarinic agonists and acetylcholinesterase inhibitors) of parasympathomimetics [797, 798]. The meta-analysis showed a small benefit in some patients with (post-procedure) urinary retention with no increase in adverse events, but without improvement of PVR. However, the results of this SR are confounded by the low number of small studies, weak data, high heterogeneity and a very short-term follow-up. Therefore, based upon the available literature, no strong evidence-based conclusions can be drawn on the role of parasympathomimetic as an effective pharmaceutical treatment for UAB.

5.7.4.b Alpha-adrenergic blockers

One alternative to improve bladder emptying and micturition is by reducing outflow resistance in patients with UAB. Although there is a lack of high-quality RCTs, some evidence exists that lowering outflow resistance improves voiding functions and bothersome symptoms in men with UAB. A single-blind prospective RCT investigated 119 patients with UAB treating them with a cholinergic drug, an alpha-adrenergic blocker or both. They showed both a significant improvement in symptoms as well as PVR and flow rate in patients treated with combination therapy compared to monotherapy [799]. A study evaluated the effects of tadalafil (a PDE5 inhibitor) and silodosin on voiding function in male patients with non-neurogenic DU. After propensity score matching, they showed improvement of both QoL and UDS parameters and voiding parameters in both subgroups [779]. Overall, the clinical rigor required to provide evidence-based support for the use of this class of medications in treating UAB is still lacking.

5.7.4.c Prostaglandins

Prostaglandins are involved in the modulation of bladder function. There are five subtypes, of which prostaglandins E2 and F2a appear to be predominant in stimulating detrusor contractions. A Cochrane review analysing three RCTs using intravesical instillation of PGE2 and PGF2a suggests a reduction of postoperative retention after catheter removal [800]. However, due to methodological limitations of the included trials, the use in clinical practice remains uncertain. One placebo-controlled trial investigated the combination of intravesical PGE2 with bethanechol chloride in 19 patients with UAB [801]. Although they showed a reduction in PVR compared to placebo, clinical relevance is questioned. Overall, the efficacy of the prostaglandin agents in treating UAB is not established.

5.7.4.d Other drugs

As previously stated, treatment with PDE5 inhibitors (such as tadalafil) showed improvement of both QoL and UDS parameters and voiding parameters in male patients with UAB [779]. For more information on PDE5s, please see Section 5.2.5.

Summary of evidence	LE
Evidence on the effect of parasympathomimetics on clinical or urodynamic parameters of UAB is lacking. Possible serious adverse effects should be considered before administration.	4
There is limited evidence about effectiveness of alpha-adrenergic blockers in men with UAB.	4
The efficacy of the prostaglandin agents in treating UAB is not established.	4

Recommendations	Strength rating
Do not routinely recommend parasympathomimetics for treatment of men with underactive bladder.	Strong
Offer alpha-adrenergic blockers before more-invasive techniques.	Weak

5.7.5 Surgical treatment for underactive bladder

Surgical options for male patients with non-neurogenic UAB/DU include benign prostatic surgery and SNM [170, 802-808].

5.7.5.a Benign prostatic surgery in patients with UAB

An SR evaluated the outcomes of BPS for BPE in men with preoperative DU or acontractile detrusor [170]. Mean total IPSS variation following surgery was reported to range from -3 to -19.5 points. A > 3 points improvement in terms of total IPSS score was evident in 14 studies included into the SR [170]. Mean QoL variation ranged from -0.9 to -3 points [170]. Mean Q_{max} improvement ranged from +1.4 to +11.7mL/s. Mean PVR improvement ranged from -16.5 to -736mL [170].

Direct comparisons between patients with DU versus without DU provided conflicting results [170]. A study found that postoperative outcomes one month after photoselective laser vaporization prostatectomy (PVP) were worse in patients with DU compared to patients without DU [809]. In men with preoperative DU, mean total IPSS score improved from 12.0 to 15.2, mean Q_{max} improved from 4.8ml/sec. to 8.2ml/sec., and mean PVR improved from 918.3mL to 325.9mL. In patients without preoperative DU mean total IPSS improved from 17.5 to 9.7, mean Q_{max} improved from 6.9mL/sec. to 17.6mL/sec., and mean PVR improved from 225.0mL to 99.2mL [805]. A statistically significant difference ($p \leq 0.05$) was observed in terms of mean IPSS, mean Q_{max}, and mean PVR when comparing patients with and without preoperative DU at one month follow-up [805].

In a study, the outcomes of BPO patients with and without DU after HoLEP were assessed at 6-month follow-up: there were no differences with regards to perioperative complications. However, Q_{max} (30.52 vs. 23.26mL/s) and total IPSS (6.66 vs. 5.42) were significantly better improved in patients without DU than in those with DU. Recatherisation rate was significantly higher in the DU group (10.7 vs. 5.8%, $p = 0.022$) [810].

Similarly, another study found that patients with DU had smaller decrease in terms of median total IPSS (-6.5 vs. -11) and a smaller increase in the Q_{max} (+3.5mL/s vs. +8.2mL/s) after PVP than did those without DU [804]. Statistical analysis found a significant differences between the two groups at follow-up evaluations only for Q_{max} ($p = 0.023$).

A study from a prospective cohort on 158 men with DU (Group 1: 41 patients BCI < 100 and BOOI < 40; Group 2: 77 patients: BCI < 100 and BOOI ≥ 40) versus non-DU patients (BCI ≥ 100 and BOOI ≥ 40) showed a similar decrease for IPSS in all groups, however, the postoperative Q_{max} at 12 month was lowest in DU group 1, when compared to group 2 and the non-DU patients (group 1: Q_{max} 12 months, mL/s 10.1 ± 4.32, group 2: 12.9 ± 7.51, group 3: 14.6 ± 6.95), as well as greater postoperative PVR > 80mL (5.1% in group one, 7.3% in group 2 and 33.9% in group 3) [112].

Other authors failed to find differences in terms of symptom improvement and success rates between patients with and without preoperative DU [170]. Mean BCI Index improvement was reported to range from 4 to 44.6 [170].

A retrospective study found that 81.7% of patients with DU or acontractile detrusor undergoing TURP or TUIP achieved a satisfactory treatment outcome defined as improved QoL and voiding efficiency of > 50% [806]. Among these patients, mean BCI significantly increased from 16.4 to 61.0 and 69.4% of them had recovery of detrusor function within three months [806].

A prospective case series found that 78% of patients with DU or acontractile detrusor and concurrent BPO undergoing HoLEP exhibited significant return of bladder contractility, determined by the presence of a sustained, volitional detrusor contraction at six-months follow-up [807]. Of note, 94.7% of patients were voiding spontaneously with acceptable PVR volume, whereas 5.3% required continued IC postoperatively [807].

A retrospective study investigated the effect of DU on the efficacy of TURP by comparing the subjective and objective parameters preoperatively and three months postoperatively between severe (BCI < 82), mild (82 ≤ BCI < 100), and absent DU (BCI ≥ 100) in two obstruction groups (20 ≤ BOOI < 40 and BOOI ≥ 40) [808]. Successful improvement after the operation was defined according to established criteria [32]. In patients with preoperative BOOI ≥ 40 the successful improvement rates for the IPSS, IPSS-Storage, IPSS-Voiding, QoL and free Q_{max} were 60.6%, 54.5%, 54.5%, 63.6% and 66.6% in patients with severe DU. The same figures in patients with BOOI ≥ 40 and mild DU were: 87.7%, 63.2%, 94.7%, 75.4% and 75.4%, respectively. Finally, in patients with BOOI ≥ 40 and absent DU the successful improvement rates were 94.1%, 82.8%, 95.6%, 90.6% and 71.4%, respectively.

In the 20 ≤ BOOI < 40 group, the successful improvement rates for the IPSS, IPSS-Storage, IPSS-Voiding, QoL and free Q_{max} in the severe DU patients were only 38.2%, 38.2%, 44.1%, 41.2% and 38.2%, respectively. The same figures in patients with mild DU were: 83.3%, 66.7%, 83.3%, 75.0% and 41.7%, respectively. Finally, in patients with absent DU the successful improvement rates were 90.9%, 90.9%, 90.9%, 90.9% and 81.8%, respectively.

Therefore, patients with varying degrees of BPO can benefit from TURP, but for patients with severe DU in the 20 ≤ BOOI < 40 group, TURP should be carefully considered only after adequate counselling [808].

The few long-term data available seem to reveal poor durability of benefits [170].

Factors influencing the surgical outcomes have been investigated: older age, lack of obstruction, concomitant DO, lower detrusor contractility and use of TURP or PVP instead of HoLEP were associated with worse outcomes [170].

5.7.5.b Sacral neuromodulation

Sacral neuromodulation has been reported to improve idiopathic urinary retention in women in long-term studies [811]. However, only scarce evidence exists in men with DU or acontractile detrusor. A multicentric, retrospective case series reported the outcomes of SNM in adults with a urodynamic-based diagnosis of DU and symptom duration of more than six months who failed to respond to first and second-line treatment options [803]. Patients with cognitive disabilities, BOO and those who had any contraindication for SNM were excluded. Overall, 35 males were included. Of these, 51.4% responded to the first stage and were candidates for the full implant. Overall, 72% of male patients had favourable responses after the full implantation. Voided volume, PVR, and the median Q_{max} improved in both sexes [803]. In men who underwent full implantation voided volume improved from 75.0mL to 300.0mL, PVR improved from 350.0mL to 90.0mL, and mean Q_{max} improved from 7.0mL/sec. to 16.0mL/sec. Evidence from another retrospective study suggests that residual detrusor contractility is more likely to respond to a trial of SNM compared to detrusor acontractility [812].

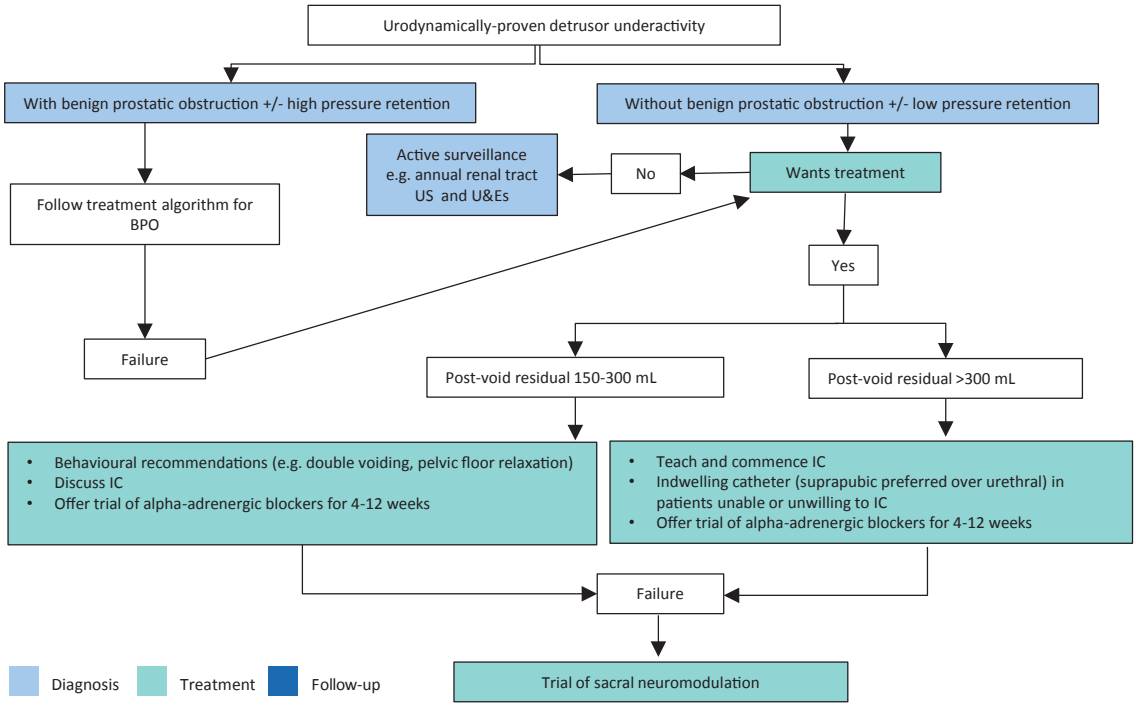
Summary of evidence	LE
In patients with DU or acontractile detrusor and concomitant BPO, de-obstruction procedures are associated with improvements in BCI mean total IPSS, mean maximum urinary flow and mean PVR.	3
Older age, lack of BOO, concomitant DO, lower bladder contractility and use of transurethral resection of the prostate or photovaporisation instead of laser enucleation of the prostate are associated with worse postoperative outcomes after de-obstruction procedures.	3
Sacral neuromodulation provides statistically significant improvement in terms of voided volume, PVR, and median maximum flow rate in men with refractory DU and no BPO.	3

Recommendations	Strength rating
Counsel patients with evidence of detrusor underactivity (DU) or acontractile detrusor and concomitant benign prostatic enlargement about the potential subjective and objective benefits of benign prostatic surgery.	Weak
Offer men with DU and no benign prostatic obstruction, test phase sacral neuromodulation.	Weak

5.7.6 Follow-up

The natural history and clinical evolution at long-term follow-up of men with UAB is not well documented. A small retrospective cohort evaluated recovery of detrusor contraction one year after (medical or surgical) treatment through videourodynamic studies [813]. In this small cohort, bladder contractility recovery was seen in 43.9% of patients and an optimal bladder compliance cut-off value of < 80mL/cmH_2O was predictive of better recovery. The interval between follow-up visits depends on patient characteristics, treatments given and the frequency of urinary complications. Two studies looked at the natural evolution of detrusor contractility with or without TURP for BOO [109, 772]. Although retrospective, they showed that detrusor contractility does not get worse with persisting BOO nor that it improves after performing a TURP. The underactive detrusor seems to remain underactive, but at least it does not deteriorate with time.

Figure 7: Management of detrusor underactivity



Inform patients of the benefits and harms of each treatment, and of the lack of solid evidence of their efficacy prior to surgery.
Initial assessment follows the EAU MLUTS Guidelines algorithm.
BPO = benign prostatic obstruction; IC = intermittent catheterisation; SNM = sacral neuromodulation; U&Es = urea and electrolytes; US = ultrasound.

5.8 Voiding dysfunction in young men

Up to 20% of men aged < 50 years report at least moderate LUTS [814, 815]. Primary bladder neck obstruction (PBNO) (defined as the inability of the bladder neck smooth muscle to open adequately during voiding, with a subsequent increase of detrusor pressure to try to overcome the resistance of the bladder neck and allow urine to flow) and DV (a condition characterised by an intermittent and/or fluctuating flow due to inadequate or variable relaxation generally of the sphincters during voiding in neurologically normal men) represent the two most common voiding disorders in men aged 18-50 years, leading to functional BOO and non-neurogenic LUTS [816]. Although the exact prevalence of PBNO and DV in the general population is largely unknown, epidemiological studies involving VUDS in selected populations of men aged 18-50 years with non-neurogenic LUTS showed a prevalence of PBNO and DV up to 54% and 43%, respectively [814-818].

5.8.1 Diagnostic evaluation

5.8.1.a Medical history

Most patients with PBNO and DV complain of long-lasting LUTS, with a mean duration of symptoms before diagnosis reaching up to 53.8 months and nearly 88% of patients complaining of symptoms for > one year [814-818]. Although being disorders of the voiding phase, and voiding symptoms are more frequently reported in some series, there is no pivotal symptom, and the spectrum of LUTS may include storage, voiding and postmicturition symptoms [814-818]. Chronic pelvic pain is evident in up to 24.5% of PBNO patients, while recurrent UTI is observed in 28% of cases [819, 820].

5.8.1.b Questionnaires

Currently, there is no specific validated questionnaire for the assessment of patients with PBNO and DV. Therefore, physicians can refer to a validated questionnaire for MLUTS, such as the IPSS, the ICIQ-MLUTS or the American Urological Association (AUA) questionnaire.

5.8.1.b.1 Physical examination

Pelvic examination, in addition to conventional physical examination, helps in evaluating anatomical and functional abnormalities of the pelvic-perineal area. This involves external visual inspection/palpation of the perineal/perianal regions and internal digital palpation of the perianal musculature to identify muscular tone abnormalities [821].

5.8.1.c Uroflowmetry and PVR measurement

Although a Q_{max} of < 15mL/s has frequently been observed in patients diagnosed with PBNO and DV, this finding is not specific [770, 814]. A clinical trial failed to find statistically significant differences in terms of Q_{max} between patients with PBNO, DV and BPO (12.0, 11.8 and 9.8mL/s, respectively) [770]. Similarly, although an elevated PVR is frequently observed, it lacks specificity [770].

5.8.1.d Ultrasound scan

Although young men with PBNO and DV tend to have a prostate volume of < 30cm^3, the value of this finding in predicting PBNO and DV from other causes of LUTS in men remains controversial [770, 814, 822].

5.8.1.e VUDS and electromyography

The definitive diagnosis of PBNO and DV formally relies on the findings from in-depth functional assessments, with VUDS representing the gold standard approach [814]. The VUDS criteria for PBNO are the followings: high-pressure/low-flow voiding pattern, radiographic evidence of obstruction at the bladder neck, relaxation of the striated sphincter, and no evidence of distal obstruction. Currently, however, there are no commonly accepted urodynamic threshold parameters in this subset of patients [603, 814]. Although electromyography (EMG) demonstrates relaxation of the striated sphincter concomitant with the detrusor contractions during micturition or an attempt at micturition in PBNO patients, the presence of increased EMG activity should not in and of itself exclude the diagnosis of PBNO due to false-positive results that can occur with surface EMG, which assesses pelvic floor activity rather than sphincter activity [819, 823].

The criteria adopted to diagnose DV include the following: electrical activity of the external sphincter during voiding detected on EMG in the absence of abdominal straining; brief and intermittent closing of the membranous urethra during voiding detected on fluoroscopy; and intermittent increases and decreases of flow in an undulating fashion detected on uroflowmetry performed in a private setting [814, 824].

A study showed a significant association between the extent of bladder neck opening impairment observed on VCUG and obstruction and contraction urodynamic parameters, but no association with the severity of urinary symptoms [820]. In details, the detrusor $P_{det}Q_{max}$, BOOI and BCI were significantly higher in patients with absence of bladder neck opening compared to those with incomplete bladder neck opening [820].

However, VUDS can be expensive, time consuming, unpleasant for the patient and often unavailable in everyday clinical practice [820, 825]. Additionally, some patients fail to void during the study due to psychological and physical discomfort [814, 820]. Evaluation of data separately collected by standard UDS and VCUG has been considered a reliable alternative approach by some authors [820], although it is difficult to correlate anatomy with physiology at various points in time.

5.8.1.f Magnetic resonance imaging

Preliminary data exist regarding the value of MRI in the diagnosis of PBNO. Reported accuracies of MRI and MR voiding cystourethrography in identifying PBNO of 87% and 100%, respectively [825].

5.8.1.g Urethrocystoscopy

Some authors consider urethrocystoscopy a useful test to rule out urethral strictures or enlarged prostate in selected cases. However, the role of urethrocystoscopy in the diagnosis of PBNO and DV remains controversial [814].

Summary of evidence	LE
Most patients with PBNO and DV complain of long-lasting LUTS, with a mean duration of symptoms before diagnosis reaching up to several years.	4
Videourodynamics represents the gold standard approach for the diagnosis of PBNO and DV.	4
Evaluation of data separately collected by standard UDS and VCUG has been considered a reliable alternative approach by some authors.	4
Electromyography demonstrates relaxation of the striated sphincter concomitant with the detrusor contractions during micturition or an attempt at micturition in PBNO patients and electrical activity of the external sphincter during voiding in DV patients.	4

Recommendations	Strength rating
Suspect primary bladder neck obstruction (PBNO)/dysfunctional voiding (DV) in young men complaining of long-lasting LUTS.	Weak
Perform videourodynamics (VUDS) studies (or standard urodynamic studies with voiding cysto-urethrography if VUDS studies are unavailable) ± electromyography in young men with suspected PBNO or DV as initial diagnostic assessment or after failed first-line therapy.	Weak

5.8.2 Treatment

The goals of therapies in young men with LUTS secondary to PBNO and DV include improvement of symptoms and QoL, relief of obstruction, prevention of disease-related complications, and preservation of sexual/reproductive health [814].

5.8.2.a Conservative treatment

5.8.2.a.1 Observation

Observation has been proposed as an option for PBNO patients with minimal symptom bother and without clinical or urodynamic evidence of upper or LUT decompensation [814]. Available evidence in men aged 18-50 years only derives from one study describing the outcomes of no treatment in nine PBNO patients unresponsive to α1-blockers refusing surgery demonstrating not statistically significant variations in terms of the mean AUA-6 score, mean Q_{max} and mean PVR at a mean follow-up of 36 months [826].

5.8.2.a.2 Behavioural modifications plus biofeedback

Behavioural modifications (instructions to relax the pelvic floor muscles during voiding) plus biofeedback were assessed in one study involving 43 patients with DV unresponsive to alpha blockers [824]. Treatment success, defined as a decrease of symptoms of at least 50% in two consecutive visits, was observed in 35 patients (83%) at three months [824].

Individual treatment programs administered by pelvic floor physical therapists typically include an initial phase when patients are familiarised with the anatomy and physiology of the pelvic organs and muscles, and subsequent phases when verbal guidance and feedback through palpation of the pelvic floor muscles and biofeedback measurements were used to teach how to correctly contract and relax the pelvic floor muscles [827].

5.8.2.b Pharmacological treatment

5.8.2.b.1 Alpha-blockers

Alpha-blockers are commonly prescribed as first-line treatment in patients with PBNO. A meta-analysis found a mean total IPSS improvement ranging from -1 to -12 points (pooled estimate at three months: -7.0 [95% CI: -8.3 to -5.8; $p < 0.000$]), a mean IPSS QoL sub-score improvement ranging from -1.5 to -1.9 points (pooled estimate at three months: -1.7 points [95% CI: -2.0 to -1.3; $p < 0.000$]), a mean Q_{max} variation ranging from 3.7 to 11.1mL/s (pooled estimate at three months: 4.0mL/s [95% CI: 3.1-4.9; $p < 0.001$]), a mean PVR variation ranging from to 26.9 to -70mL (pooled estimate at 3 months: -31.1mL [95% CI: -36.3 to -25.9; $p < 0.001$) [814]. Two studies evaluated BOOI variation following treatment with α1-blockers. One reported a median BOOI improvement of 21 points, while another reported a mean BOOI improvement of 34.5 points [828, 829]. A major drawback of α1-blockers is the considerable discontinuation rate, ranging from 4.7% to 55%, mainly due to unsuccessful outcomes or adverse events [814]. A higher baseline urodynamic obstruction grade and younger age have been identified as predictors of α1-blockers failure [814]. Unsuccessful outcomes were reported in a percentage of patients ranging from 23% to 52% [814]. Systemic adverse events were reported by 0-16.1% of patients, with giddiness being the most frequent adverse event. The incidence of retrograde ejaculation ranged from 47% to 50% [814].

5.8.2.c Surgical treatment

Surgery typically involves BNI and is mostly performed in patients failing therapy with α1-blockers [814]. It aims to relieve the obstruction by interrupting muscular fibres of the internal sphincter located at the bladder neck [814]. Outcomes of surgery have been assessed in PBNO patients. Surgical procedures include bladder neck incision (single or bilateral), TURP and/or transurethral resection of the bladder neck. Globally, a meta-analysis found a mean total IPSS improvement ranging from -8.8 to -23.3 points (pooled estimate at three months: -11.2 points [95% CI: -16.12 to -6.33; $p < 0.0001$]); a mean IPSS QoL subscore improvement ranging from -1.9 to -2.2 points; a mean Q_{max} improvement ranging from 4.2 to 18.5mL/s (pooled estimate at three months: 6.9mL/s [95% CI: 1.4-12.5; $p = 0.014$]); and a mean PVR variation ranging from to 7.6 to -156 mL [1]. One study evaluated $P_{det}Q_{max}$ variation after treatment by reporting an improvement in terms of the mean $P_{det}Q_{max}$ by 68cmH_2O

[16]. An unsuccessful outcome was reported in 0-15.3% of patients [814]. Overall, EjD rates ranged from 0 to 88.8% (pooled estimate following BNI: 3.0% [95% CI: 1-6%]) [814]. Results stratified according to the type of BNI revealed pooled EjD rates of 0% (95% CI: 0-1%) and 9% (95% CI: 2-21%) following single and bilateral BNI, respectively ($p = 0.128$) [814]. A retrospective analysis was recently conducted on 67 males < 40 years with PBNO therapies with ABs or surgery (BNI or TUIP). Both groups showed significant improvements, but the surgical group demonstrated superior outcomes. At six months, the surgical group had a greater reduction in IPSS (11.9 ± 4.40 vs. 4.38 ± 3.73; $p < 0.001$) and greater improvements in Q_{max} (+5.59 ± 4.08mL/s vs. +2.54 ± 3.85mL/s; $p < 0.001$) [830].

5.8.2.d Onabotulinumtoxin A (BoNTA) injection therapy

A single study assessed the outcomes of a transurethral bladder neck injection of BoNTA in 30 patients with PBNO after unsuccessful α1-blockers therapy [831]. The mean total IPSS varied from 21.9 at baseline to 7.8, 10.3, 16.6 and 19.9 at two-, six-, nine- and 12-months follow-up, respectively. The mean Q_{max} varied from 7.8mL/s at baseline to 16.9, 15.5, 12.7 and 8.6mL/s at two-, six-, nine- and 12-month follow-up, respectively. None of the patients reported EjD. Erectile dysfunction was not assessed [831]. Currently, this procedure should be considered as experimental.

5.8.2.e Intermittent catheterisation

Intermittent catheterisation remains a further option in patients with both PBNO and DV refractory to first-line therapy [814].

5.8.2.f Sacral neurostimulation

Some authors consider SNM an exciting new treatment for refractory voiding disorders, including DV [814]. Currently, this procedure should be considered as experimental, but having a trial phase using percutaneous nerve evaluation is likely the only method that could confirm whether a permanent implant would be suitable.

Summary of evidence	LE
Alpha-blockers provide a mean total IPSS improvement ranging from -1 to -12 points (pooled estimate at three months: -7.0); a mean IPSS QoL subscore improvement ranging from -1.5 to -1.9 points (pooled estimate at three months: -1.7 points); a mean Q_{max} variation ranging from 3.7 to 11.1mL/ s (pooled estimate at three months: 4.0mL/s); and a mean PVR variation ranging from to 26.9 to -70mL (pooled estimate at three months: -31.1mL) in young men with PBNO.	3
Behavioural modifications (instructions to relax the pelvic floor muscles during voiding) plus biofeedback provide a decrease of symptoms of at least 50% in two consecutive visits in 83% of patients with DV at three months.	4
Bladder neck incision provide a mean total IPSS improvement ranging from -8.8 to -23.3 points (pooled estimate at three months: -11.2 points); a mean IPSS QoL sub-score improvement ranging from -1.9 to 2.2 points; a mean Q_{max} improvement ranging from 4.2 to 18.5mL/s (pooled estimate at three months: 6.9mL/s); and a mean PVR variation ranging from to 7.6 to -156mL in young men with PBNO.	3
Ejaculation dysfunction rates following BNI range from 0% to 88.8% (pooled estimate: 3.0%).	3

Recommendations	Strength rating
Consider alpha blockers as first-line treatment in young men with primary bladder neck obstruction (PBNO).	Weak
Consider behavioural modifications plus biofeedback as first-line therapy in young men with dysfunctional voiding (DV).	Weak
Consider bladder neck incision or intermittent catheterisation (IC) in well-informed young men with PBNO unresponsive to alpha blockers.	Weak
Consider IC in young men with DV unresponsive to behavioural modifications plus biofeedback.	Weak

6. FOLLOW-UP

6.1 Watchful waiting (behavioural)

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

6.2 Medical treatment

Patients receiving α1-blockers, muscarinic receptor antagonists, beta-3 agonists, PDE5Is or the combination of α1-blockers and 5-ARIs or muscarinic receptor antagonists should be reviewed four to six weeks after drug initiation to determine the treatment response. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at six months and then annually, provided there is no deterioration of symptoms or development of absolute indications for surgical treatment. The following are recommended at follow-up visits: history, IPSS/ICIQ-MLUTS, uroflowmetry and PVR volume. Frequency volume charts or bladder diaries should be used to assess response to treatment for predominant storage symptoms or NP.

Patients receiving 5-ARIs should be reviewed after 12 weeks and again at six months to determine their response and adverse events. The following are recommended at follow-up visits: history, IPSS/ICIQ-MLUTS, uroflowmetry and PVR volume. Men taking 5-ARIs should be followed up regularly using serial PSA testing if life expectancy is greater than ten years and if a diagnosis of PCa could alter management. A new baseline PSA should be determined at six months, and any confirmed increase in PSA while on 5-ARIs should be evaluated.

In patients receiving desmopressin, serum sodium concentration should be measured at day three and seven, one month after initiating therapy and periodically during treatment. If serum sodium concentration has remained normal during periodic screening, follow-up screening can be carried out every three months thereafter. However, serum sodium concentration should be monitored more frequently in patients ≥ 65 years of age and in patients at increased risk of hyponatremia. The following tests are recommended at follow-up visits: serum-sodium concentration and FVC. The follow-up sequence should be restarted after dose escalation.

6.3 Surgical treatment

After prostate surgery, patients should be reviewed four to six weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events, no further re-assessment is necessary. The following tests are recommended at follow-up visit after four to six weeks: IPSS/ICIQ-MLUTS, uroflowmetry, erectile and ejaculatory function and PVR volume.

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

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

7. REFERENCES

1. Phillips, B. Oxford Centre for Evidence-based Medicine Levels of Evidence. Updated by Jeremy Howick March 2009. 1998.
https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009
2. Guyatt, G.H., *et al.* Going from evidence to recommendations. BMJ, 2008. 336: 1049.
https://www.ncbi.nlm.nih.gov/pubmed/18467413
3. Abrams, P., *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn, 2002. 21: 167.
https://www.ncbi.nlm.nih.gov/pubmed/11857671
4. Martin, S.A., *et al.* Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. World J Urol, 2011. 29: 179.
https://www.ncbi.nlm.nih.gov/pubmed/20963421
5. Société Internationale d'Urologie (SIU), Lower Urinary Tract Symptoms (LUTS): An International Consultation on Male LUTS. , C. Chapple, *et al.*, Editors. 2013.
https://www.siu-urology.org/themes/web/assets/files/ICUD/pdf/Male%20Lower%20Urinary%20Tract%20Symptoms%20(LUTS).pdf
6. Kupelian, V., *et al.* Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. Arch Intern Med, 2006. 166: 2381.
https://www.ncbi.nlm.nih.gov/pubmed/17130393
7. Agarwal, A., *et al.* What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. Eur Urol, 2014. 65: 1211.
https://www.ncbi.nlm.nih.gov/pubmed/24486308
8. De Ridder, D., *et al.* Urgency and other lower urinary tract symptoms in men aged >/= 40 years: a Belgian epidemiological survey using the ICIQ-MLUTS questionnaire. Int J Clin Pract, 2015. 69: 358.
https://www.ncbi.nlm.nih.gov/pubmed/25648652
9. Taub, D.A., *et al.* The economics of benign prostatic hyperplasia and lower urinary tract symptoms in the United States. Curr Urol Rep, 2006. 7: 272.
https://www.ncbi.nlm.nih.gov/pubmed/16930498
10. Gacci, M., *et al.* Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analysis. BJU Int, 2015. 115: 24.
https://www.ncbi.nlm.nih.gov/pubmed/24602293
11. Gacci, M., *et al.* Male Lower Urinary Tract Symptoms and Cardiovascular Events: A Systematic Review and Meta-analysis. Eur Urol, 2016. 70: 788.
https://www.ncbi.nlm.nih.gov/pubmed/27451136
12. Kogan, M.I., *et al.* Epidemiology and impact of urinary incontinence, overactive bladder, and other lower urinary tract symptoms: results of the EPIC survey in Russia, Czech Republic, and Turkey. Curr Med Res Opin, 2014. 30: 2119.
https://www.ncbi.nlm.nih.gov/pubmed/24932562
13. Chapple, C.R., *et al.* Lower urinary tract symptoms revisited: a broader clinical perspective. Eur Urol, 2008. 54: 563.
https://www.ncbi.nlm.nih.gov/pubmed/18423969
14. Ficarra, V., *et al.* The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. Curr Urol Rep, 2014. 15: 463.
https://www.ncbi.nlm.nih.gov/pubmed/25312251
15. He, Q., *et al.* Metabolic syndrome, inflammation and lower urinary tract symptoms: possible translational links. Prostate Cancer Prostatic Dis, 2016. 19: 7.
https://www.ncbi.nlm.nih.gov/pubmed/26391088
16. Drake, M.J. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. Neurourol Urodyn, 2014. 33: 622.
https://www.ncbi.nlm.nih.gov/pubmed/24838519
17. Chapple, C.R., *et al.* Terminology report from the International Continence Society (ICS) Working Group on Underactive Bladder (UAB). Neurourol Urodyn, 2018. 37: 2928.
https://www.ncbi.nlm.nih.gov/pubmed/30203560

18. Novara, G., *et al.* Critical Review of Guidelines for BPH Diagnosis and Treatment Strategy. Eur Urol Suppl, 2006. 5: 418.
https://www.sciencedirect.com/science/article/abs/pii/S1569905606000121
19. McVary, K.T., *et al.* Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol, 2011. 185: 1793.
https://www.ncbi.nlm.nih.gov/pubmed/21420124
20. Bosch, J., *et al.*, Lower Urinary Tract Symptoms in Men (Male LUTS): Etiology, Patient Assessment and Predicting Outcome from Therapy. Male Lower Urinary Tract Symptoms (LUTS), An International Consultation on Male LUTS. 2013.
https://snu.elsevierpure.com/en/publications/lower-urinary-tract-symptoms-in-men-male-luts-etiology-patient-as/
21. Martin, R.M., *et al.* Lower urinary tract symptoms and risk of prostate cancer: the HUNT 2 Cohort, Norway. Int J Cancer, 2008. 123: 1924.
https://www.ncbi.nlm.nih.gov/pubmed/18661522
22. Young, J.M., *et al.* Are men with lower urinary tract symptoms at increased risk of prostate cancer? A systematic review and critique of the available evidence. BJU Int, 2000. 85: 1037.
https://www.ncbi.nlm.nih.gov/pubmed/10848691
23. Bright, E., *et al.* Urinary diaries: evidence for the development and validation of diary content, format, and duration. Neurourol Urodyn, 2011. 30: 348.
https://www.ncbi.nlm.nih.gov/pubmed/21284023
24. De Nunzio, C., *et al.* Erectile Dysfunction and Lower Urinary Tract Symptoms. Eur Urol Focus, 2017. 3: 352.
https://www.ncbi.nlm.nih.gov/pubmed/29191671
25. Rosen, R.C., *et al.* Development and validation of four-item version of Male Sexual Health Questionnaire to assess ejaculatory dysfunction. Urology, 2007. 69: 805.
https://www.ncbi.nlm.nih.gov/pubmed/17482908
26. Barqawi, A.B., *et al.* Methods of developing UWIN, the modified American Urological Association symptom score. J Urol, 2011. 186: 940.
https://www.ncbi.nlm.nih.gov/pubmed/21791346
27. Barry, M.J., *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol, 1992. 148: 1549.
https://www.ncbi.nlm.nih.gov/pubmed/1279218
28. Donovan, J.L., *et al.* Scoring the short form ICSmaleSF questionnaire. International Continence Society. J Urol, 2000. 164: 1948.
https://www.ncbi.nlm.nih.gov/pubmed/11061889
29. Epstein, R.S., *et al.* Validation of a new quality of life questionnaire for benign prostatic hyperplasia. J Clin Epidemiol, 1992. 45: 1431.
https://www.ncbi.nlm.nih.gov/pubmed/1281223
30. Homma, Y., *et al.* Symptom assessment tool for overactive bladder syndrome--overactive bladder symptom score. Urology, 2006. 68: 318.
https://www.ncbi.nlm.nih.gov/pubmed/16904444
31. Schou, J., *et al.* The value of a new symptom score (DAN-PSS) in diagnosing uro-dynamic infravesical obstruction in BPH. Scand J Urol Nephrol, 1993. 27: 489.
https://www.ncbi.nlm.nih.gov/pubmed/7512747
32. Homma, Y., *et al.* Core Lower Urinary Tract Symptom score (CLSS) questionnaire: a reliable tool in the overall assessment of lower urinary tract symptoms. Int J Urol, 2008. 15: 816.
https://www.ncbi.nlm.nih.gov/pubmed/18657204
33. D'Silva, K.A., *et al.* Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. JAMA, 2014. 312: 535.
https://www.ncbi.nlm.nih.gov/pubmed/25096693
34. ICIQ. International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms Module (ICIQ-MLUTS). 2022. 2022.
https://iciq.net/iciq-mluts
35. Ito, H., *et al.* Grading Severity and Bother Using the International Prostate Symptom Score and International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms Score in Men Seeking Lower Urinary Tract Symptoms Therapy. J Urol, 2020. 204: 1003.
https://www.ncbi.nlm.nih.gov/pubmed/32469267

36. Glaser, A.P., *et al.* The 10-item LURN Symptom Index (LURN SI-10) Detects Additional Symptoms and Shows Convergent Validity With the IPSS in Men Presenting With Lower Urinary Tract Symptoms. Urology, 2023. 171: 184.
https://www.ncbi.nlm.nih.gov/pubmed/36370771
37. Bryan, N.P., *et al.* Frequency volume charts in the assessment and evaluation of treatment: how should we use them? Eur Urol, 2004. 46: 636.
https://www.ncbi.nlm.nih.gov/pubmed/15474275
38. Gisolf, K.W., *et al.* Analysis and reliability of data from 24-hour frequency-volume charts in men with lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol, 2000. 38: 45.
https://www.ncbi.nlm.nih.gov/pubmed/10859441
39. Cornu, J.N., *et al.* A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol, 2012. 62: 877.
https://www.ncbi.nlm.nih.gov/pubmed/22840350
40. Weiss, J.P. Nocturia: "do the math". J Urol, 2006. 175: S16.
https://www.ncbi.nlm.nih.gov/pubmed/16458734
41. Weiss, J.P., *et al.* Nocturia Think Tank: focus on nocturnal polyuria: ICI-RS 2011. Neurourol Urodyn, 2012. 31: 330.
https://www.ncbi.nlm.nih.gov/pubmed/22415907
42. Vaughan, C.P., *et al.* Military exposure and urinary incontinence among American men. J Urol, 2014. 191: 125.
https://www.ncbi.nlm.nih.gov/pubmed/23871759
43. Yap, T.L., *et al.* A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int, 2007. 99: 9.
https://www.ncbi.nlm.nih.gov/pubmed/16956355
44. Bright, E., *et al.* Developing and validating the International Consultation on Incontinence Questionnaire bladder diary. Eur Urol, 2014. 66: 294.
https://www.ncbi.nlm.nih.gov/pubmed/24647230
45. Weissfeld, J.L., *et al.* Quality control of cancer screening examination procedures in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials, 2000. 21: 390S.
https://www.ncbi.nlm.nih.gov/pubmed/11189690
46. Roehrborn, C.G. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. Urology, 1998. 51: 19.
https://www.ncbi.nlm.nih.gov/pubmed/9586592
47. Roehrborn, C.G., *et al.* Interexaminer reliability and validity of a three-dimensional model to assess prostate volume by digital rectal examination. Urology, 2001. 57: 1087.
https://www.ncbi.nlm.nih.gov/pubmed/11377314
48. Bosch, J.L., *et al.* Validity of digital rectal examination and serum prostate specific antigen in the estimation of prostate volume in community-based men aged 50 to 78 years: the Krimpen Study. Eur Urol, 2004. 46: 753.
https://www.ncbi.nlm.nih.gov/pubmed/15548443
49. Burger, M., *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol, 2013. 63: 36.
https://www.ncbi.nlm.nih.gov/pubmed/22981672
50. Bonkat, G., *et al.* EAU Guidelines on Urological Infections Edn. presented at EAU Annual Congress, London, 2026.
https://uroweb.org/guidelines/urological-infections
51. Palou, J., *et al.* ICUD-EAU International Consultation on Bladder Cancer 2012: Urothelial carcinoma of the prostate. Eur Urol, 2013. 63: 81.
https://www.ncbi.nlm.nih.gov/pubmed/22938869
52. Masson-Lecomte, A., *et al.* EAU Guidelines on Urothelial Carcinomas of the Upper Urinary Tract. 2026. Edn. presented at the 41st EAU Annual Congress London 2026.
https://uroweb.org/guidelines/upper-urinary-tract-urothelial-cell-carcinoma
53. Roehrborn, C.G., *et al.* Guidelines for the diagnosis and treatment of benign prostatic hyperplasia: a comparative, international overview. Urology, 2001. 58: 642.
https://www.ncbi.nlm.nih.gov/pubmed/11711329
54. Abrams, P., *et al.* Evaluation and treatment of lower urinary tract symptoms in older men. J Urol, 2013. 189: S93.
https://www.ncbi.nlm.nih.gov/pubmed/23234640

55. European Confederation of Laboratory, M. European urinalysis guidelines. Scand J Clin Lab Invest Suppl, 2000. 231: 1.
https://www.ncbi.nlm.nih.gov/pubmed/12647764
56. Khasriya, R., *et al.* The inadequacy of urinary dipstick and microscopy as surrogate markers of urinary tract infection in urological outpatients with lower urinary tract symptoms without acute frequency and dysuria. J Urol, 2010. 183: 1843.
https://www.ncbi.nlm.nih.gov/pubmed/20303096
57. Roehrborn, C.G., *et al.* Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. Urology, 1999. 53: 581.
https://www.ncbi.nlm.nih.gov/pubmed/10096388
58. Bohnen, A.M., *et al.* Serum prostate-specific antigen as a predictor of prostate volume in the community: the Krimpen study. Eur Urol, 2007. 51: 1645.
https://www.ncbi.nlm.nih.gov/pubmed/17320271
59. Kayikci, A., *et al.* Free prostate-specific antigen is a better tool than total prostate-specific antigen at predicting prostate volume in patients with lower urinary tract symptoms. Urology, 2012. 80: 1088.
https://www.ncbi.nlm.nih.gov/pubmed/23107399
60. Morote, J., *et al.* Prediction of prostate volume based on total and free serum prostate-specific antigen: is it reliable? Eur Urol, 2000. 38: 91.
https://www.ncbi.nlm.nih.gov/pubmed/10859448
61. Cornford, P., *et al.*, EAU Guidelines on prostate cancer. Edn. presented at the 41st EAU Annual Congress London 2026.
https://uroweb.org/guidelines/prostate-cancer
62. Roehrborn, C.G., *et al.* Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long-term efficacy and safety study. J Urol, 2000. 163: 13.
https://www.ncbi.nlm.nih.gov/pubmed/10604304
63. Roehrborn, C.G., *et al.* Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology, 1999. 54: 662.
https://www.ncbi.nlm.nih.gov/pubmed/10510925
64. Djavan, B., *et al.* Longitudinal study of men with mild symptoms of bladder outlet obstruction treated with watchful waiting for four years. Urology, 2004. 64: 1144.
https://www.ncbi.nlm.nih.gov/pubmed/15596187
65. Patel, D.N., *et al.* PSA predicts development of incident lower urinary tract symptoms: results from the REDUCE study. Prostate Cancer Prostatic Dis, 2018. 21: 238.
https://www.ncbi.nlm.nih.gov/pubmed/29795141
66. McConnell, J.D., *et al.* The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med, 2003. 349: 2387.
https://www.ncbi.nlm.nih.gov/pubmed/14681504
67. Roehrborn, C.G. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. BJU Int, 2006. 97: 734.
https://www.ncbi.nlm.nih.gov/pubmed/16536764
68. Jacobsen, S.J., *et al.* Treatment for benign prostatic hyperplasia among community dwelling men: the Olmsted County study of urinary symptoms and health status. J Urol, 1999. 162: 1301.
https://www.ncbi.nlm.nih.gov/pubmed/10492184
69. Lim, K.B., *et al.* Comparison of intravesical prostatic protrusion, prostate volume and serum prostatic-specific antigen in the evaluation of bladder outlet obstruction. Int J Urol, 2006. 13: 1509.
https://www.ncbi.nlm.nih.gov/pubmed/17118026
70. Meigs, J.B., *et al.* Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. J Clin Epidemiol, 2001. 54: 935.
https://www.ncbi.nlm.nih.gov/pubmed/11520654
71. Gerber, G.S., *et al.* Serum creatinine measurements in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology, 1997. 49: 697.
https://www.ncbi.nlm.nih.gov/pubmed/9145973
72. Oelke, M., *et al.* Can we identify men who will have complications from benign prostatic obstruction (BPO)? ICI-RS 2011. Neurourol Urodyn, 2012. 31: 322.
https://www.ncbi.nlm.nih.gov/pubmed/22415947

73. Comiter, C.V., *et al.* Urodynamic risk factors for renal dysfunction in men with obstructive and nonobstructive voiding dysfunction. J Urol, 1997. 158: 181.
https://www.ncbi.nlm.nih.gov/pubmed/9186351
74. Koch, W.F., *et al.* The outcome of renal ultrasound in the assessment of 556 consecutive patients with benign prostatic hyperplasia. J Urol, 1996. 155: 186.
https://www.ncbi.nlm.nih.gov/pubmed/7490828
75. Rule, A.D., *et al.* The association between benign prostatic hyperplasia and chronic kidney disease in community-dwelling men. Kidney Int, 2005. 67: 2376.
https://www.ncbi.nlm.nih.gov/pubmed/15882282
76. Hong, S.K., *et al.* Chronic kidney disease among men with lower urinary tract symptoms due to benign prostatic hyperplasia. BJU Int, 2010. 105: 1424.
https://www.ncbi.nlm.nih.gov/pubmed/19874305
77. Lee, J.H., *et al.* Relationship of estimated glomerular filtration rate with lower urinary tract symptoms/ benign prostatic hyperplasia measures in middle-aged men with moderate to severe lower urinary tract symptoms. Urology, 2013. 82: 1381.
https://www.ncbi.nlm.nih.gov/pubmed/24063940
78. Mebust, W.K., *et al.* Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. J Urol, 1989. 141: 243.
https://www.ncbi.nlm.nih.gov/pubmed/2643719
79. Rule, A.D., *et al.* Longitudinal changes in post-void residual and voided volume among community dwelling men. J Urol, 2005. 174: 1317.
https://www.ncbi.nlm.nih.gov/pubmed/16145411
80. Sullivan, M.P., *et al.* Detrusor contractility and compliance characteristics in adult male patients with obstructive and nonobstructive voiding dysfunction. J Urol, 1996. 155: 1995.
https://www.ncbi.nlm.nih.gov/pubmed/8618307
81. Oelke, M., *et al.* Diagnostic accuracy of noninvasive tests to evaluate bladder outlet obstruction in men: detrusor wall thickness, uroflowmetry, postvoid residual urine, and prostate volume. Eur Urol, 2007. 52: 827.
https://www.ncbi.nlm.nih.gov/pubmed/17207910
82. Emberton, M. Definition of at-risk patients: dynamic variables. BJU Int, 2006. 97 Suppl 2: 12.
https://www.ncbi.nlm.nih.gov/pubmed/16507047
83. Mochtar, C.A., *et al.* Post-void residual urine volume is not a good predictor of the need for invasive therapy among patients with benign prostatic hyperplasia. J Urol, 2006. 175: 213.
https://www.ncbi.nlm.nih.gov/pubmed/16406914
84. Abrams, P. Bladder outlet obstruction index, bladder contractility index and bladder voiding efficiency: three simple indices to define bladder voiding function. BJU Int, 1999. 84: 14.
https://www.ncbi.nlm.nih.gov/pubmed/10444116
85. Nitti, V.W. Pressure flow urodynamic studies: the gold standard for diagnosing bladder outlet obstruction. Rev Urol, 2005. 7 Suppl 6: S14.
https://www.ncbi.nlm.nih.gov/pubmed/16986024
86. Rubilotta, E., *et al.* Post-void residual urine ratio: A novel clinical approach to the post-void residual urine in the assessment of males with lower urinary tract symptoms. Investig Clin Urol, 2021. 62: 470.
https://www.ncbi.nlm.nih.gov/pubmed/34085789
87. Jorgensen, J.B., *et al.* Age-related variation in urinary flow variables and flow curve patterns in elderly males. Br J Urol, 1992. 69: 265.
https://www.ncbi.nlm.nih.gov/pubmed/1373664
88. Kranse, R., *et al.* Causes for variability in repeated pressure-flow measurements. Urology, 2003. 61: 930.
https://www.ncbi.nlm.nih.gov/pubmed/12736007
89. Reynard, J.M., *et al.* The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. Br J Urol, 1998. 82: 619.
https://www.ncbi.nlm.nih.gov/pubmed/9839573
90. Idzenga, T., *et al.* Accuracy of maximum flow rate for diagnosing bladder outlet obstruction can be estimated from the ICS nomogram. Neurourol Urodyn, 2008. 27: 97.
https://www.ncbi.nlm.nih.gov/pubmed/17600368
91. Siroky, M.B., *et al.* The flow rate nomogram: I. Development. J Urol, 1979. 122: 665.
https://www.ncbi.nlm.nih.gov/pubmed/159366
92. Siroky, M.B., *et al.* The flow rate nomogram: II. Clinical correlation. J Urol, 1980. 123: 208.
https://www.ncbi.nlm.nih.gov/pubmed/7354519

93. Reynard, J.M., *et al.* The value of multiple free-flow studies in men with lower urinary tract symptoms. Br J Urol, 1996. 77: 813.
https://www.ncbi.nlm.nih.gov/pubmed/8705213
94. Lee, H.J., *et al.* Development and Validation of a Deep Learning System for Sound-based Prediction of Urinary Flow. Eur Urol Focus, 2023. 9: 209.
https://www.ncbi.nlm.nih.gov/pubmed/35835694
95. Grossfeld, G.D., *et al.* Benign prostatic hyperplasia: clinical overview and value of diagnostic imaging. Radiol Clin North Am, 2000. 38: 31.
https://www.ncbi.nlm.nih.gov/pubmed/10664665
96. Thorpe, A., *et al.* Benign prostatic hyperplasia. Lancet, 2003. 361: 1359.
https://www.ncbi.nlm.nih.gov/pubmed/12711484
97. Wilkinson, A.G., *et al.* Is pre-operative imaging of the urinary tract worthwhile in the assessment of prostatism? Br J Urol, 1992. 70: 53.
https://www.ncbi.nlm.nih.gov/pubmed/1379105
98. Loch, A.C., *et al.* Technical and anatomical essentials for transrectal ultrasound of the prostate. World J Urol, 2007. 25: 361.
https://www.ncbi.nlm.nih.gov/pubmed/17701043
99. Stravodimos, K.G., *et al.* TRUS versus transabdominal ultrasound as a predictor of enucleated adenoma weight in patients with BPH: a tool for standard preoperative work-up? Int Urol Nephrol, 2009. 41: 767.
https://www.ncbi.nlm.nih.gov/pubmed/19350408
100. Shoukry, I., *et al.* Role of uroflowmetry in the assessment of lower urinary tract obstruction in adult males. Br J Urol, 1975. 47: 559.
https://www.ncbi.nlm.nih.gov/pubmed/1191927
101. Anikwe, R.M. Correlations between clinical findings and urinary flow rate in benign prostatic hypertrophy. Int Surg, 1976. 61: 392.
https://www.ncbi.nlm.nih.gov/pubmed/61184
102. el Din, K.E., *et al.* The correlation between bladder outlet obstruction and lower urinary tract symptoms as measured by the international prostate symptom score. J Urol, 1996. 156: 1020.
https://www.ncbi.nlm.nih.gov/pubmed/8709300
103. Griffiths, D., *et al.* Standardization of terminology of lower urinary tract function: pressure-flow studies of voiding, urethral resistance, and urethral obstruction. International Continence Society Subcommittee on Standardization of Terminology of Pressure-Flow Studies. Neurourol Urodyn, 1997. 16: 1.
https://www.ncbi.nlm.nih.gov/pubmed/9021786
104. Mei, H., *et al.* Deep Learning and Numerical Analysis for Bladder Outflow Obstruction and Detrusor Underactivity Diagnosis in Men: A Novel Urodynamic Evaluation Scheme. Neurourol Urodyn, 2025. 44: 512.
https://www.ncbi.nlm.nih.gov/pubmed/39803869
105. Oelke, M., *et al.* Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. Eur Urol, 2008. 54: 419.
https://www.ncbi.nlm.nih.gov/pubmed/18325657
106. Oh, M.M., *et al.* Is there a correlation between the presence of idiopathic detrusor overactivity and the degree of bladder outlet obstruction? Urology, 2011. 77: 167.
https://www.ncbi.nlm.nih.gov/pubmed/20934743
107. Jeong, S.J., *et al.* Prevalence and Clinical Features of Detrusor Underactivity among Elderly with Lower Urinary Tract Symptoms: A Comparison between Men and Women. Korean J Urol, 2012. 53: 342.
https://www.ncbi.nlm.nih.gov/pubmed/22670194
108. Thomas, A.W., *et al.* The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. BJU Int, 2004. 93: 745.
https://www.ncbi.nlm.nih.gov/pubmed/15049984
109. Al-Hayek, S., *et al.* Natural history of detrusor contractility--minimum ten-year urodynamic follow-up in men with bladder outlet obstruction and those with detrusor. Scand J Urol Nephrol Suppl, 2004: 101.
https://www.ncbi.nlm.nih.gov/pubmed/15545204
110. Thomas, A.W., *et al.* The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic followup of transurethral resection of prostate for bladder outlet obstruction. J Urol, 2005. 174: 1887.
https://www.ncbi.nlm.nih.gov/pubmed/16217330

111. Drake, M.J., *et al.* Diagnostic Assessment of Lower Urinary Tract Symptoms in Men Considering Prostate Surgery: A Noninferiority Randomised Controlled Trial of Urodynamics in 26 Hospitals. Eur Urol, 2020. 78: 701.
https://www.ncbi.nlm.nih.gov/pubmed/32616406
112. Lebani, B.R., *et al.* The role of transurethral resection of prostate (TURP) in patients with underactive bladder: 12 months follow-up in different grades of detrusor contractility. Prostate, 2023. 83: 857.
https://www.ncbi.nlm.nih.gov/pubmed/36945749
113. Aiello, M., *et al.* Quality control of uroflowmetry and urodynamic data from two large multicenter studies of male lower urinary tract symptoms. Neurourol Urodyn, 2020. 39: 1170.
https://www.ncbi.nlm.nih.gov/pubmed/32187720
114. Young, G.J., *et al.* Prostate Surgery for Men with Lower Urinary Tract Symptoms: Do We Need Urodynamics to Find the Right Candidates? Exploratory Findings from the UPSTREAM Trial. Eur Urol Focus, 2022. 8: 1331.
https://www.ncbi.nlm.nih.gov/pubmed/34922898
115. Blok, B., *et al.* EAU Guidelines on Neuro-Urology. 2026. Edn. presented at the 41st EAU Annual Congress London 2026.
https://uroweb.org/guidelines/neuro-urology
116. Kojima, M., *et al.* Correlation of presumed circle area ratio with infravesical obstruction in men with lower urinary tract symptoms. Urology, 1997. 50: 548.
https://www.ncbi.nlm.nih.gov/pubmed/9338730
117. Chia, S.J., *et al.* Correlation of intravesical prostatic protrusion with bladder outlet obstruction. BJU Int, 2003. 91: 371.
https://www.ncbi.nlm.nih.gov/pubmed/12603417
118. Tan, Y.G., *et al.* A Systemic Review and Meta-analysis of Transabdominal Intravesical Prostatic Protrusion Assessment in Determining Bladder Outlet Obstruction and Unsuccessful Trial Without Catheter. Eur Urol Focus, 2022. 8: 1003.
https://www.ncbi.nlm.nih.gov/pubmed/34561198
119. Keqin, Z., *et al.* Clinical significance of intravesical prostatic protrusion in patients with benign prostatic enlargement. Urology, 2007. 70: 1096.
https://www.ncbi.nlm.nih.gov/pubmed/18158025
120. Mariappan, P., *et al.* Intravesical prostatic protrusion is better than prostate volume in predicting the outcome of trial without catheter in white men presenting with acute urinary retention: a prospective clinical study. J Urol, 2007. 178: 573.
https://www.ncbi.nlm.nih.gov/pubmed/17570437
121. Tan, Y.H., *et al.* Intravesical prostatic protrusion predicts the outcome of a trial without catheter following acute urine retention. J Urol, 2003. 170: 2339.
https://www.ncbi.nlm.nih.gov/pubmed/14634410
122. Arnolds, M., *et al.* Positioning invasive versus noninvasive urodynamics in the assessment of bladder outlet obstruction. Curr Opin Urol, 2009. 19: 55.
https://www.ncbi.nlm.nih.gov/pubmed/19057217
123. Manieri, C., *et al.* The diagnosis of bladder outlet obstruction in men by ultrasound measurement of bladder wall thickness. J Urol, 1998. 159: 761.
https://www.ncbi.nlm.nih.gov/pubmed/9474143
124. Kessler, T.M., *et al.* Ultrasound assessment of detrusor thickness in men-can it predict bladder outlet obstruction and replace pressure flow study? J Urol, 2006. 175: 2170.
https://www.ncbi.nlm.nih.gov/pubmed/16697831
125. Cheng, Y., *et al.* The diagnostic value of non-invasive methods for diagnosing bladder outlet obstruction in men with lower urinary tract symptoms: A meta-analysis. Front Surg, 2022. 9: 986679.
https://www.ncbi.nlm.nih.gov/pubmed/36338622
126. Blatt, A.H., *et al.* Ultrasound measurement of bladder wall thickness in the assessment of voiding dysfunction. J Urol, 2008. 179: 2275.
https://www.ncbi.nlm.nih.gov/pubmed/18423703
127. Oelke, M. International Consultation on Incontinence-Research Society (ICI-RS) report on non-invasive urodynamics: the need of standardization of ultrasound bladder and detrusor wall thickness measurements to quantify bladder wall hypertrophy. Neurourol Urodyn, 2010. 29: 634.
https://www.ncbi.nlm.nih.gov/pubmed/20432327
128. Kojima, M., *et al.* Ultrasonic estimation of bladder weight as a measure of bladder hypertrophy in men with infravesical obstruction: a preliminary report. Urology, 1996. 47: 942.
https://www.ncbi.nlm.nih.gov/pubmed/8677600

129. Kojima, M., *et al.* Noninvasive quantitative estimation of infravesical obstruction using ultrasonic measurement of bladder weight. J Urol, 1997. 157: 476.
https://www.ncbi.nlm.nih.gov/pubmed/8996337
130. Akino, H., *et al.* Ultrasound-estimated bladder weight predicts risk of surgery for benign prostatic hyperplasia in men using alpha-adrenoceptor blocker for LUTS. Urology, 2008. 72: 817.
https://www.ncbi.nlm.nih.gov/pubmed/18597835
131. McIntosh, S.L., *et al.* Noninvasive assessment of bladder contractility in men. J Urol, 2004. 172: 1394.
https://www.ncbi.nlm.nih.gov/pubmed/15371853
132. Drinnan, M.J., *et al.* Inter-observer agreement in the estimation of bladder pressure using a penile cuff. Neurourol Urodyn, 2003. 22: 296.
https://www.ncbi.nlm.nih.gov/pubmed/12808703
133. Griffiths, C.J., *et al.* A nomogram to classify men with lower urinary tract symptoms using urine flow and noninvasive measurement of bladder pressure. J Urol, 2005. 174: 1323.
https://www.ncbi.nlm.nih.gov/pubmed/16145412
134. Clarkson, B., *et al.* Continuous non-invasive measurement of bladder voiding pressure using an experimental constant low-flow test. Neurourol Urodyn, 2012. 31: 557.
https://www.ncbi.nlm.nih.gov/pubmed/22190105
135. Khosla, L., *et al.* Use of the penile cuff test to diagnose bladder outlet obstruction: A systematic review and meta-analysis. Low Urin Tract Symptoms, 2022. 14: 318.
https://www.ncbi.nlm.nih.gov/pubmed/35716000
136. Van Mastrigt, R., *et al.* Towards a noninvasive urodynamic diagnosis of infravesical obstruction. BJU Int, 1999. 84: 195.
https://www.ncbi.nlm.nih.gov/pubmed/10444152
137. Pel, J.J., *et al.* Development of a non-invasive strategy to classify bladder outlet obstruction in male patients with LUTS. Neurourol Urodyn, 2002. 21: 117.
https://www.ncbi.nlm.nih.gov/pubmed/11857664
138. Shinbo, H., *et al.* Application of ultrasonography and the resistive index for evaluating bladder outlet obstruction in patients with benign prostatic hyperplasia. Curr Urol Rep, 2011. 12: 255.
https://www.ncbi.nlm.nih.gov/pubmed/21475953
139. Ku, J.H., *et al.* Correlation between prostatic urethral angle and bladder outlet obstruction index in patients with lower urinary tract symptoms. Urology, 2010. 75: 1467.
https://www.ncbi.nlm.nih.gov/pubmed/19962734
140. Malde, S., *et al.* Systematic Review of the Performance of Noninvasive Tests in Diagnosing Bladder Outlet Obstruction in Men with Lower Urinary Tract Symptoms. Eur Urol, 2017. 71: 391.
https://www.ncbi.nlm.nih.gov/pubmed/27687821
141. Cicione, A., *et al.* Post-voided residual urine ratio as a predictor of bladder outlet obstruction in men with lower urinary tract symptoms: development of a clinical nomogram. World J Urol, 2023. 41: 521.
https://www.ncbi.nlm.nih.gov/pubmed/36527471
142. Els, M., *et al.* Prospective comparison of the novel visual prostate symptom score (VPSS) versus the international prostate symptom score (IPSS), and assessment of patient pain perception with regard to transrectal ultrasound guided prostate biopsy. Int Braz J Urol, 2019. 45: 137.
https://www.ncbi.nlm.nih.gov/pubmed/30620160
143. Sanman, K.N., *et al.* Can new, improvised Visual Prostate Symptom Score replace the International Prostate Symptom Score? Indian perspective. Indian J Urol, 2020. 36: 123.
https://www.ncbi.nlm.nih.gov/pubmed/32549664
144. Greco, F., *et al.* The Potential Role of MicroRNAs as Biomarkers in Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis. Eur Urol Focus, 2019. 5: 497.
https://www.ncbi.nlm.nih.gov/pubmed/29398458
145. Han, J.H., *et al.* Natural history of incidentally diagnosed prostate cancer after holmium laser enucleation of the prostate. PLoS One, 2023. 18: e0278931.
https://www.ncbi.nlm.nih.gov/pubmed/36730281
146. Cornford, P., *et al.* EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer-2024 Update. Part I: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol, 2024. 86: 148.
https://www.ncbi.nlm.nih.gov/pubmed/38614820
147. Ball, A.J., *et al.* The natural history of untreated “prostatism”. Br J Urol, 1981. 53: 613.
https://www.ncbi.nlm.nih.gov/pubmed/6172172
148. Kirby, R.S. The natural history of benign prostatic hyperplasia: what have we learned in the last decade? Urology, 2000. 56: 3.
https://www.ncbi.nlm.nih.gov/pubmed/11074195

149. Isaacs, J.T. Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. Prostate Suppl, 1990. 3: 1.
https://www.ncbi.nlm.nih.gov/pubmed/1689166
150. Netto, N.R., Jr., *et al.* Evaluation of patients with bladder outlet obstruction and mild international prostate symptom score followed up by watchful waiting. Urology, 1999. 53: 314.
https://www.ncbi.nlm.nih.gov/pubmed/9933046
151. Flanigan, R.C., *et al.* 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. J Urol, 1998. 160: 12.
https://www.ncbi.nlm.nih.gov/pubmed/9628595
152. Wasson, J.H., *et al.* A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. N Engl J Med, 1995. 332: 75.
https://www.ncbi.nlm.nih.gov/pubmed/7527493
153. Brown, C.T., *et al.* Self management for men with lower urinary tract symptoms: randomised controlled trial. BMJ, 2007. 334: 25.
https://www.ncbi.nlm.nih.gov/pubmed/17118949
154. Yap, T.L., *et al.* The impact of self-management of lower urinary tract symptoms on frequency-volume chart measures. BJU Int, 2009. 104: 1104.
https://www.ncbi.nlm.nih.gov/pubmed/19485993
155. Albarqouni, L., *et al.* Self-Management for Men With Lower Urinary Tract Symptoms: A Systematic Review and Meta-Analysis. Ann Fam Med, 2021. 19: 157.
https://www.ncbi.nlm.nih.gov/pubmed/33685877
156. Kumar, A., *et al.* Self-management interventions for men with lower urinary tract symptoms: A systematic review and meta-analysis of randomized controlled trials. Arch Gerontol Geriatr, 2025. 131: 105742.
https://www.ncbi.nlm.nih.gov/pubmed/39778302
157. Gratzke, C., *et al.* A Randomized Trial of an App-Based Therapeutic for Lower Urinary Tract Symptoms. NEJM Evid, 2025. 4: EVIDoa2400290.
https://www.ncbi.nlm.nih.gov/pubmed/40130971
158. Drake, M.J., *et al.* Treatment of lower urinary tract symptoms in men in primary care using a conservative intervention: cluster randomised controlled trial. BMJ, 2023. 383: e075219.
https://www.ncbi.nlm.nih.gov/pubmed/37967894
159. Brown, C.T., *et al.* Defining the components of a self-management programme for men with uncomplicated lower urinary tract symptoms: a consensus approach. Eur Urol, 2004. 46: 254.
https://www.ncbi.nlm.nih.gov/pubmed/15245822
160. Michel, M.C., *et al.* Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol, 2006. 147 Suppl 2: S88.
https://www.ncbi.nlm.nih.gov/pubmed/16465187
161. Kortmann, B.B., *et al.* Urodynamic effects of alpha-adrenoceptor blockers: a review of clinical trials. Urology, 2003. 62: 1.
https://www.ncbi.nlm.nih.gov/pubmed/12837408
162. Barendrecht, M.M., *et al.* Do alpha1-adrenoceptor antagonists improve lower urinary tract symptoms by reducing bladder outlet resistance? Neurourol Urodyn, 2008. 27: 226.
https://www.ncbi.nlm.nih.gov/pubmed/17638312
163. Djavan, B., *et al.* State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology, 2004. 64: 1081.
https://www.ncbi.nlm.nih.gov/pubmed/15596173
164. Michel, M.C., *et al.* Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. Prostate Cancer Prostatic Dis, 1998. 1: 332.
https://www.ncbi.nlm.nih.gov/pubmed/12496876
165. Fusco, F., *et al.* alpha1-Blockers Improve Benign Prostatic Obstruction in Men with Lower Urinary Tract Symptoms: A Systematic Review and Meta-analysis of Urodynamic Studies. Eur Urol, 2016. 69: 1091.
https://www.ncbi.nlm.nih.gov/pubmed/26831507
166. Boyle, P., *et al.* Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. Urology, 2001. 58: 717.
https://www.ncbi.nlm.nih.gov/pubmed/11711348

167. Roehrborn, C.G. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. Prostate Cancer Prostatic Dis, 2006. 9: 121.
https://www.ncbi.nlm.nih.gov/pubmed/16304557
168. Roehrborn, C.G., *et al.* The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. J Urol, 2008. 179: 616.
https://www.ncbi.nlm.nih.gov/pubmed/18082216
169. Roehrborn, C.G., *et al.* The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. Eur Urol, 2010. 57: 123.
https://www.ncbi.nlm.nih.gov/pubmed/19825505
170. Creta, M., *et al.* Detrusor overactivity and underactivity: implication for lower urinary tract symptoms related to benign prostate hyperplasia diagnosis and treatment. Minerva Urol Nephrol, 2021. 73: 59.
https://www.ncbi.nlm.nih.gov/pubmed/32026666
171. Karavitakis, M., *et al.* Management of Urinary Retention in Patients with Benign Prostatic Obstruction: A Systematic Review and Meta-analysis. Eur Urol, 2019. 75: 788.
https://www.ncbi.nlm.nih.gov/pubmed/30773327
172. Gwon, Y.N., *et al.* Comparing effects of alpha-blocker management on acute urinary retention secondary to benign prostatic hyperplasia: A systematic review and network meta-analysis. Prostate Int, 2023. 11: 91.
https://www.ncbi.nlm.nih.gov/pubmed/37409094
173. Nickel, J.C., *et al.* A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. Int J Clin Pract, 2008. 62: 1547.
https://www.ncbi.nlm.nih.gov/pubmed/18822025
174. Barendrecht, M.M., *et al.* Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. BJU Int, 2005. 95 Suppl 4: 19.
https://www.ncbi.nlm.nih.gov/pubmed/15871732
175. Chapple, C.R., *et al.* Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol, 2011. 59: 342.
https://www.ncbi.nlm.nih.gov/pubmed/21109344
176. Welk, B., *et al.* The risk of fall and fracture with the initiation of a prostate-selective alpha antagonist: a population based cohort study. BMJ, 2015. 351: h5398.
https://www.ncbi.nlm.nih.gov/pubmed/26502947
177. Lusty, A., *et al.* Cardiac Failure Associated with Medical Therapy of Benign Prostatic Hyperplasia: A Population Based Study. J Urol, 2021. 205: 1430.
https://www.ncbi.nlm.nih.gov/pubmed/33616451
178. Latvala, L., *et al.* Use of alpha1-adrenoceptor antagonists tamsulosin and alfuzosin and the risk of Alzheimer's disease. Pharmacoepidemiol Drug Saf, 2022. 31: 1110.
https://www.ncbi.nlm.nih.gov/pubmed/35751619
179. Chang, D.F., *et al.* Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg, 2005. 31: 664.
https://www.ncbi.nlm.nih.gov/pubmed/15899440
180. Chatziralli, I.P., *et al.* Risk factors for intraoperative floppy iris syndrome: a meta-analysis. Ophthalmology, 2011. 118: 730.
https://www.ncbi.nlm.nih.gov/pubmed/21168223
181. Bapir, R., *et al.* Effect of alpha-adrenoceptor antagonists on sexual function. A systematic review and meta-analysis. Arch Ital Urol Androl, 2022. 94: 252.
https://www.ncbi.nlm.nih.gov/pubmed/35775356
182. Gacci, M., *et al.* Impact of medical treatments for male lower urinary tract symptoms due to benign prostatic hyperplasia on ejaculatory function: a systematic review and meta-analysis. J Sex Med, 2014. 11: 1554.
https://www.ncbi.nlm.nih.gov/pubmed/24708055
183. Andriole, G., *et al.* Dihydrotestosterone and the prostate: the scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol, 2004. 172: 1399.
https://www.ncbi.nlm.nih.gov/pubmed/15371854
184. Rittmaster, R.S., *et al.* Evidence for atrophy and apoptosis in the prostates of men given finasteride. J Clin Endocrinol Metab, 1996. 81: 814.
https://www.ncbi.nlm.nih.gov/pubmed/8636309

185. Naslund, M.J., *et al.* A review of the clinical efficacy and safety of 5alpha-reductase inhibitors for the enlarged prostate. Clin Ther, 2007. 29: 17.
https://www.ncbi.nlm.nih.gov/pubmed/17379044
186. Andersen, J.T., *et al.* Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. The Scandinavian BPH Study Group. Urology, 1995. 46: 631.
https://www.ncbi.nlm.nih.gov/pubmed/7495111
187. Kirby, R.S., *et al.* Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology, 2003. 61: 119.
https://www.ncbi.nlm.nih.gov/pubmed/12559281
188. Lepor, H., *et al.* The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. N Engl J Med, 1996. 335: 533.
https://www.ncbi.nlm.nih.gov/pubmed/8684407
189. Marberger, M.J. Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. PROWESS Study Group. Urology, 1998. 51: 677.
https://www.ncbi.nlm.nih.gov/pubmed/9610579
190. McConnell, J.D., *et al.* The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. N Engl J Med, 1998. 338: 557.
https://www.ncbi.nlm.nih.gov/pubmed/9475762
191. Nickel, J.C., *et al.* Efficacy and safety of finasteride therapy for benign prostatic hyperplasia: results of a 2-year randomized controlled trial (the PROSPECT study). PROscar Safety Plus Efficacy Canadian Two year Study. CMAJ, 1996. 155: 1251.
https://www.ncbi.nlm.nih.gov/pubmed/8911291
192. Roehrborn, C.G., *et al.* Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology, 2002. 60: 434.
https://www.ncbi.nlm.nih.gov/pubmed/12350480
193. Nickel, J.C., *et al.* Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int, 2011. 108: 388.
https://www.ncbi.nlm.nih.gov/pubmed/21631695
194. Boyle, P., *et al.* Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology, 1996. 48: 398.
https://www.ncbi.nlm.nih.gov/pubmed/8804493
195. Gittelman, M., *et al.* Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. J Urol, 2006. 176: 1045.
https://www.ncbi.nlm.nih.gov/pubmed/16890688
196. Roehrborn, C.G., *et al.* Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. BJU Int, 2005. 96: 572.
https://www.ncbi.nlm.nih.gov/pubmed/16104912
197. Roehrborn, C.G., *et al.* The influence of baseline parameters on changes in international prostate symptom score with dutasteride, tamsulosin, and combination therapy among men with symptomatic benign prostatic hyperplasia and an enlarged prostate: 2-year data from the CombAT study. Eur Urol, 2009. 55: 461.
https://www.ncbi.nlm.nih.gov/pubmed/19013011
198. Roehrborn, C.G. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. BJU Int, 2008. 101 Suppl 3: 17.
https://www.ncbi.nlm.nih.gov/pubmed/18307681
199. Andersen, J.T., *et al.* Finasteride significantly reduces acute urinary retention and need for surgery in patients with symptomatic benign prostatic hyperplasia. Urology, 1997. 49: 839.
https://www.ncbi.nlm.nih.gov/pubmed/9187688
200. Kirby, R.S., *et al.* Long-term urodynamic effects of finasteride in benign prostatic hyperplasia: a pilot study. Eur Urol, 1993. 24: 20.
https://www.ncbi.nlm.nih.gov/pubmed/7689971
201. Tammela, T.L., *et al.* Long-term effects of finasteride on invasive urodynamics and symptoms in the treatment of patients with bladder outflow obstruction due to benign prostatic hyperplasia. J Urol, 1995. 154: 1466.
https://www.ncbi.nlm.nih.gov/pubmed/7544845

202. Bengtsen, M.B., *et al.* Long-term risk of benign prostatic hyperplasia-related surgery and acute urinary retention in men treated with 5-alpha reductase inhibitor versus alpha-blocker monotherapy in routine clinical care. Prostate, 2023. 83: 980.
https://www.ncbi.nlm.nih.gov/pubmed/37057816
203. Donohue, J.F., *et al.* Transurethral prostate resection and bleeding: a randomized, placebo controlled trial of role of finasteride for decreasing operative blood loss. J Urol, 2002. 168: 2024.
https://www.ncbi.nlm.nih.gov/pubmed/12394700
204. Khwaja, M.A., *et al.* The Effect of Two Weeks Preoperative Finasteride Therapy in Reducing Prostate Vascularity. J Coll Physicians Surg Pak, 2016. 26: 213.
https://www.ncbi.nlm.nih.gov/pubmed/26975954
205. Elsherbini, T., *et al.* The impact of 5-ARI on perioperative and functional outcomes of GreenLight PVP: an analysis of the Global GreenLight Group database. Can J Urol, 2023. 30: 11473.
https://www.ncbi.nlm.nih.gov/pubmed/37074746
206. Corona, G., *et al.* Sexual dysfunction in subjects treated with inhibitors of 5alpha-reductase for benign prostatic hyperplasia: a comprehensive review and meta-analysis. Andrology, 2017. 5: 671.
https://www.ncbi.nlm.nih.gov/pubmed/28453908
207. Andriole, G.L., *et al.* Effect of dutasteride on the risk of prostate cancer. N Engl J Med, 2010. 362: 1192.
https://www.ncbi.nlm.nih.gov/pubmed/20357281
208. Thompson, I.M., *et al.* The influence of finasteride on the development of prostate cancer. N Engl J Med, 2003. 349: 215.
https://www.ncbi.nlm.nih.gov/pubmed/12824459
209. Baboudjian, M., *et al.* Association Between 5alpha-Reductase Inhibitors and Prostate Cancer Mortality: A Systematic Review and Meta-analysis. JAMA Oncol, 2023. 9: 847.
https://www.ncbi.nlm.nih.gov/pubmed/37079318
210. Hsieh, T.F., *et al.* Use of 5-alpha-reductase inhibitors did not increase the risk of cardiovascular diseases in patients with benign prostate hyperplasia: a five-year follow-up study. PLoS One, 2015. 10: e0119694.
https://www.ncbi.nlm.nih.gov/pubmed/25803433
211. Skeldon, S.C., *et al.* The Cardiovascular Safety of Dutasteride. J Urol, 2017. 197: 1309.
https://www.ncbi.nlm.nih.gov/pubmed/27866006
212. Wei, L., *et al.* Incidence of type 2 diabetes mellitus in men receiving steroid 5alpha-reductase inhibitors: population based cohort study. BMJ, 2019. 365: l1204.
https://www.ncbi.nlm.nih.gov/pubmed/30971393
213. Garcia-Argibay, M., *et al.* Association of 5alpha-Reductase Inhibitors With Dementia, Depression, and Suicide. JAMA Netw Open, 2022. 5: e2248135.
https://www.ncbi.nlm.nih.gov/pubmed/36547981
214. Uleri, A., *et al.* Association of 5alpha-Reductase Inhibitors with Depression and Suicide: A Mini Systematic Review and Meta-analysis. Eur Urol Focus, 2024. 10: 751.
https://www.ncbi.nlm.nih.gov/pubmed/38692949
215. Agency, E.M. Measures to minimise risk of suicidal thoughts with finasteride and dutasteride medicines 2025. 2025.
https://www.ema.europa.eu/en/medicines/human/referrals/finasteride-dutasteride-containing-medicinal-products
216. Chess-Williams, R., *et al.* The minor population of M3-receptors mediate contraction of human detrusor muscle *in vitro*. J Auton Pharmacol, 2001. 21: 243.
https://www.ncbi.nlm.nih.gov/pubmed/12123469
217. Matsui, M., *et al.* Multiple functional defects in peripheral autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype. Proc Natl Acad Sci U S A, 2000. 97: 9579.
https://www.ncbi.nlm.nih.gov/pubmed/10944224
218. Kono, M., *et al.* Central muscarinic receptor subtypes regulating voiding in rats. J Urol, 2006. 175: 353.
https://www.ncbi.nlm.nih.gov/pubmed/16406941
219. Wuest, M., *et al.* Effect of rilmakalim on detrusor contraction in the presence and absence of urothelium. Naunyn Schmiedebergs Arch Pharmacol, 2005. 372: 203.
https://www.ncbi.nlm.nih.gov/pubmed/16283254
220. Goldfischer, E.R., *et al.* Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study. Neurourol Urodyn, 2015. 34: 37.
https://www.ncbi.nlm.nih.gov/pubmed/24133005

221. Baldwin, C.M., *et al.* Transdermal oxybutynin. Drugs, 2009. 69: 327.
https://www.ncbi.nlm.nih.gov/pubmed/19275276
222. Michel, M.C., *et al.* Does gender or age affect the efficacy and safety of tolterodine? J Urol, 2002. 168: 1027.
https://www.ncbi.nlm.nih.gov/pubmed/12187215
223. Chapple, C., *et al.* Fesoterodine clinical efficacy and safety for the treatment of overactive bladder in relation to patient profiles: a systematic review. Curr Med Res Opin, 2015. 31: 1201.
https://www.ncbi.nlm.nih.gov/pubmed/25798911
224. Dmochowski, R., *et al.* Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. Eur Urol, 2007. 51: 1054.
https://www.ncbi.nlm.nih.gov/pubmed/17097217
225. Herschorn, S., *et al.* Efficacy and tolerability of fesoterodine in men with overactive bladder: a pooled analysis of 2 phase III studies. Urology, 2010. 75: 1149.
https://www.ncbi.nlm.nih.gov/pubmed/19914702
226. Hofner, K., *et al.* Safety and efficacy of tolterodine extended release in men with overactive bladder symptoms and presumed non-obstructive benign prostatic hyperplasia. World J Urol, 2007. 25: 627.
https://www.ncbi.nlm.nih.gov/pubmed/17906864
227. Roehrborn, C.G., *et al.* Efficacy and tolerability of tolterodine extended-release in men with overactive bladder and urgency urinary incontinence. BJU Int, 2006. 97: 1003.
https://www.ncbi.nlm.nih.gov/pubmed/16643482
228. Kaplan, S.A., *et al.* Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA, 2006. 296: 2319.
https://www.ncbi.nlm.nih.gov/pubmed/17105794
229. Kaplan, S.A., *et al.* Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. J Urol, 2005. 174: 2273.
https://www.ncbi.nlm.nih.gov/pubmed/16280803
230. Chapple, C.R., *et al.* A shifted paradigm for the further understanding, evaluation, and treatment of lower urinary tract symptoms in men: focus on the bladder. Eur Urol, 2006. 49: 651.
https://www.ncbi.nlm.nih.gov/pubmed/16530611
231. Kaplan, S.A., *et al.* Solifenacin treatment in men with overactive bladder: effects on symptoms and patient-reported outcomes. Aging Male, 2010. 13: 100.
https://www.ncbi.nlm.nih.gov/pubmed/20001469
232. Gacci, M., *et al.* Tolterodine in the Treatment of Male LUTS. Curr Urol Rep, 2015. 16: 60.
https://www.ncbi.nlm.nih.gov/pubmed/26149965
233. Roehrborn, C.G., *et al.* Effects of serum PSA on efficacy of tolterodine extended release with or without tamsulosin in men with LUTS, including OAB. Urology, 2008. 72: 1061.
https://www.ncbi.nlm.nih.gov/pubmed/18817961
234. Yokoyama, T., *et al.* Naftopidil and propiverine hydrochloride for treatment of male lower urinary tract symptoms suggestive of benign prostatic hyperplasia and concomitant overactive bladder: a prospective randomized controlled study. Scand J Urol Nephrol, 2009. 43: 307.
https://www.ncbi.nlm.nih.gov/pubmed/19396723
235. Abrams, P., *et al.* Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol, 2006. 175: 999.
https://www.ncbi.nlm.nih.gov/pubmed/16469601
236. Andersson, K.E. On the Site and Mechanism of Action of beta(3)-Adrenoceptor Agonists in the Bladder. Int Neurourol J, 2017. 21: 6.
https://www.ncbi.nlm.nih.gov/pubmed/28361520
237. Chapple, C.R., *et al.* Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. Eur Urol, 2013. 63: 296.
https://www.ncbi.nlm.nih.gov/pubmed/23195283
238. Herschorn, S., *et al.* A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta(3) adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology, 2013. 82: 313.
https://www.ncbi.nlm.nih.gov/pubmed/23769122
239. Khullar, V., *et al.* Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol, 2013. 63: 283.
https://www.ncbi.nlm.nih.gov/pubmed/23182126

240. Nitti, V.W., *et al.* Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol, 2013. 189: 1388.
https://www.ncbi.nlm.nih.gov/pubmed/23079373
241. Yamaguchi, O., *et al.* Efficacy and Safety of the Selective beta3 -Adrenoceptor Agonist Mirabegron in Japanese Patients with Overactive Bladder: A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study. Low Urin Tract Symptoms, 2015. 7: 84.
https://www.ncbi.nlm.nih.gov/pubmed/26663687
242. Sebastianelli, A., *et al.* Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: Comparison with placebo and tolterodine. Int J Urol, 2018. 25: 196.
https://www.ncbi.nlm.nih.gov/pubmed/29205506
243. Dey, A., *et al.* Mirabegron Versus Placebo and Other Therapeutic Modalities in the Treatment of Patients with Overactive Bladder Syndrome-A Systematic Review. Eur Urol Focus, 2025. 11: 323.
https://www.ncbi.nlm.nih.gov/pubmed/39343691
244. Liao, C.H., *et al.* Mirabegron 25 mg Monotherapy Is Safe but Less Effective in Male Patients With Overactive Bladder and Bladder Outlet Obstruction. Urology, 2018. 117: 115.
https://www.ncbi.nlm.nih.gov/pubmed/29630956
245. Drake, M.J., *et al.* Efficacy and Safety of Mirabegron Add-on Therapy to Solifenacin in Incontinent Overactive Bladder Patients with an Inadequate Response to Initial 4-Week Solifenacin Monotherapy: A Randomised Double-blind Multicentre Phase 3B Study (BESIDE). Eur Urol, 2016. 70: 136.
https://www.ncbi.nlm.nih.gov/pubmed/26965560
246. Kuo, H.C., *et al.* Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a beta3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn, 2015. 34: 685.
https://www.ncbi.nlm.nih.gov/pubmed/25130281
247. Abrams, P., *et al.* Combination treatment with mirabegron and solifenacin in patients with overactive bladder: exploratory responder analyses of efficacy and evaluation of patient-reported outcomes from a randomized, double-blind, factorial, dose-ranging, Phase II study (SYMPHONY). World J Urol, 2017. 35: 827.
https://www.ncbi.nlm.nih.gov/pubmed/27514371
248. Khullar, V., *et al.* Patient-reported outcomes with the beta(3) -adrenoceptor agonist mirabegron in a phase III trial in patients with overactive bladder. Neurourol Urodyn, 2016. 35: 987.
https://www.ncbi.nlm.nih.gov/pubmed/26288118
249. Yamaguchi, O., *et al.* Safety and efficacy of mirabegron as 'add-on' therapy in patients with overactive bladder treated with solifenacin: a post-marketing, open-label study in Japan (MILAI study). BJU Int, 2015. 116: 612.
https://www.ncbi.nlm.nih.gov/pubmed/25639296
250. Elbaz, R., *et al.* Mirabegron for treatment of erectile dysfunction concomitant with lower urinary tract symptoms in patients with benign prostatic obstruction: A randomized controlled trial. Int J Urol, 2022. 29: 390.
https://www.ncbi.nlm.nih.gov/pubmed/35043484
251. White, W.B., *et al.* Cardiovascular safety of mirabegron: analysis of an integrated clinical trial database of patients with overactive bladder syndrome. J Am Soc Hypertens, 2018. 12: 768.
https://www.ncbi.nlm.nih.gov/pubmed/30181042
252. Nitti, V.W., *et al.* Urodynamics and safety of the beta(3)-adrenoceptor agonist mirabegron in males with lower urinary tract symptoms and bladder outlet obstruction. J Urol, 2013. 190: 1320.
https://www.ncbi.nlm.nih.gov/pubmed/23727415
253. Lee, Y.K., *et al.* Safety and therapeutic efficacy of mirabegron 25 mg in older patients with overactive bladder and multiple comorbidities. Geriatr Gerontol Int, 2018. 18: 1330.
https://www.ncbi.nlm.nih.gov/pubmed/29931793
254. Wagg, A., *et al.* Oral pharmacotherapy for overactive bladder in older patients: mirabegron as a potential alternative to antimuscarinics. Curr Med Res Opin, 2016. 32: 621.
https://www.ncbi.nlm.nih.gov/pubmed/26828974
255. Wagg, A., *et al.* Efficacy, safety, and tolerability of mirabegron in patients aged >/=65yr with overactive bladder wet: a phase IV, double-blind, randomised, placebo-controlled study (PILLAR). Eur Urol, 2020. 77: 211.
https://www.ncbi.nlm.nih.gov/pubmed/31733990

256. Herschorn, S., *et al.* Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int, 2017. 120: 562.
https://www.ncbi.nlm.nih.gov/pubmed/28418102
257. Chapple, C.R., *et al.* Persistence and Adherence with Mirabegron versus Antimuscarinic Agents in Patients with Overactive Bladder: A Retrospective Observational Study in UK Clinical Practice. Eur Urol, 2017. 72: 389.
https://www.ncbi.nlm.nih.gov/pubmed/28196724
258. Staskin, D., *et al.* International Phase III, Randomized, Double-Blind, Placebo and Active Controlled Study to Evaluate the Safety and Efficacy of Vibegron in Patients with Symptoms of Overactive Bladder: EMPOWUR. J Urol, 2020. 204: 316.
https://www.ncbi.nlm.nih.gov/pubmed/32068484
259. Giuliano, F., *et al.* The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. Eur Urol, 2013. 63: 506.
https://www.ncbi.nlm.nih.gov/pubmed/23018163
260. Morelli, A., *et al.* Phosphodiesterase type 5 expression in human and rat lower urinary tract tissues and the effect of tadalafil on prostate gland oxygenation in spontaneously hypertensive rats. J Sex Med, 2011. 8: 2746.
https://www.ncbi.nlm.nih.gov/pubmed/21812935
261. Vignozzi, L., *et al.* PDE5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE5 inhibitors in LUTS. Prostate, 2013. 73: 1391.
https://www.ncbi.nlm.nih.gov/pubmed/23765639
262. Nagasubramanian, S., *et al.* Tamsulosin and placebo vs tamsulosin and tadalafil in male lower urinary tract symptoms: a double-blinded, randomised controlled trial. BJU Int, 2020. 125: 718.
https://www.ncbi.nlm.nih.gov/pubmed/32012409
263. Pattanaik, S., *et al.* Phosphodiesterase inhibitors for lower urinary tract symptoms consistent with benign prostatic hyperplasia. Cochrane Database Syst Rev, 2018. 11: CD010060.
https://www.ncbi.nlm.nih.gov/pubmed/30480763
264. Guo, B., *et al.* Comparative Effectiveness of Tadalafil versus Tamsulosin in Treating Lower Urinary Tract Symptoms Suggestive of Benign Prostate Hyperplasia: A Meta-Analysis of Randomized Controlled Trials. Med Sci Monit, 2020. 26: e923179.
https://www.ncbi.nlm.nih.gov/pubmed/32327621
265. Gacci, M., *et al.* A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with alpha-blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol, 2012. 61: 994.
https://www.ncbi.nlm.nih.gov/pubmed/22405510
266. Wang, Y., *et al.* Tadalafil 5 mg Once Daily Improves Lower Urinary Tract Symptoms and Erectile Dysfunction: A Systematic Review and Meta-analysis. Low Urin Tract Symptoms, 2018. 10: 84.
https://www.ncbi.nlm.nih.gov/pubmed/29341503
267. Oelke, M., *et al.* Time to onset of clinically meaningful improvement with tadalafil 5 mg once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: analysis of data pooled from 4 pivotal, double-blind, placebo controlled studies. J Urol, 2015. 193: 1581.
https://www.ncbi.nlm.nih.gov/pubmed/25437533
268. Donatucci, C.F., *et al.* Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open-label extension study. BJU Int, 2011. 107: 1110.
https://www.ncbi.nlm.nih.gov/pubmed/21244606
269. Porst, H., *et al.* Efficacy and safety of tadalafil 5 mg once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: subgroup analyses of pooled data from 4 multinational, randomized, placebo-controlled clinical studies. Urology, 2013. 82: 667.
https://www.ncbi.nlm.nih.gov/pubmed/23876588
270. Brock, G.B., *et al.* Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies. J Urol, 2014. 191: 405.
https://www.ncbi.nlm.nih.gov/pubmed/24096120
271. Roehrborn, C.G., *et al.* Effects of tadalafil once daily on maximum urinary flow rate in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. J Urol, 2014. 191: 1045.
https://www.ncbi.nlm.nih.gov/pubmed/24445278

272. Oelke, M., *et al.* Efficacy and safety of tadalafil 5 mg once daily in the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia in men aged >/=75 years: integrated analyses of pooled data from multinational, randomized, placebo-controlled clinical studies. BJU Int, 2017. 119: 793.
https://www.ncbi.nlm.nih.gov/pubmed/27988986
273. Buck, A.C. Is there a scientific basis for the therapeutic effects of serenoa repens in benign prostatic hyperplasia? Mechanisms of action. J Urol, 2004. 172: 1792.
https://www.ncbi.nlm.nih.gov/pubmed/15540722
274. Dmochowski, R., *et al.* Urodynamic effects of once daily tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized, placebo controlled 12-week clinical trial. J Urol, 2013. 189: S135.
https://www.ncbi.nlm.nih.gov/pubmed/23234619
275. Kosilov, K., *et al.* Efficacy of a combination of dutasteride, tadalafil, and solifenacin in the treatment of previously unsuccessful patients. Asian J Urol, 2022. 9: 42.
https://www.ncbi.nlm.nih.gov/pubmed/35198395
276. EMA, Tadalafil Lilly : EPAR - Product Information, in EMA, E.M. Agency, Editor. 2017.
https://www.ema.europa.eu/en/medicines/human/EPAR/tadalafil-lilly
277. Salonia, A.B., *et al.* EAU Guidelines on Sexual and Reproductive Health. 2026. Edn. presented at the 41st EAU Annual Congress London 2026.
https://uroweb.org/guidelines/sexual-and-reproductive-health
278. Madersbacher, S., *et al.* Plant extracts: sense or nonsense? Curr Opin Urol, 2008. 18: 16.
https://www.ncbi.nlm.nih.gov/pubmed/18090484
279. Levin, R.M., *et al.* A scientific basis for the therapeutic effects of Pygeum africanum and Serenoa repens. Urol Res, 2000. 28: 201.
https://www.ncbi.nlm.nih.gov/pubmed/10929430
280. Habib, F.K., *et al.* Not all brands are created equal: a comparison of selected components of different brands of Serenoa repens extract. Prostate Cancer Prostatic Dis, 2004. 7: 195.
https://www.ncbi.nlm.nih.gov/pubmed/15289814
281. Scaglione, F., *et al.* Comparison of the potency of different brands of Serenoa repens extract on 5alpha-reductase types I and II in prostatic co-cultured epithelial and fibroblast cells. Pharmacology, 2008. 82: 270.
https://www.ncbi.nlm.nih.gov/pubmed/18849646
282. De Monte, C., *et al.* Modern extraction techniques and their impact on the pharmacological profile of Serenoa repens extracts for the treatment of lower urinary tract symptoms. BMC Urol, 2014. 14: 63.
https://www.ncbi.nlm.nih.gov/pubmed/25112532
283. EMA. Herbal Medicinal Product.
https://www.ema.europa.eu/en/human-regulatory-overview/herbal-medicinal-products/european-union-monographs-list-entries
284. Committee on Herbal Medicinal Products. European Union herbal monograph on Serenoa repens (W. Bartram) Small, fructus. EMA/HMPC/280079/2013, 2015.
https://www.ema.europa.eu/en/documents/herbal-monograph/draft-european-union-herbal-monograph-serenoa-repens-w-bartram-small-fructus_en.pdf
285. Committee on Herbal Medicinal Products. Community herbal monograph on Cucurbita pepo L., semen. EMA/HMPC/136024/2010, 2012.
https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-cucurbita-pepo-l-semen_en.pdf
286. Committee on Herbal Medicinal Products. European Union herbal monograph on Prunus africana (Hook f.) Kalkm., cortex. EMA/HMPC/680626/2013, 2016.
https://www.ema.europa.eu/en/documents/herbal-monograph/draft-european-union-herbal-monograph-prunus-africana-hook-f-kalkm-cortex_en.pdf
287. Committee on Herbal Medicinal Products. Community herbal monograph on Urtica dioica L., Urtica urens L., their hybrids or their mixtures, radix. EMA/HMPC/461160/2008, 2012.
https://www.ema.europa.eu/en/documents/herbal-monograph/final-community-herbal-monograph-urtica-dioica-l-urtica-urens-l-their-hybrids-their-mixtures-radix_en.pdf
288. Committee on Herbal Medicinal Products. European Union herbal monograph on Epilobium angustifolium L. and/or Epilobium parviflorum Schreb., herba EMA/HMPC/712511/2014, 2015.
https://www.ema.europa.eu/en/documents/herbal-monograph/final-european-union-herbal-

monograph-epilobium-angustifolium-l/epilobium-parviflorum-schreb-herba_en.pdf
289. Tacklind, J., *et al.* Serenoa repens for benign prostatic hyperplasia. Cochrane Database Syst Rev, 2009: CD001423.
https://www.ncbi.nlm.nih.gov/pubmed/19370565
290. Novara, G., *et al.* Efficacy and Safety of Hexanic Lipidosterolic Extract of Serenoa repens (Permixon) in the Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: Systematic Review and Meta-analysis of Randomized Controlled Trials. Eur Urol Focus, 2016. 2: 553.
https://www.ncbi.nlm.nih.gov/pubmed/28723522
291. Vela-Navarrete, R., *et al.* Efficacy and safety of a hexanic extract of Serenoa repens (Permixon((R))) for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (LUTS/BPH): systematic review and meta-analysis of randomised controlled trials and observational studies. BJU Int, 2018. 122: 1049.
https://www.ncbi.nlm.nih.gov/pubmed/29694707
292. Russo, G.I., *et al.* Clinical Efficacy of Serenoa repens Versus Placebo Versus Alpha-blockers for the Treatment of Lower Urinary Tract Symptoms/Benign Prostatic Enlargement: A Systematic Review and Network Meta-analysis of Randomized Placebo-controlled Clinical Trials. Eur Urol Focus, 2021. 7: 420.
https://www.ncbi.nlm.nih.gov/pubmed/31952967
293. Boeri, L., *et al.* Clinically Meaningful Improvements in LUTS/BPH Severity in Men Treated with Silodosin Plus Hexanic Extract of Serenoa Repens or Silodosin Alone. Sci Rep, 2017. 7: 15179.
https://www.ncbi.nlm.nih.gov/pubmed/29123161
294. Debruyne, F.M., *et al.* Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. Eur Urol, 1998. 34: 169.
https://www.ncbi.nlm.nih.gov/pubmed/9732187
295. Barkin, J., *et al.* Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. Eur Urol, 2003. 44: 461.
https://www.ncbi.nlm.nih.gov/pubmed/14499682
296. Nickel, J.C., *et al.* Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. Can Urol Assoc J, 2008. 2: 16.
https://www.ncbi.nlm.nih.gov/pubmed/18542722
297. Athanasopoulos, A., *et al.* Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. J Urol, 2003. 169: 2253.
https://www.ncbi.nlm.nih.gov/pubmed/12771763
298. Roehrborn, C.G., *et al.* Efficacy and safety of a fixed-dose combination of dutasteride and tamsulosin treatment (Duodart((R))) compared with watchful waiting with initiation of tamsulosin therapy if symptoms do not improve, both provided with lifestyle advice, in the management of treatment-naive men with moderately symptomatic benign prostatic hyperplasia: 2-year CONDUCT study results. BJU Int, 2015. 116: 450.
https://www.ncbi.nlm.nih.gov/pubmed/25565364
299. Roehrborn, C.G., *et al.* Influence of baseline variables on changes in International Prostate Symptom Score after combined therapy with dutasteride plus tamsulosin or either monotherapy in patients with benign prostatic hyperplasia and lower urinary tract symptoms: 4-year results of the CombAT study. BJU Int, 2014. 113: 623.
https://www.ncbi.nlm.nih.gov/pubmed/24127818
300. Casabe, A., *et al.* Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. J Urol, 2014. 191: 727.
https://www.ncbi.nlm.nih.gov/pubmed/24096118
301. Kaplan, S.A., *et al.* Time Course of Incident Adverse Experiences Associated with Doxazosin, Finasteride and Combination Therapy in Men with Benign Prostatic Hyperplasia: The MTOPS Trial. J Urol, 2016. 195: 1825.
https://www.ncbi.nlm.nih.gov/pubmed/26678956
302. Chapple, C., *et al.* Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers. Eur Urol, 2009. 56: 534.
https://www.ncbi.nlm.nih.gov/pubmed/19070418
303. Kaplan, S.A., *et al.* Safety and tolerability of solifenacin add-on therapy to alpha-blocker treated men with residual urgency and frequency. J Urol, 2009. 182: 2825.
https://www.ncbi.nlm.nih.gov/pubmed/19837435

304. Lee, K.S., *et al.* Combination treatment with propiverine hydrochloride plus doxazosin controlled release gastrointestinal therapeutic system formulation for overactive bladder and coexisting benign prostatic obstruction: a prospective, randomized, controlled multicenter study. J Urol, 2005. 174: 1334.
https://www.ncbi.nlm.nih.gov/pubmed/16145414
305. MacDiarmid, S.A., *et al.* Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. Mayo Clin Proc, 2008. 83: 1002.
https://www.ncbi.nlm.nih.gov/pubmed/18775200
306. van Kerrebroeck, P., *et al.* Combination therapy with solifenacin and tamsulosin oral controlled absorption system in a single tablet for lower urinary tract symptoms in men: efficacy and safety results from the randomised controlled NEPTUNE trial. Eur Urol, 2013. 64: 1003.
https://www.ncbi.nlm.nih.gov/pubmed/23932438
307. Lenfant, L., *et al.* Role of Antimuscarinics Combined With Alpha-blockers in the Management of Urinary Storage Symptoms in Patients With Benign Prostatic Hyperplasia: An Updated Systematic Review and Meta-analysis. J Urol, 2023. 209: 314.
https://www.ncbi.nlm.nih.gov/pubmed/36395428
308. Pang, R., *et al.* Anticholinergics combined with alpha-blockers for treating lower urinary tract symptoms related to benign prostatic obstruction. Cochrane Database Syst Rev, 2021. 2: CD012336.
https://www.ncbi.nlm.nih.gov/pubmed/33567116
309. Kim, H.J., *et al.* Efficacy and Safety of Initial Combination Treatment of an Alpha Blocker with an Anticholinergic Medication in Benign Prostatic Hyperplasia Patients with Lower Urinary Tract Symptoms: Updated Meta-Analysis. PLoS One, 2017. 12: e0169248.
https://www.ncbi.nlm.nih.gov/pubmed/28072862
310. Van Kerrebroeck, P., *et al.* Efficacy and safety of solifenacin plus tamsulosin OCAS in men with voiding and storage lower urinary tract symptoms: results from a phase 2, dose-finding study (SATURN). Eur Urol, 2013. 64: 398.
https://www.ncbi.nlm.nih.gov/pubmed/23537687
311. Drake, M.J., *et al.* Long-term safety and efficacy of single-tablet combinations of solifenacin and tamsulosin oral controlled absorption system in men with storage and voiding lower urinary tract symptoms: results from the NEPTUNE Study and NEPTUNE II open-label extension. Eur Urol, 2015. 67: 262.
https://www.ncbi.nlm.nih.gov/pubmed/25070148
312. Drake, M.J., *et al.* Responder and health-related quality of life analyses in men with lower urinary tract symptoms treated with a fixed-dose combination of solifenacin and tamsulosin oral-controlled absorption system: results from the NEPTUNE study. BJU Int, 2016. 117: 165.
https://www.ncbi.nlm.nih.gov/pubmed/25907003
313. Burgio, K.L., *et al.* Effectiveness of Combined Behavioral and Drug Therapy for Overactive Bladder Symptoms in Men: A Randomized Clinical Trial. JAMA Intern Med, 2020. 180: 411.
https://www.ncbi.nlm.nih.gov/pubmed/31930360
314. Athanasopoulos, A., *et al.* The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. Eur Urol, 2011. 60: 94.
https://www.ncbi.nlm.nih.gov/pubmed/21497434
315. Drake, M.J., *et al.* Incidence of urinary retention during treatment with single tablet combinations of solifenacin+tamsulosin OCAS for up to 1 year in adult men with both storage and voiding LUTS: A subanalysis of the NEPTUNE/NEPTUNE II randomized controlled studies. PLoS One, 2017. 12: e0170726.
https://www.ncbi.nlm.nih.gov/pubmed/28166296
316. Gong, M., *et al.* Tamsulosin combined with solifenacin versus tamsulosin monotherapy for male lower urinary tract symptoms: a meta-analysis. Curr Med Res Opin, 2015. 31: 1781.
https://www.ncbi.nlm.nih.gov/pubmed/26211817
317. Kaplan, S.A., *et al.* Solifenacin plus tamsulosin combination treatment in men with lower urinary tract symptoms and bladder outlet obstruction: a randomized controlled trial. Eur Urol, 2013. 63: 158.
https://www.ncbi.nlm.nih.gov/pubmed/22831853
318. Kakizaki, H., *et al.* Mirabegron Add-on Therapy to Tamsulosin for the Treatment of Overactive Bladder in Men with Lower Urinary Tract Symptoms: A Randomized, Placebo-controlled Study (MATCH). Eur Urol Focus, 2020. 6: 729.
https://www.ncbi.nlm.nih.gov/pubmed/31718957

319. Kaplan, S.A., *et al.* Efficacy and Safety of Mirabegron versus Placebo Add-On Therapy in Men with Overactive Bladder Symptoms Receiving Tamsulosin for Underlying Benign Prostatic Hyperplasia: A Randomized, Phase 4 Study (PLUS). J Urol, 2020. 203: 1163.
https://www.ncbi.nlm.nih.gov/pubmed/31895002
320. Ichihara, K., *et al.* A randomized controlled study of the efficacy of tamsulosin monotherapy and its combination with mirabegron for overactive bladder induced by benign prostatic obstruction. J Urol, 2015. 193: 921.
https://www.ncbi.nlm.nih.gov/pubmed/25254938
321. Staskin, D., *et al.* Efficacy and Safety of Vibegron for Persistent Symptoms of Overactive Bladder in Men Being Pharmacologically Treated for Benign Prostatic Hyperplasia: Results From the Phase 3 Randomized Controlled COURAGE Trial. J Urol, 2024. 212: 256.
https://www.ncbi.nlm.nih.gov/pubmed/38708869
322. van Gelderen, M., *et al.* Absence of clinically relevant cardiovascular interaction upon add-on of mirabegron or tamsulosin to an established tamsulosin or mirabegron treatment in healthy middle-aged to elderly men. Int J Clin Pharmacol Ther, 2014. 52: 693.
https://www.ncbi.nlm.nih.gov/pubmed/24755125
323. Soliman, M.G., *et al.* Efficacy and safety of mirabegron versus solifenacin as additional therapy for persistent OAB symptoms after tamsulosin monotherapy in men with probable BPO. World J Urol, 2021. 39: 2049.
https://www.ncbi.nlm.nih.gov/pubmed/32869151
324. Chen, P.-C., *et al.* Combination Alpha Blocker and Phosphodiesterase 5 Inhibitor Versus Alpha-Blocker Monotherapy for Lower Urinary Tract Symptoms Associated with Benign Prostate Hyperplasia. Urol Sci, 2020. 31: 99.
hhttps://journals.lww.com/ursc/fulltext/2020/31030/combination_alpha_blocker_and_phosphodiesterase_5.3.aspx
325. Fan, Z., *et al.* Comparative Efficacy of Different Drugs for Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia: A Bayesian Network Meta-Analysis. Front Pharmacol, 2022. 13: 763184.
https://www.ncbi.nlm.nih.gov/pubmed/35330833
326. Sebastianelli, A., *et al.* Outcomes of combination therapy with daily tadalafil 5 mg plus tamsulosin 0.4 mg to treat lower urinary tract symptoms and erectile dysfunction in men with or without metabolic syndrome. Minerva Urol Nephrol, 2021. 73: 836.
https://www.ncbi.nlm.nih.gov/pubmed/33200905
327. Speakman, M.J., *et al.* What Is the Required Certainty of Evidence for the Implementation of Novel Techniques for the Treatment of Benign Prostatic Obstruction? Eur Urol Focus, 2019. 5: 351.
https://www.ncbi.nlm.nih.gov/pubmed/31204291
328. Issa, M.M. Technological advances in transurethral resection of the prostate: bipolar versus monopolar TURP. J Endourol, 2008. 22: 1587.
https://www.ncbi.nlm.nih.gov/pubmed/18721041
329. Rassweiler, J., *et al.* Bipolar transurethral resection of the prostate--technical modifications and early clinical experience. Minim Invasive Ther Allied Technol, 2007. 16: 11.
https://www.ncbi.nlm.nih.gov/pubmed/17365673
330. Cornu, J.N., *et al.* A Systematic Review and Meta-analysis of Functional Outcomes and Complications Following Transurethral Procedures for Lower Urinary Tract Symptoms Resulting from Benign Prostatic Obstruction: An Update. Eur Urol, 2015. 67: 1066.
https://www.ncbi.nlm.nih.gov/pubmed/24972732
331. Reich, O., *et al.* Techniques and long-term results of surgical procedures for BPH. Eur Urol, 2006. 49: 970.
https://www.ncbi.nlm.nih.gov/pubmed/16481092
332. Madersbacher, S., *et al.* Is transurethral resection of the prostate still justified? BJU Int, 1999. 83: 227.
https://www.ncbi.nlm.nih.gov/pubmed/10233485
333. Madersbacher, S., *et al.* Reoperation, myocardial infarction and mortality after transurethral and open prostatectomy: a nation-wide, long-term analysis of 23,123 cases. Eur Urol, 2005. 47: 499.
https://www.ncbi.nlm.nih.gov/pubmed/15774249
334. Eredics, K., *et al.* Reoperation Rates and Mortality After Transurethral and Open Prostatectomy in a Long-term Nationwide Analysis: Have We Improved Over a Decade? Urology, 2018. 118: 152.
https://www.ncbi.nlm.nih.gov/pubmed/29733869

335. Alexander, C.E., *et al.* Bipolar versus monopolar transurethral resection of the prostate for lower urinary tract symptoms secondary to benign prostatic obstruction. Cochrane Database Syst Rev, 2019. 12: CD009629.
https://www.ncbi.nlm.nih.gov/pubmed/31792928
336. Mamoulakis, C., *et al.* Bipolar versus monopolar transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. Eur Urol, 2009. 56: 798.
https://www.ncbi.nlm.nih.gov/pubmed/19595501
337. Burke, N., *et al.* Systematic review and meta-analysis of transurethral resection of the prostate versus minimally invasive procedures for the treatment of benign prostatic obstruction. Urology, 2010. 75: 1015.
https://www.ncbi.nlm.nih.gov/pubmed/19854492
338. Omar, M.I., *et al.* Systematic review and meta-analysis of the clinical effectiveness of bipolar compared with monopolar transurethral resection of the prostate (TURP). BJU Int, 2014. 113: 24.
https://www.ncbi.nlm.nih.gov/pubmed/24053602
339. Inzunza, G., *et al.* Bipolar or monopolar transurethral resection for benign prostatic hyperplasia? Medwave, 2018. 18: e7134.
https://www.ncbi.nlm.nih.gov/pubmed/29351269
340. Treharne, C., *et al.* Economic Value of the Transurethral Resection in Saline System for Treatment of Benign Prostatic Hyperplasia in England and Wales: Systematic Review, Meta-analysis, and Cost-Consequence Model. Eur Urol Focus, 2018. 4: 270.
https://www.ncbi.nlm.nih.gov/pubmed/28753756
341. Autorino, R., *et al.* Four-year outcome of a prospective randomised trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. Eur Urol, 2009. 55: 922.
https://www.ncbi.nlm.nih.gov/pubmed/19185975
342. Chen, Q., *et al.* Bipolar transurethral resection in saline vs traditional monopolar resection of the prostate: results of a randomized trial with a 2-year follow-up. BJU Int, 2010. 106: 1339.
https://www.ncbi.nlm.nih.gov/pubmed/20477825
343. Fagerstrom, T., *et al.* Complications and clinical outcome 18 months after bipolar and monopolar transurethral resection of the prostate. J Endourol, 2011. 25: 1043.
https://www.ncbi.nlm.nih.gov/pubmed/21568691
344. Geavlete, B., *et al.* Bipolar plasma vaporization vs monopolar and bipolar TURP-A prospective, randomized, long-term comparison. Urology, 2011. 78: 930.
https://www.ncbi.nlm.nih.gov/pubmed/21802121
345. Giulianelli, R., *et al.* Comparative randomized study on the efficaciousness of endoscopic bipolar prostate resection versus monopolar resection technique. 3 year follow-up. Arch Ital Urol Androl, 2013. 85: 86.
https://www.ncbi.nlm.nih.gov/pubmed/23820656
346. Mamoulakis, C., *et al.* Midterm results from an international multicentre randomised controlled trial comparing bipolar with monopolar transurethral resection of the prostate. Eur Urol, 2013. 63: 667.
https://www.ncbi.nlm.nih.gov/pubmed/23102675
347. Xie, C.Y., *et al.* Five-year follow-up results of a randomized controlled trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. Yonsei Med J, 2012. 53: 734.
https://www.ncbi.nlm.nih.gov/pubmed/22665339
348. Komura, K., *et al.* Incidence of urethral stricture after bipolar transurethral resection of the prostate using TURis: results from a randomised trial. BJU Int, 2015. 115: 644.
https://www.ncbi.nlm.nih.gov/pubmed/24909399
349. Kumar, N., *et al.* Prospective Randomized Comparison of Monopolar TURP, Bipolar TURP and Photoselective Vaporization of the Prostate in Patients with Benign Prostatic Obstruction: 36 Months Outcome. Low Urin Tract Symptoms, 2018. 10: 17.
https://www.ncbi.nlm.nih.gov/pubmed/27168018
350. Huang, S.W., *et al.* Comparative efficacy and safety of new surgical treatments for benign prostatic hyperplasia: systematic review and network meta-analysis. BMJ, 2019. 367: l5919.
https://www.ncbi.nlm.nih.gov/pubmed/31727627
351. Reich, O., *et al.* Morbidity, mortality and early outcome of transurethral resection of the prostate: a prospective multicenter evaluation of 10,654 patients. J Urol, 2008. 180: 246.
https://www.ncbi.nlm.nih.gov/pubmed/18499179
352. Rassweiler, J., *et al.* Complications of transurethral resection of the prostate (TURP)--incidence, management, and prevention. Eur Urol, 2006. 50: 969.
https://www.ncbi.nlm.nih.gov/pubmed/16469429

353. Stucki, P., *et al.* Bipolar versus monopolar transurethral resection of the prostate: a prospective randomized trial focusing on bleeding complications. J Urol, 2015. 193: 1371.
https://www.ncbi.nlm.nih.gov/pubmed/25464004
354. Akman, T., *et al.* Effects of bipolar and monopolar transurethral resection of the prostate on urinary and erectile function: a prospective randomized comparative study. BJU Int, 2013. 111: 129.
https://www.ncbi.nlm.nih.gov/pubmed/22672229
355. El-Assmy, A., *et al.* Erectile and ejaculatory functions changes following bipolar versus monopolar transurethral resection of the prostate: a prospective randomized study. Int Urol Nephrol, 2018. 50: 1569.
https://www.ncbi.nlm.nih.gov/pubmed/30083842
356. Mamoulakis, C., *et al.* Bipolar vs monopolar transurethral resection of the prostate: evaluation of the impact on overall sexual function in an international randomized controlled trial setting. BJU Int, 2013. 112: 109.
https://www.ncbi.nlm.nih.gov/pubmed/23490008
357. Ruhle, A., *et al.* Safety and Effectiveness of Bipolar Transurethral Resection of the Prostate in Patients Under Ongoing Oral Anticoagulation with Coumarins or Antiplatelet Drug Therapy Compared to Patients Without Anticoagulation/Antiplatelet Therapy. J Endourol, 2019. 33: 455.
https://www.ncbi.nlm.nih.gov/pubmed/30834782
358. Aizezi, X., *et al.* Comparison of the efficacy of HoLEP and TURP in the treatment of elderly benign prostatic hyperplasia patients: a retrospective study. Aktuelle Urol, 2025. 56: 470.
https://www.ncbi.nlm.nih.gov/pubmed/38262432
359. Riedinger, C.B., *et al.* The impact of surgical duration on complications after transurethral resection of the prostate: an analysis of NSQIP data. Prostate Cancer Prostatic Dis, 2019. 22: 303.
https://www.ncbi.nlm.nih.gov/pubmed/30385836
360. Bach, T., *et al.* Laser treatment of benign prostatic obstruction: basics and physical differences. Eur Urol, 2012. 61: 317.
https://www.ncbi.nlm.nih.gov/pubmed/22033173
361. Xia, S.J., *et al.* Thulium laser versus standard transurethral resection of the prostate: a randomized prospective trial. Eur Urol, 2008. 53: 382.
https://www.ncbi.nlm.nih.gov/pubmed/17566639
362. Jiang, H., *et al.* Safety and Efficacy of Thulium Laser Prostatectomy Versus Transurethral Resection of Prostate for Treatment of Benign Prostate Hyperplasia: A Meta-Analysis. Low Urin Tract Symptoms, 2016. 8: 165.
https://www.ncbi.nlm.nih.gov/pubmed/27619781
363. Zhang, X., *et al.* Different lasers in the treatment of benign prostatic hyperplasia: a network meta-analysis. Sci Rep, 2016. 6: 23503.
https://www.ncbi.nlm.nih.gov/pubmed/27009501
364. Zhu, Y., *et al.* Thulium laser versus standard transurethral resection of the prostate for benign prostatic obstruction: a systematic review and meta-analysis. World J Urol, 2015. 33: 509.
https://www.ncbi.nlm.nih.gov/pubmed/25298242
365. Zhao, C., *et al.* Thulium Laser Resection Versus Plasmakinetic Resection of Prostates in the Treatment of Benign Prostate Hyperplasia: A Meta-Analysis. J Laparoendosc Adv Surg Tech A, 2016. 26: 789.
https://www.ncbi.nlm.nih.gov/pubmed/27500451
366. Deng, Z., *et al.* Thulium laser VapoResection of the prostate versus traditional transurethral resection of the prostate or transurethral plasmakinetic resection of prostate for benign prostatic obstruction: a systematic review and meta-analysis. World J Urol, 2018. 36: 1355.
https://www.ncbi.nlm.nih.gov/pubmed/29651642
367. Lan, Y., *et al.* Thulium (Tm:YAG) laser vaporesection of prostate and bipolar transurethral resection of prostate in patients with benign prostate hyperplasia: a systematic review and meta-analysis. Lasers Med Sci, 2018. 33: 1411.
https://www.ncbi.nlm.nih.gov/pubmed/29947009
368. Hashim, H., *et al.* Thulium laser transurethral vaporesection of the prostate versus transurethral resection of the prostate for men with lower urinary tract symptoms or urinary retention (UNBLOCS): a randomised controlled trial. Lancet, 2020. 396: 50.
https://www.ncbi.nlm.nih.gov/pubmed/32622397
369. Cui, D., *et al.* A randomized trial comparing thulium laser resection to standard transurethral resection of the prostate for symptomatic benign prostatic hyperplasia: four-year follow-up results. World J Urol, 2014. 32: 683.
https://www.ncbi.nlm.nih.gov/pubmed/23913094

370. Sun, F., *et al.* Long-term results of thulium laser resection of the prostate: a prospective study at multiple centers. World J Urol, 2015. 33: 503.
https://www.ncbi.nlm.nih.gov/pubmed/25487702
371. Worthington, J., *et al.* Thulium laser transurethral vaporesection versus transurethral resection of the prostate for benign prostatic obstruction: the UNBLOCS RCT. Health Technol Assess, 2020. 24: 1.
https://www.ncbi.nlm.nih.gov/pubmed/32901611
372. Yang, Z., *et al.* Thulium laser enucleation versus plasmakinetic resection of the prostate: a randomized prospective trial with 18-month follow-up. Urology, 2013. 81: 396.
https://www.ncbi.nlm.nih.gov/pubmed/23374815
373. Wei, H., *et al.* Thulium laser resection versus plasmakinetic resection of prostates larger than 80 ml. World J Urol, 2014. 32: 1077.
https://www.ncbi.nlm.nih.gov/pubmed/24264126
374. Sener, T.E., *et al.* Thulium laser vaporesection of the prostate: Can we operate without interrupting oral antiplatelet/anticoagulant therapy? Investig Clin Urol, 2017. 58: 192.
https://www.ncbi.nlm.nih.gov/pubmed/28480345
375. Bansal, A., *et al.* Holmium Laser vs Monopolar Electrocautery Bladder Neck Incision for Prostates Less Than 30 Grams: A Prospective Randomized Trial. Urology, 2016. 93: 158.
https://www.ncbi.nlm.nih.gov/pubmed/27058689
376. Lourenco, T., *et al.* The clinical effectiveness of transurethral incision of the prostate: a systematic review of randomised controlled trials. World J Urol, 2010. 28: 23.
https://www.ncbi.nlm.nih.gov/pubmed/20033744
377. Kuntz, R.M., *et al.* Holmium laser enucleation of the prostate versus open prostatectomy for prostates greater than 100 grams: 5-year follow-up results of a randomised clinical trial. Eur Urol, 2008. 53: 160.
https://www.ncbi.nlm.nih.gov/pubmed/17869409
378. Naspro, R., *et al.* Holmium laser enucleation of the prostate versus open prostatectomy for prostates >70 g: 24-month follow-up. Eur Urol, 2006. 50: 563.
https://www.ncbi.nlm.nih.gov/pubmed/16713070
379. Skolarikos, A., *et al.* Eighteen-month results of a randomized prospective study comparing transurethral photoselective vaporization with transvesical open enucleation for prostatic adenomas greater than 80 cc. J Endourol, 2008. 22: 2333.
https://www.ncbi.nlm.nih.gov/pubmed/18837655
380. Varkarakis, I., *et al.* Long-term results of open transvesical prostatectomy from a contemporary series of patients. Urology, 2004. 64: 306.
https://www.ncbi.nlm.nih.gov/pubmed/15302484
381. Gratzke, C., *et al.* Complications and early postoperative outcome after open prostatectomy in patients with benign prostatic enlargement: results of a prospective multicenter study. J Urol, 2007. 177: 1419.
https://www.ncbi.nlm.nih.gov/pubmed/17382744
382. Chen, S., *et al.* Plasmakinetic enucleation of the prostate compared with open prostatectomy for prostates larger than 100 grams: a randomized noninferiority controlled trial with long-term results at 6 years. Eur Urol, 2014. 66: 284.
https://www.ncbi.nlm.nih.gov/pubmed/24502959
383. Li, M., *et al.* Endoscopic enucleation versus open prostatectomy for treating large benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. PLoS One, 2015. 10: e0121265.
https://www.ncbi.nlm.nih.gov/pubmed/25826453
384. Lin, Y., *et al.* Transurethral enucleation of the prostate versus transvesical open prostatectomy for large benign prostatic hyperplasia: a systematic review and meta-analysis of randomized controlled trials. World J Urol, 2016. 34: 1207.
https://www.ncbi.nlm.nih.gov/pubmed/26699627
385. Ou, R., *et al.* Transurethral enucleation and resection of the prostate vs transvesical prostatectomy for prostate volumes >80 mL: a prospective randomized study. BJU Int, 2013. 112: 239.
https://www.ncbi.nlm.nih.gov/pubmed/23795788
386. Rao, J.M., *et al.* Plasmakinetic enucleation of the prostate versus transvesical open prostatectomy for benign prostatic hyperplasia >80 mL: 12-month follow-up results of a randomized clinical trial. Urology, 2013. 82: 176.
https://www.ncbi.nlm.nih.gov/pubmed/23601443
387. Geavlete, B., *et al.* Bipolar vaporization, resection, and enucleation versus open prostatectomy: optimal treatment alternatives in large prostate cases? J Endourol, 2015. 29: 323.
https://www.ncbi.nlm.nih.gov/pubmed/25111385

388. Geavlete, B., *et al.* Bipolar plasma enucleation of the prostate vs open prostatectomy in large benign prostatic hyperplasia cases - a medium term, prospective, randomized comparison. BJU Int, 2013. 111: 793.
https://www.ncbi.nlm.nih.gov/pubmed/23469933
389. Salonia, A., *et al.* Holmium laser enucleation versus open prostatectomy for benign prostatic hyperplasia: an inpatient cost analysis. Urology, 2006. 68: 302.
https://www.ncbi.nlm.nih.gov/pubmed/16904441
390. Zhang, Y., *et al.* [Transurethral holmium laser enucleation for prostate adenoma greater than 100 g]. Zhonghua Nan Ke Xue, 2007. 13: 1091.
https://www.ncbi.nlm.nih.gov/pubmed/18284057
391. Gilfrich, C., *et al.* Morbidity and mortality after surgery for lower urinary tract symptoms: a study of 95 577 cases from a nationwide German health insurance database. Prostate Cancer Prostatic Dis, 2016. 19: 406.
https://www.ncbi.nlm.nih.gov/pubmed/27502738
392. Tubaro, A., *et al.* A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. J Urol, 2001. 166: 172.
https://www.ncbi.nlm.nih.gov/pubmed/11435849
393. Zhang, K., *et al.* Plasmakinetic Vapor Enucleation of the Prostate with Button Electrode versus Plasmakinetic Resection of the Prostate for Benign Prostatic Enlargement >90 ml: Perioperative and 3-Month Follow-Up Results of a Prospective, Randomized Clinical Trial. Urol Int, 2015. 95: 260.
https://www.ncbi.nlm.nih.gov/pubmed/26044933
394. Wang, Z., *et al.* A prospective, randomised trial comparing transurethral enucleation with bipolar system (TUEB) to monopolar resectoscope enucleation of the prostate for symptomatic benign prostatic hyperplasia. Biomed Res, 2017. 28.
https://www.alliedacademies.org/articles/a-prospective-randomised-trial-comparing-transurethral-enucleation-with-bipolar-system-tueb-to-monopolar-resectoscope-enucleation-.pdf
395. Neill, M.G., *et al.* Randomized trial comparing holmium laser enucleation of prostate with plasmakinetic enucleation of prostate for treatment of benign prostatic hyperplasia. Urology, 2006. 68: 1020.
https://www.ncbi.nlm.nih.gov/pubmed/17095078
396. Ran, L., *et al.* Comparison of fluid absorption between transurethral enucleation and transurethral resection for benign prostate hyperplasia. Urol Int, 2013. 91: 26.
https://www.ncbi.nlm.nih.gov/pubmed/23571450
397. Zhao, Z., *et al.* A prospective, randomised trial comparing plasmakinetic enucleation to standard transurethral resection of the prostate for symptomatic benign prostatic hyperplasia: three-year follow-up results. Eur Urol, 2010. 58: 752.
https://www.ncbi.nlm.nih.gov/pubmed/20800340
398. Li, K., *et al.* A Novel Modification of Transurethral Enucleation and Resection of the Prostate in Patients With Prostate Glands Larger than 80 mL: Surgical Procedures and Clinical Outcomes. Urology, 2018. 113: 153.
https://www.ncbi.nlm.nih.gov/pubmed/29203184
399. Luo, Y.H., *et al.* Plasmakinetic enucleation of the prostate vs plasmakinetic resection of the prostate for benign prostatic hyperplasia: comparison of outcomes according to prostate size in 310 patients. Urology, 2014. 84: 904.
https://www.ncbi.nlm.nih.gov/pubmed/25150180
400. Zhu, L., *et al.* Electrosurgical enucleation versus bipolar transurethral resection for prostates larger than 70 ml: a prospective, randomized trial with 5-year followup. J Urol, 2013. 189: 1427.
https://www.ncbi.nlm.nih.gov/pubmed/23123549
401. Zhang, Y., *et al.* Efficacy and safety of enucleation vs. resection of prostate for treatment of benign prostatic hyperplasia: a meta-analysis of randomized controlled trials. Prostate Cancer Prostatic Dis, 2019. 22: 493.
https://www.ncbi.nlm.nih.gov/pubmed/30816336
402. Arcaniolo, D., *et al.* Bipolar endoscopic enucleation versus bipolar transurethral resection of the prostate: an ESUT systematic review and cumulative analysis. World J Urol, 2020. 38: 1177.
https://www.ncbi.nlm.nih.gov/pubmed/31346761
403. Jiang, Y., *et al.* Comparative Study of the Effectiveness and Safety of Transurethral Bipolar Plasmakinetic Enucleation of the Prostate and Transurethral Bipolar Plasmakinetic Resection of the Prostate for Massive Benign Prostate Hyperplasia (>80 ml). Med Sci Monit, 2020. 26: e921272.
https://www.ncbi.nlm.nih.gov/pubmed/32339160

404. Samir, M., *et al.* Two-year Follow-up in Bipolar Transurethral Enucleation and Resection of the Prostate in Comparison with Bipolar Transurethral Resection of the Prostate in Treatment of Large Prostates. Randomized Controlled Trial. Urology, 2019. 133: 192.
https://www.ncbi.nlm.nih.gov/pubmed/31404581
405. Liu, Q.L., *et al.* Comparison of the Transurethral Resection of the Prostate by Traditional Versus Preserved Urethral Mucosa of the Prostatic Apex. J Endourol, 2020. 34: 482.
https://www.ncbi.nlm.nih.gov/pubmed/31964193
406. Gilling, P.J., *et al.* Long-term results of a randomized trial comparing holmium laser enucleation of the prostate and transurethral resection of the prostate: results at 7 years. BJU Int, 2012. 109: 408.
https://www.ncbi.nlm.nih.gov/pubmed/21883820
407. Tan, A., *et al.* Meta-analysis of holmium laser enucleation versus transurethral resection of the prostate for symptomatic prostatic obstruction. Br J Surg, 2007. 94: 1201.
https://www.ncbi.nlm.nih.gov/pubmed/17729384
408. Yin, L., *et al.* Holmium laser enucleation of the prostate versus transurethral resection of the prostate: a systematic review and meta-analysis of randomized controlled trials. J Endourol, 2013. 27: 604.
https://www.ncbi.nlm.nih.gov/pubmed/23167266
409. Qian, X., *et al.* Functional outcomes and complications following B-TURP versus HoLEP for the treatment of benign prostatic hyperplasia: a review of the literature and Meta-analysis. Aging Male, 2017. 20: 184.
https://www.ncbi.nlm.nih.gov/pubmed/28368238
410. Chen, Y.B., *et al.* A prospective, randomized clinical trial comparing plasmakinetic resection of the prostate with holmium laser enucleation of the prostate based on a 2-year followup. J Urol, 2013. 189: 217.
https://www.ncbi.nlm.nih.gov/pubmed/23174256
411. Elshal, A.M., *et al.* Randomised trial of bipolar resection vs holmium laser enucleation vs Greenlight laser vapo-enucleation of the prostate for treatment of large benign prostate obstruction: 3-years outcomes. BJU Int, 2020. 126: 731.
https://www.ncbi.nlm.nih.gov/pubmed/32633020
412. Bhandarkar, A., *et al.* Comparison of Holmium Laser Enucleation of the Prostate with Bipolar Plasmakinetic Enucleation of the Prostate: A Randomized, Prospective Controlled Trial at Midterm Follow-Up. J Endourol, 2022. 36: 1567.
https://www.ncbi.nlm.nih.gov/pubmed/35943885
413. Wei, Z., *et al.* Plasma Kinetic Enucleation vs Holmium Laser Enucleation for Treating Benign Prostatic Hyperplasia: A Randomized Controlled Trial with a 3-Year Follow-Up. J Endourol, 2021. 35: 1533.
https://www.ncbi.nlm.nih.gov/pubmed/33779288
414. Higazy, A., *et al.* Holmium laser enucleation of the prostate versus bipolar transurethral enucleation of the prostate in management of benign prostatic hyperplasia: A randomized controlled trial. Int J Urol, 2021. 28: 333.
https://www.ncbi.nlm.nih.gov/pubmed/33327043
415. You, C., *et al.* Comparison of different laser-based enucleation techniques for benign prostate hyperplasia: A systematic review and meta-analysis. Int J Surg, 2021. 94: 106135.
https://www.ncbi.nlm.nih.gov/pubmed/34600125
416. Pyrgidis, N., *et al.* Enucleation of the prostate as retreatment for recurrent or residual benign prostatic obstruction: a systematic review and a meta-analysis. Prostate Cancer Prostatic Dis, 2023. 26: 693.
https://www.ncbi.nlm.nih.gov/pubmed/37193777
417. Lourenco, T., *et al.* Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials. BMJ, 2008. 337: a449.
https://www.ncbi.nlm.nih.gov/pubmed/18595932
418. Huang, K.C., *et al.* Combination of Thulium Laser Incision and Bipolar Resection Offers Higher Resection Velocity than Bipolar Resection Alone in Large Prostates. Urol J, 2019. 16: 397.
https://www.ncbi.nlm.nih.gov/pubmed/30318570
419. Heidar, N.A., *et al.* Laser enucleation of the prostate versus transurethral resection of the prostate: perioperative outcomes from the ACS NSQIP database. World J Urol, 2020. 38: 2891.
https://www.ncbi.nlm.nih.gov/pubmed/32036397
420. Shah, H.N., *et al.* A randomized controlled trial comparing high and medium power settings for holmium laser enucleation of prostate. World J Urol, 2021. 39: 3005.
https://www.ncbi.nlm.nih.gov/pubmed/33398423

421. Du, R., *et al.* Comparative study of low-power versus high-power holmium laser enucleation of the prostate for large volume benign prostatic hyperplasia. Lasers Med Sci, 2025. 40: 68.
https://www.ncbi.nlm.nih.gov/pubmed/39907814
422. Gauhar, V., *et al.* Does MOSES Technology Enhance the Efficiency and Outcomes of Standard Holmium Laser Enucleation of the Prostate? Results of a Systematic Review and Meta-analysis of Comparative Studies. Eur Urol Focus, 2022. 8: 1362.
https://www.ncbi.nlm.nih.gov/pubmed/35105516
423. Netsch, C., *et al.* Recent evidence for anatomic endoscopic enucleation of the prostate (AEEP) in patients with benign prostatic obstruction on antiplatelet or anticoagulant therapy. World J Urol, 2021. 39: 3187.
https://www.ncbi.nlm.nih.gov/pubmed/33721062
424. Liu, Y., *et al.* Impact on Sexual Function of Endoscopic Enucleation vs Transurethral Resection of the Prostate for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: A Systematic Review and Meta-Analysis. J Endourol, 2020. 34: 1064.
https://www.ncbi.nlm.nih.gov/pubmed/32242462
425. Cacciamani, G.E., *et al.* Anterograde ejaculation preservation after endoscopic treatments in patients with bladder outlet obstruction: systematic review and pooled-analysis of randomized clinical trials. Minerva Urol Nefrol, 2019. 71: 427.
https://www.ncbi.nlm.nih.gov/pubmed/31487977
426. Briganti, A., *et al.* Impact on sexual function of holmium laser enucleation versus transurethral resection of the prostate: results of a prospective, 2-center, randomized trial. J Urol, 2006. 175: 1817.
https://www.ncbi.nlm.nih.gov/pubmed/16600770
427. Li, Z., *et al.* The impact of surgical treatments for lower urinary tract symptoms/benign prostatic hyperplasia on male erectile function: A systematic review and network meta-analysis. Medicine (Baltimore), 2016. 95: e3862.
https://www.ncbi.nlm.nih.gov/pubmed/27310968
428. Kim, M., *et al.* Pilot study of the clinical efficacy of ejaculatory hood sparing technique for ejaculation preservation in Holmium laser enucleation of the prostate. Int J Impot Res, 2015. 27: 20.
https://www.ncbi.nlm.nih.gov/pubmed/25007827
429. Gao, Z., *et al.* Technological innovation of HoLEP: a multicenter, randomized, controlled study for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. World J Urol, 2025. 43: 64.
https://www.ncbi.nlm.nih.gov/pubmed/39789390
430. Long Depaquit, T., *et al.* Modified holmium laser enucleation for benign prostatic obstruction to preserve sexual and ejaculatory function. Fr J Urol, 2024. 34: 102581.
https://www.ncbi.nlm.nih.gov/pubmed/38717462
431. Elzayat, E.A., *et al.* Holmium laser enucleation of the prostate (HoLEP): long-term results, reoperation rate, and possible impact of the learning curve. Eur Urol, 2007. 52: 1465.
https://www.ncbi.nlm.nih.gov/pubmed/17498867
432. Du, C., *et al.* Holmium laser enucleation of the prostate: the safety, efficacy, and learning experience in China. J Endourol, 2008. 22: 1031.
https://www.ncbi.nlm.nih.gov/pubmed/18377236
433. Robert, G., *et al.* Multicentre prospective evaluation of the learning curve of holmium laser enucleation of the prostate (HoLEP). BJU Int, 2016. 117: 495.
https://www.ncbi.nlm.nih.gov/pubmed/25781490
434. Aho, T., *et al.* Description of a modular mentorship programme for holmium laser enucleation of the prostate. World J Urol, 2015. 33: 497.
https://www.ncbi.nlm.nih.gov/pubmed/25271105
435. Enikeev, D., *et al.* A Randomized Trial Comparing The Learning Curve of 3 Endoscopic Enucleation Techniques (HoLEP, ThuFLEP, and MEP) for BPH Using Mentoring Approach-Initial Results. Urology, 2018. 121: 51.
https://www.ncbi.nlm.nih.gov/pubmed/30053397
436. Yang, Z., *et al.* Comparison of thulium laser enucleation and plasmakinetic resection of the prostate in a randomized prospective trial with 5-year follow-up. Lasers Med Sci, 2016. 31: 1797.
https://www.ncbi.nlm.nih.gov/pubmed/27677474
437. Hartung, F.O., *et al.* Holmium Versus Thulium Laser Enucleation of the Prostate: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Eur Urol Focus, 2022. 8: 545.
https://www.ncbi.nlm.nih.gov/pubmed/33840611

438. Zhang, F., *et al.* Thulium laser versus holmium laser transurethral enucleation of the prostate: 18-month follow-up data of a single center. Urology, 2012. 79: 869.
https://www.ncbi.nlm.nih.gov/pubmed/22342411
439. Feng, L., *et al.* Thulium Laser Enucleation Versus Plasmakinetic Enucleation of the Prostate: A Randomized Trial of a Single Center. J Endourol, 2016. 30: 665.
https://www.ncbi.nlm.nih.gov/pubmed/26886719
440. Bach, T., *et al.* Thulium:YAG vapoenucleation in large volume prostates. J Urol, 2011. 186: 2323.
https://www.ncbi.nlm.nih.gov/pubmed/22014812
441. Hauser, S., *et al.* Thulium laser (Revolix) vapoenucleation of the prostate is a safe procedure in patients with an increased risk of hemorrhage. Urol Int, 2012. 88: 390.
https://www.ncbi.nlm.nih.gov/pubmed/22627127
442. Netsch, C., *et al.* Safety and effectiveness of Thulium VapoEnucleation of the prostate (ThuVEP) in patients on anticoagulant therapy. World J Urol, 2014. 32: 165.
https://www.ncbi.nlm.nih.gov/pubmed/23657354
443. Netsch, C., *et al.* Comparison of 120-200 W 2 mum thulium:yttrium-aluminum-garnet vapoenucleation of the prostate. J Endourol, 2012. 26: 224.
https://www.ncbi.nlm.nih.gov/pubmed/22191688
444. Bozzini, G., *et al.* Thulium: YAG vs continuous-wave thulium fiber laser enucleation of the prostate: do potential advantages of thulium fiber lasers translate into relevant clinical differences? World J Urol, 2023. 41: 143.
https://www.ncbi.nlm.nih.gov/pubmed/36357602
445. Shoji, S., *et al.* Functional outcomes of transurethral thulium laser enucleation versus bipolar transurethral resection for benign prostatic hyperplasia over a period of 12 months: A prospective randomized study. Int J Urol, 2020. 27: 974.
https://www.ncbi.nlm.nih.gov/pubmed/33241599
446. Chang, C.H., *et al.* Vapoenucleation of the prostate using a high-power thulium laser: a one-year follow-up study. BMC Urol, 2015. 15: 40.
https://www.ncbi.nlm.nih.gov/pubmed/25956819
447. Gross, A.J., *et al.* Complications and early postoperative outcome in 1080 patients after thulium vapoenucleation of the prostate: results at a single institution. Eur Urol, 2013. 63: 859.
https://www.ncbi.nlm.nih.gov/pubmed/23245687
448. Becker, B., *et al.* Thulium vapoenucleation of the prostate versus holmium laser enucleation of the prostate for the treatment of large volume prostates: preliminary 6-month safety and efficacy results of a prospective randomized trial. World J Urol, 2018. 36: 1663.
https://www.ncbi.nlm.nih.gov/pubmed/29730838
449. Netsch, C., *et al.* A prospective, randomized trial comparing thulium vapoenucleation with holmium laser enucleation of the prostate for the treatment of symptomatic benign prostatic obstruction: perioperative safety and efficacy. World J Urol, 2017. 35: 1913.
https://www.ncbi.nlm.nih.gov/pubmed/28698991
450. Lusuardi, L., *et al.* Update on the use of diode laser in the management of benign prostate obstruction in 2014. World J Urol, 2015. 33: 555.
https://www.ncbi.nlm.nih.gov/pubmed/24859776
451. Mariano, M.B., *et al.* Laparoscopic prostatectomy with vascular control for benign prostatic hyperplasia. J Urol, 2002. 167: 2528.
https://www.ncbi.nlm.nih.gov/pubmed/11992078
452. Sotelo, R., *et al.* Robotic simple prostatectomy. J Urol, 2008. 179: 513.
https://www.ncbi.nlm.nih.gov/pubmed/18076926
453. Ramos, R., *et al.* Single-port Transvesical Robot-Assisted Simple Prostatectomy: Surgical Technique and Clinical Outcomes. Eur Urol, 2024. 85: 445.
https://www.ncbi.nlm.nih.gov/pubmed/38057210
454. Lucca, I., *et al.* Outcomes of minimally invasive simple prostatectomy for benign prostatic hyperplasia: a systematic review and meta-analysis. World J Urol, 2015. 33: 563.
https://www.ncbi.nlm.nih.gov/pubmed/24879405
455. Li, J., *et al.* Comparison Between Minimally Invasive Simple Prostatectomy and Open Simple Prostatectomy for Large Prostates: A Systematic Review and Meta-Analysis of Comparative Trials. J Endourol, 2019. 33: 767.
https://www.ncbi.nlm.nih.gov/pubmed/31244334

456. Fuschi, A., *et al.* Holmium laser enucleation of prostate versus minimally invasive simple prostatectomy for large volume (>/=120 mL) prostate glands: a prospective multicenter randomized study. Minerva Urol Nephrol, 2021. 73: 638.
https://www.ncbi.nlm.nih.gov/pubmed/33200899
457. Li, Y., *et al.* Association of sleep quality with lower urinary tract symptoms/benign prostatic hyperplasia among men in China: A cross-sectional study. Front Aging Neurosci, 2022. 14: 938407.
https://www.ncbi.nlm.nih.gov/pubmed/36353690
458. Lee, C.L., *et al.* Treating overactive bladder symptoms after transurethral prostatic surgery for benign prostatic hyperplasia - Which medication to choose? Tzu Chi Med J, 2023. 35: 312.
https://www.ncbi.nlm.nih.gov/pubmed/38035054
459. Scarcella, S., *et al.* Robotic-assisted versus open simple prostatectomy: Results from a systematic review and meta-analysis of comparative studies. Investig Clin Urol, 2021. 62: 631.
https://www.ncbi.nlm.nih.gov/pubmed/34729963
460. Shuai, H., *et al.* Comparison of the efficacy and safety of robotic-assisted simple prostatectomy and laser enucleation of prostate for large benign prostatic hyperplasia. J Robot Surg, 2023. 17: 2687.
https://www.ncbi.nlm.nih.gov/pubmed/37796379
461. Sorokin, I., *et al.* Robot-Assisted Versus Open Simple Prostatectomy for Benign Prostatic Hyperplasia in Large Glands: A Propensity Score-Matched Comparison of Perioperative and Short-Term Outcomes. J Endourol, 2017. 31: 1164.
https://www.ncbi.nlm.nih.gov/pubmed/28854815
462. Van der Jeugt, J., *et al.* Holmium Laser Enucleation of the Prostate vs Robot-Assisted Simple Prostatectomy for Lower Urinary Tract Symptoms in Patients with Extremely Large Prostates >/=200 cc: A Comparative Analysis. J Endourol, 2023. 37: 895.
https://www.ncbi.nlm.nih.gov/pubmed/37335047
463. Talamini, S., *et al.* Surgical treatment of benign prostatic hyperplasia: Thulium enucleation versus single-port transvesical robotic simple prostatectomy. BJUI Compass, 2023. 4: 549.
https://www.ncbi.nlm.nih.gov/pubmed/37636211
464. Stoddard, M.D., *et al.* Standardization of 532 nm Laser Terminology for Surgery in Benign Prostatic Hyperplasia: A Systematic Review. J Endourol, 2020. 34: 121.
https://www.ncbi.nlm.nih.gov/pubmed/31880953
465. Gomez Sancha, F., *et al.* Common trend: move to enucleation-Is there a case for GreenLight enucleation? Development and description of the technique. World J Urol, 2015. 33: 539.
https://www.ncbi.nlm.nih.gov/pubmed/24929643
466. Law, K.W., *et al.* Anatomic GreenLight laser vaporization-incision technique for benign prostatic hyperplasia using the XPS LBO-180W system: How I do it. Can J Urol, 2019. 26: 9963.
https://www.ncbi.nlm.nih.gov/pubmed/31629449
467. Elshal, A.M., *et al.* Prospective Assessment of Learning Curve of Holmium Laser Enucleation of the Prostate for Treatment of Benign Prostatic Hyperplasia Using a Multidimensional Approach. J Urol, 2017. 197: 1099.
https://www.ncbi.nlm.nih.gov/pubmed/27825972
468. Elshal, A.M., *et al.* GreenLight laser (XPS) photoselective vapo-enucleation versus holmium laser enucleation of the prostate for the treatment of symptomatic benign prostatic hyperplasia: a randomized controlled study. J Urol, 2015. 193: 927.
https://www.ncbi.nlm.nih.gov/pubmed/25261801
469. Botto, H., *et al.* Electrovaporization of the prostate with the Gyrus device. J Endourol, 2001. 15: 313.
https://www.ncbi.nlm.nih.gov/pubmed/11339400
470. Reich, O., *et al.* Plasma vaporisation of the prostate: initial clinical results. Eur Urol, 2010. 57: 693.
https://www.ncbi.nlm.nih.gov/pubmed/19482414
471. Reich, O., *et al.* *In vitro* comparison of transurethral vaporization of the prostate (TUVP), resection of the prostate (TURP), and vaporization-resection of the prostate (TUVRP). Urol Res, 2002. 30: 15.
https://www.ncbi.nlm.nih.gov/pubmed/11942320
472. Gallucci, M., *et al.* Transurethral electrovaporization of the prostate vs. transurethral resection. Results of a multicentric, randomized clinical study on 150 patients. Eur Urol, 1998. 33: 359.
https://www.ncbi.nlm.nih.gov/pubmed/9612677
473. Poulakis, V., *et al.* Transurethral electrovaporization vs transurethral resection for symptomatic prostatic obstruction: a meta-analysis. BJU Int, 2004. 94: 89.
https://www.ncbi.nlm.nih.gov/pubmed/15217438

474. Dunsmuir, W.D., *et al.* Gyrus bipolar electrovaporization vs transurethral resection of the prostate: a randomized prospective single-blind trial with 1 y follow-up. Prostate Cancer Prostatic Dis, 2003. 6: 182.
https://www.ncbi.nlm.nih.gov/pubmed/12806380
475. Fung, B.T., *et al.* Prospective randomized controlled trial comparing plasmakinetic vaporesection and conventional transurethral resection of the prostate. Asian J Surg, 2005. 28: 24.
https://www.ncbi.nlm.nih.gov/pubmed/15691793
476. Karaman, M.I., *et al.* Comparison of transurethral vaporization using PlasmaKinetic energy and transurethral resection of prostate: 1-year follow-up. J Endourol, 2005. 19: 734.
https://www.ncbi.nlm.nih.gov/pubmed/16053367
477. Hon, N.H., *et al.* A prospective, randomized trial comparing conventional transurethral prostate resection with PlasmaKinetic vaporization of the prostate: physiological changes, early complications and long-term followup. J Urol, 2006. 176: 205.
https://www.ncbi.nlm.nih.gov/pubmed/16753403
478. Kaya, C., *et al.* The long-term results of transurethral vaporization of the prostate using plasmakinetic energy. BJU Int, 2007. 99: 845.
https://www.ncbi.nlm.nih.gov/pubmed/17378844
479. Geavlete, B., *et al.* Transurethral resection (TUR) in saline plasma vaporization of the prostate vs standard TUR of the prostate: 'the better choice' in benign prostatic hyperplasia? BJU Int, 2010. 106: 1695.
https://www.ncbi.nlm.nih.gov/pubmed/20518763
480. Nuhoglu, B., *et al.* The role of bipolar transurethral vaporization in the management of benign prostatic hyperplasia. Urol Int, 2011. 87: 400.
https://www.ncbi.nlm.nih.gov/pubmed/22086154
481. Zhang, S.Y., *et al.* Efficacy and safety of bipolar plasma vaporization of the prostate with "button-type" electrode compared with transurethral resection of prostate for benign prostatic hyperplasia. Chin Med J (Engl), 2012. 125: 3811.
https://www.ncbi.nlm.nih.gov/pubmed/23106879
482. Falahatkar, S., *et al.* Bipolar transurethral vaporization: a superior procedure in benign prostatic hyperplasia: a prospective randomized comparison with bipolar TURP. Int Braz J Urol, 2014. 40: 346.
https://www.ncbi.nlm.nih.gov/pubmed/25010300
483. Geavlete, B., *et al.* Continuous vs conventional bipolar plasma vaporisation of the prostate and standard monopolar resection: a prospective, randomised comparison of a new technological advance. BJU Int, 2014. 113: 288.
https://www.ncbi.nlm.nih.gov/pubmed/24053794
484. Yip, S.K., *et al.* A randomized controlled trial comparing the efficacy of hybrid bipolar transurethral vaporization and resection of the prostate with bipolar transurethral resection of the prostate. J Endourol, 2011. 25: 1889.
https://www.ncbi.nlm.nih.gov/pubmed/21923418
485. Elsakka, A.M., *et al.* A prospective randomised controlled study comparing bipolar plasma vaporisation of the prostate to monopolar transurethral resection of the prostate. Arab J Urol, 2016. 14: 280.
https://www.ncbi.nlm.nih.gov/pubmed/27900218
486. Lee, S.W., *et al.* Transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement: a quality and meta-analysis. Int Neurourol J, 2013. 17: 59.
https://www.ncbi.nlm.nih.gov/pubmed/23869269
487. Wroclawski, M.L., *et al.* 'Button type' bipolar plasma vaporisation of the prostate compared with standard transurethral resection: a systematic review and meta-analysis of short-term outcome studies. BJU Int, 2016. 117: 662.
https://www.ncbi.nlm.nih.gov/pubmed/26299915
488. Robert, G., *et al.* Bipolar plasma vaporization of the prostate: ready to replace GreenLight? A systematic review of randomized control trials. World J Urol, 2015. 33: 549.
https://www.ncbi.nlm.nih.gov/pubmed/25159871
489. Thangasamy, I.A., *et al.* Photoselective vaporisation of the prostate using 80-W and 120-W laser versus transurethral resection of the prostate for benign prostatic hyperplasia: a systematic review with meta-analysis from 2002 to 2012. Eur Urol, 2012. 62: 315.
https://www.ncbi.nlm.nih.gov/pubmed/22575913

490. Kang, D.H., *et al.* A Systematic Review and Meta-Analysis of Functional Outcomes and Complications Following the Photoselective Vaporization of the Prostate and Monopolar Transurethral Resection of the Prostate. World J Mens Health, 2016. 34: 110.
https://www.ncbi.nlm.nih.gov/pubmed/27574594
491. Zhou, Y., *et al.* Greenlight high-performance system (HPS) 120-W laser vaporization versus transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: a meta-analysis of the published results of randomized controlled trials. Lasers Med Sci, 2016. 31: 485.
https://www.ncbi.nlm.nih.gov/pubmed/26868032
492. Thomas, J.A., *et al.* A Multicenter Randomized Noninferiority Trial Comparing GreenLight-XPS Laser Vaporization of the Prostate and Transurethral Resection of the Prostate for the Treatment of Benign Prostatic Obstruction: Two-yr Outcomes of the GOLIATH Study. Eur Urol, 2016. 69: 94.
https://www.ncbi.nlm.nih.gov/pubmed/26283011
493. Elmansy, H., *et al.* Holmium laser enucleation versus photoselective vaporization for prostatic adenoma greater than 60 ml: preliminary results of a prospective, randomized clinical trial. J Urol, 2012. 188: 216.
https://www.ncbi.nlm.nih.gov/pubmed/22591968
494. Ghobrial, F.K., *et al.* A randomized trial comparing bipolar transurethral vaporization of the prostate with GreenLight laser (xps-180watt) photoselective vaporization of the prostate for treatment of small to moderate benign prostatic obstruction: outcomes after 2 years. BJU Int, 2020. 125: 144.
https://www.ncbi.nlm.nih.gov/pubmed/31621175
495. Al-Ansari, A., *et al.* GreenLight HPS 120-W laser vaporization versus transurethral resection of the prostate for treatment of benign prostatic hyperplasia: a randomized clinical trial with midterm follow-up. Eur Urol, 2010. 58: 349.
https://www.ncbi.nlm.nih.gov/pubmed/20605316
496. Erazo, J.C., *et al.* Outpatient 180 W XPS GreenLight Laser Photoselective Vaporization of the Prostate: 7-Year Experience. J Endourol, 2022. 36: 548.
https://www.ncbi.nlm.nih.gov/pubmed/34779677
497. Salmivalli, A., *et al.* Short- and long-term risks of photoselective laser vaporization of the prostate: a population-based comparison with transurethral resection of the prostate. Ann Med, 2023. 55: 1287.
https://www.ncbi.nlm.nih.gov/pubmed/36974584
498. Chung, D.E., *et al.* Outcomes and complications after 532 nm laser prostatectomy in anticoagulated patients with benign prostatic hyperplasia. J Urol, 2011. 186: 977.
https://www.ncbi.nlm.nih.gov/pubmed/21791350
499. Reich, O., *et al.* High power (80 W) potassium-titanyl-phosphate laser vaporization of the prostate in 66 high risk patients. J Urol, 2005. 173: 158.
https://www.ncbi.nlm.nih.gov/pubmed/15592063
500. Ruszat, R., *et al.* Safety and effectiveness of photoselective vaporization of the prostate (PVP) in patients on ongoing oral anticoagulation. Eur Urol, 2007. 51: 1031.
https://www.ncbi.nlm.nih.gov/pubmed/16945475
501. Sandhu, J.S., *et al.* Photoselective laser vaporization prostatectomy in men receiving anticoagulants. J Endourol, 2005. 19: 1196.
https://www.ncbi.nlm.nih.gov/pubmed/16359214
502. Lee, D.J., *et al.* Laser Vaporization of the Prostate With the 180-W XPS-Greenlight Laser in Patients With Ongoing Platelet Aggregation Inhibition and Oral Anticoagulation. Urology, 2016. 91: 167.
https://www.ncbi.nlm.nih.gov/pubmed/26829717
503. Jackson, R.E., *et al.* Risk factors for delayed hematuria following photoselective vaporization of the prostate. J Urol, 2013. 190: 903.
https://www.ncbi.nlm.nih.gov/pubmed/23538242
504. Knapp, G.L., *et al.* Perioperative adverse events in patients on continued anticoagulation undergoing photoselective vaporisation of the prostate with the 180-W Greenlight lithium triborate laser. BJU Int, 2017. 119 Suppl 5: 33.
https://www.ncbi.nlm.nih.gov/pubmed/28544292
505. Feiertag, J.H., *et al.* Incidence of Surgical Reintervention for Benign Prostatic Hyperplasia Following Prostatic Urethral Lift, Transurethral Resection of the Prostate, and Photoselective Vaporization of the Prostate: A TriNetX Analysis. Eur Urol Open Sci, 2024. 59: 63.
https://www.ncbi.nlm.nih.gov/pubmed/38298771
506. Campobasso, D., *et al.* Efficacy and safety profile of GreenLight laser photoselective vaporization of the prostate in >/= 75 years old patients: results from the Italian GreenLight Laser Study Group. Aging Clin Exp Res, 2023. 35: 877.
https://www.ncbi.nlm.nih.gov/pubmed/36763245

507. Woo, H., *et al.* Outcome of GreenLight HPS 120-W laser therapy in specific patient populations: those in retention, on anticoagulants, and with large prostates (>80 ml). . Eur Urol Suppl 2008. 7: 378.
https://www.sciencedirect.com/science/article/abs/pii/S1569905608000274
508. Rajbabu, K., *et al.* Photoselective vaporization of the prostate with the potassium-titanyl-phosphate laser in men with prostates of >100 mL. BJU Int, 2007. 100: 593.
https://www.ncbi.nlm.nih.gov/pubmed/17511771
509. Ruszat, R., *et al.* Photoselective vaporization of the prostate: subgroup analysis of men with refractory urinary retention. Eur Urol, 2006. 50: 1040.
https://www.ncbi.nlm.nih.gov/pubmed/16481099
510. Alivizatos, G., *et al.* Transurethral photoselective vaporization versus transvesical open enucleation for prostatic adenomas >80ml: 12-mo results of a randomized prospective study. Eur Urol, 2008. 54: 427.
https://www.ncbi.nlm.nih.gov/pubmed/18069117
511. Bouchier-Hayes, D.M., *et al.* KTP laser versus transurethral resection: early results of a randomized trial. J Endourol, 2006. 20: 580.
https://www.ncbi.nlm.nih.gov/pubmed/16903819
512. Bruyere, F., *et al.* Influence of photoselective vaporization of the prostate on sexual function: results of a prospective analysis of 149 patients with long-term follow-up. Eur Urol, 2010. 58: 207.
https://www.ncbi.nlm.nih.gov/pubmed/20466480
513. MacRae, C., *et al.* How I do it: Aquablation of the prostate using the AQUABEAM system. Can J Urol, 2016. 23: 8590.
https://www.ncbi.nlm.nih.gov/pubmed/27995858
514. Berjaoui, M.B., *et al.* WATER versus WATER II 5-year update: Comparing Aquablation therapy for benign prostatic hyperplasia in 30-80-cm(3) and 80-150-cm(3) prostates. BJUI Compass, 2024. 5: 1023.
https://www.ncbi.nlm.nih.gov/pubmed/39539565
515. Gilling, P., *et al.* WATER: A Double-Blind, Randomized, Controlled Trial of Aquablation((R)) vs Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia. J Urol, 2018. 199: 1252.
https://www.ncbi.nlm.nih.gov/pubmed/29360529
516. Kasivisvanathan, V., *et al.* Aquablation versus transurethral resection of the prostate: 1 year United States - cohort outcomes. Can J Urol, 2018. 25: 9317.
https://www.ncbi.nlm.nih.gov/pubmed/29900819
517. Gilling, P.J., *et al.* Randomized Controlled Trial of Aquablation versus Transurethral Resection of the Prostate in Benign Prostatic Hyperplasia: One-year Outcomes. Urology, 2019. 125: 169.
https://www.ncbi.nlm.nih.gov/pubmed/30552937
518. Gilling, P.J., *et al.* Five-year outcomes for Aquablation therapy compared to TURP: results from a double-blind, randomized trial in men with LUTS due to BPH. Can J Urol, 2022. 29: 10960.
https://www.ncbi.nlm.nih.gov/pubmed/35150215
519. Bhojani, N., *et al.* Aquablation Therapy in Large Prostates (80-150 mL) for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia: Final WATER II 5-Year Clinical Trial Results. J Urol, 2023. 210: 143.
https://www.ncbi.nlm.nih.gov/pubmed/37115632
520. Bhatia, A., *et al.* Comparing outcomes of Aquablation versus holmium laser enucleation of prostate in the treatment of benign prostatic hyperplasia: A network meta-analysis. BJUI Compass, 2024. 5: 1231.
https://www.ncbi.nlm.nih.gov/pubmed/39744077
521. Pimentel, M.A., *et al.* Urodynamic Outcomes After Aquablation. Urology, 2019. 126: 165.
https://www.ncbi.nlm.nih.gov/pubmed/30721737
522. Desai, M., *et al.* Aquablation for benign prostatic hyperplasia in large prostates (80-150 mL): 6-month results from the WATER II trial. BJU Int, 2019. 124: 321.
https://www.ncbi.nlm.nih.gov/pubmed/30734990
523. Nguyen, D.D., *et al.* Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue trial (WATER) vs WATER II: comparing Aquablation therapy for benign prostatic hyperplasia in 30-80 and 80-150 mL prostates. BJU Int, 2020. 125: 112.
https://www.ncbi.nlm.nih.gov/pubmed/31599044
524. Bhojani, N., *et al.* Aquablation for Benign Prostatic Hyperplasia in Large Prostates (80-150 cc): 1-Year Results. Urology, 2019. 129: 1.
https://www.ncbi.nlm.nih.gov/pubmed/31059728

525. Bach, T., *et al.* Aquablation Outcomes in Men With LUTS Due to BPH Following Single Versus Multi-pass Treatments. Urology, 2022. 169: 167.
https://www.ncbi.nlm.nih.gov/pubmed/35863498
526. Justo Quintas, J., *et al.* Aquablation vs. holmium laser enucleation of the prostate for benign prostatic hyperplasia: a 150-patients prospective comparative multicenter study. Minerva Urol Nephrol, 2025. 77: 111.
https://www.ncbi.nlm.nih.gov/pubmed/39932697
527. Abt, D., *et al.* Comparison of prostatic artery embolisation (PAE) versus transurethral resection of the prostate (TURP) for benign prostatic hyperplasia: randomised, open label, non-inferiority trial. BMJ, 2018. 361: k2338.
https://www.ncbi.nlm.nih.gov/pubmed/29921613
528. Zhang, J.L., *et al.* Effectiveness of Contrast-enhanced MR Angiography for Visualization of the Prostatic Artery prior to Prostatic Arterial Embolization. Radiology, 2019. 291: 370.
https://www.ncbi.nlm.nih.gov/pubmed/30806596
529. Pisco, J.M., *et al.* Randomised Clinical Trial of Prostatic Artery Embolisation Versus a Sham Procedure for Benign Prostatic Hyperplasia. Eur Urol, 2020. 77: 354.
https://www.ncbi.nlm.nih.gov/pubmed/31831295
530. Zumstein, V., *et al.* Prostatic Artery Embolization versus Standard Surgical Treatment for Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Systematic Review and Meta-analysis. Eur Urol Focus, 2019. 5: 1091.
https://www.ncbi.nlm.nih.gov/pubmed/30292422
531. Franco, J.V.A., *et al.* Minimally invasive treatments for benign prostatic hyperplasia: a Cochrane network meta-analysis. BJU Int, 2022. 130: 142.
https://www.ncbi.nlm.nih.gov/pubmed/34820997
532. Xiang, P., *et al.* Efficacy and safety of prostatic artery embolization for benign prostatic hyperplasia: a systematic review and meta-analysis of randomized controlled trials. Eur Radiol, 2021. 31: 4929.
https://www.ncbi.nlm.nih.gov/pubmed/33449181
533. Mullhaupt, G., *et al.* Prostatic Artery Embolisation Versus Transurethral Resection of the Prostate for Benign Prostatic Obstruction: 5-year Outcomes of a Randomised, Open-label, Noninferiority Trial. Eur Urol Focus, 2024. 10: 788.
https://www.ncbi.nlm.nih.gov/pubmed/38531756
534. Lewer, O., *et al.* Prostate Size and Its Effect on Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia Improvement After Convective Water Vapor Thermal Therapy. J Urol, 2025. 214: 48.
https://www.ncbi.nlm.nih.gov/pubmed/40043254
535. Jung, J.H., *et al.* Prostatic arterial embolisation for men with benign prostatic hyperplasia: a Cochrane review. BJU Int, 2023. 131: 32.
https://www.ncbi.nlm.nih.gov/pubmed/35696302
536. Shim, S.R., *et al.* Efficacy and Safety of Prostatic Arterial Embolization: Systematic Review with Meta-Analysis and Meta-Regression. J Urol, 2017. 197: 465.
https://www.ncbi.nlm.nih.gov/pubmed/27592008
537. Knight, G.M., *et al.* Systematic Review and Meta-analysis Comparing Prostatic Artery Embolization to Gold-Standard Transurethral Resection of the Prostate for Benign Prostatic Hyperplasia. Cardiovasc Intervent Radiol, 2021. 44: 183.
https://www.ncbi.nlm.nih.gov/pubmed/33078236
538. Jiang, Y.L., *et al.* Transurethral resection of the prostate versus prostatic artery embolization in the treatment of benign prostatic hyperplasia: a meta-analysis. BMC Urol, 2019. 19: 11.
https://www.ncbi.nlm.nih.gov/pubmed/30691478
539. Xu, X.J., *et al.* An updated meta-analysis of prostatic arterial embolization versus transurethral resection of the prostate in the treatment of benign prostatic hyperplasia. World J Urol, 2020. 38: 2455.
https://www.ncbi.nlm.nih.gov/pubmed/31813027
540. Moreira, A.M., *et al.* A Review of Adverse Events Related to Prostatic Artery Embolization for Treatment of Bladder Outlet Obstruction Due to BPH. Cardiovasc Intervent Radiol, 2017. 40: 1490.
https://www.ncbi.nlm.nih.gov/pubmed/28795212
541. Ray, A.F., *et al.* Efficacy and safety of prostate artery embolization for benign prostatic hyperplasia: an observational study and propensity-matched comparison with transurethral resection of the prostate (the UK-ROPE study). BJU Int, 2018. 122: 270.
https://www.ncbi.nlm.nih.gov/pubmed/29645352

542. Sapoval, M.R., *et al.* Two-Year Outcomes of Prostatic Artery Embolization for Symptomatic Benign Prostatic Hyperplasia: An International, Multicenter, Prospective Study. Cardiovasc Intervent Radiol, 2024. 47: 1515.
https://www.ncbi.nlm.nih.gov/pubmed/39230672
543. Zumstein, V., *et al.* Radiation Exposure During Prostatic Artery Embolisation: A Systematic Review and Calculation of Associated Risks. Eur Urol Focus, 2021. 7: 608.
https://www.ncbi.nlm.nih.gov/pubmed/32418877
544. National Institute for Health and Care Excellence. NICE Guidance - Prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia: (c) NICE (2018) Prostate artery embolisation for lower urinary tract symptoms caused by benign prostatic hyperplasia. BJU Int, 2018. 122: 11.
https://www.ncbi.nlm.nih.gov/pubmed/29894572
545. Abt, D., *et al.* Outcome prediction of prostatic artery embolization: *post hoc* analysis of a randomized, open-label, non-inferiority trial. BJU Int, 2019. 124: 134.
https://www.ncbi.nlm.nih.gov/pubmed/30499637
546. McVary, K.T., *et al.* Erectile and Ejaculatory Function Preserved With Convective Water Vapor Energy Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: Randomized Controlled Study. J Sex Med, 2016. 13: 924.
https://www.ncbi.nlm.nih.gov/pubmed/27129767
547. Roehrborn, C.G., *et al.* Convective Thermal Therapy: Durable 2-Year Results of Randomized Controlled and Prospective Crossover Studies for Treatment of Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. J Urol, 2017. 197: 1507.
https://www.ncbi.nlm.nih.gov/pubmed/27993667
548. Samir, M., *et al.* Two-year follow-up comparing Rezum therapy versus bipolar transurethral resection of the prostate for treating benign prostatic hyperplasia. A prospective randomized study. Int J Urol, 2024. 31: 545.
https://www.ncbi.nlm.nih.gov/pubmed/38291876
549. Kang, T.W., *et al.* Convective radiofrequency water vapour thermal therapy for lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database Syst Rev, 2020. 3: CD013251.
https://www.ncbi.nlm.nih.gov/pubmed/32212174
550. Cornu, J.N., *et al.* Minimally Invasive Treatments for Benign Prostatic Obstruction: A Systematic Review and Network Meta-analysis. Eur Urol, 2023. 83: 534.
https://www.ncbi.nlm.nih.gov/pubmed/36964042
551. Baboudjian, M., *et al.* Pharmacologic and Surgical Retreatment After Office-based Treatments for Benign Prostatic Hyperplasia: A Systematic Review. Eur Urol Focus, 2023. 9: 727.
https://www.ncbi.nlm.nih.gov/pubmed/36906484
552. Miller, L.E., *et al.* Water vapor thermal therapy for lower urinary tract symptoms secondary to benign prostatic hyperplasia: Systematic review and meta-analysis. Medicine (Baltimore), 2020. 99: e21365.
https://www.ncbi.nlm.nih.gov/pubmed/32791742
553. McVary, K.T., *et al.* Water Vapor Thermal Therapy in Men With Prostate Volume >/=80 cm(3): A Systematic Review and Meta-Analysis. Urology, 2024. 184: 244.
https://www.ncbi.nlm.nih.gov/pubmed/38006957
554. de Rienzo, G., *et al.* Transperineal interstitial laser ablation of the prostate, a novel option for minimally invasive treatment of benign prostatic obstruction. Eur Urol, 2021. 80: 95.
https://www.ncbi.nlm.nih.gov/pubmed/32868137
555. Canat, H.L., *et al.* Transurethral resection of the prostate (TURP) versus transperineal laser ablation (TPLA) due to benign prostatic hyperplasia (BPH): prospective and comparative study. Int Urol Nephrol, 2023. 55: 2747.
https://www.ncbi.nlm.nih.gov/pubmed/37498422
556. Bertolo, R., *et al.* Ejaculatory function following transperineal laser ablation vs TURP for benign prostatic obstruction: a randomized trial. BJU Int, 2023. 132: 100.
https://www.ncbi.nlm.nih.gov/pubmed/36917033
557. Lagana, A., *et al.* Ultrasound-guided SoracteLite transperineal laser ablation (TPLA) of the prostate for the treatment of symptomatic benign prostatic hyperplasia (BPH): a prospective single-center experience. World J Urol, 2023. 41: 1157.
https://www.ncbi.nlm.nih.gov/pubmed/36853444
558. Tafuri, A., *et al.* Transperineal Laser Ablation for Benign Prostatic Enlargement: A Systematic Review and Pooled Analysis of Pilot Studies. J Clin Med, 2023. 12.
https://www.ncbi.nlm.nih.gov/pubmed/36902647

559. Sessa, F., *et al.* Transperineal Laser Ablation of the Prostate (TPLA) for Lower Urinary Tract Symptoms Due to Benign Prostatic Obstruction. J Clin Med, 2023. 12.
https://www.ncbi.nlm.nih.gov/pubmed/36769454
560. Chin, P.T., *et al.* Prostatic urethral lift: two-year results after treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. Urology, 2012. 79: 5.
https://www.ncbi.nlm.nih.gov/pubmed/22202539
561. McNicholas, T.A., *et al.* Minimally invasive prostatic urethral lift: surgical technique and multinational experience. Eur Urol, 2013. 64: 292.
https://www.ncbi.nlm.nih.gov/pubmed/23357348
562. Roehrborn, C.G., *et al.* The prostatic urethral lift for the treatment of lower urinary tract symptoms associated with prostate enlargement due to benign prostatic hyperplasia: the L.I.F.T. Study. J Urol, 2013. 190: 2161.
https://www.ncbi.nlm.nih.gov/pubmed/23764081
563. Woo, H.H., *et al.* Safety and feasibility of the prostatic urethral lift: a novel, minimally invasive treatment for lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). BJU Int, 2011. 108: 82.
https://www.ncbi.nlm.nih.gov/pubmed/21554526
564. Woo, H.H., *et al.* Preservation of sexual function with the prostatic urethral lift: a novel treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Sex Med, 2012. 9: 568.
https://www.ncbi.nlm.nih.gov/pubmed/22172161
565. Perera, M., *et al.* Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. Eur Urol, 2015. 67: 704.
https://www.ncbi.nlm.nih.gov/pubmed/25466940
566. Jung, J.H., *et al.* Prostatic urethral lift for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database Syst Rev, 2019. 5: CD012832.
https://www.ncbi.nlm.nih.gov/pubmed/31128077
567. Roehrborn, C.G., *et al.* Three year results of the prostatic urethral L.I.F.T. study. Can J Urol, 2015. 22: 7772.
https://www.ncbi.nlm.nih.gov/pubmed/26068624
568. Roehrborn, C.G., *et al.* Five year results of the prospective randomized controlled prostatic urethral L.I.F.T. study. Can J Urol, 2017. 24: 8802.
https://www.ncbi.nlm.nih.gov/pubmed/28646935
569. Eure, G., *et al.* Real-World Evidence of Prostatic Urethral Lift Confirms Pivotal Clinical Study Results: 2-Year Outcomes of a Retrospective Multicenter Study. J Endourol, 2019. 33: 576.
https://www.ncbi.nlm.nih.gov/pubmed/31115257
570. Sonksen, J., *et al.* Prospective, randomized, multinational study of prostatic urethral lift versus transurethral resection of the prostate: 12-month results from the BPH6 study. Eur Urol, 2015. 68: 643.
https://www.ncbi.nlm.nih.gov/pubmed/25937539
571. Xiang, P., *et al.* A Systematic Review and Meta-analysis of Prostatic Urethral Lift for Male Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. Eur Urol Open Sci, 2020. 19: 3.
https://www.ncbi.nlm.nih.gov/pubmed/34337448
572. Miller, L.E., *et al.* Surgical Reintervention Rate after Prostatic Urethral Lift: Systematic Review and Meta-Analysis Involving over 2,000 Patients. J Urol, 2020. 204: 1019.
https://www.ncbi.nlm.nih.gov/pubmed/32396049
573. Rukstalis, D., *et al.* Prostatic Urethral Lift (PUL) for obstructive median lobes: 12 month results of the MedLift Study. Prostate Cancer Prostatic Dis, 2019. 22: 411.
https://www.ncbi.nlm.nih.gov/pubmed/30542055
574. Porpiglia, F., *et al.* Temporary implantable nitinol device (TIND): a novel, minimally invasive treatment for relief of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH): feasibility, safety and functional results at 1 year of follow-up. BJU Int, 2015. 116: 278.
https://www.ncbi.nlm.nih.gov/pubmed/25382816
575. Porpiglia, F., *et al.* 3-Year follow-up of temporary implantable nitinol device implantation for the treatment of benign prostatic obstruction. BJU Int, 2018. 122: 106.
https://www.ncbi.nlm.nih.gov/pubmed/29359881
576. Chughtai, B., *et al.* The iTind Temporarily Implanted Nitinol Device for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia: A Multicenter, Randomized, Controlled Trial. Urology, 2021. 153: 270.
https://www.ncbi.nlm.nih.gov/pubmed/33373708

577. Porpiglia, F., *et al.* Second-generation of temporary implantable nitinol device for the relief of lower urinary tract symptoms due to benign prostatic hyperplasia: results of a prospective, multicentre study at 1 year of follow-up. BJU Int, 2019. 123: 1061.
https://www.ncbi.nlm.nih.gov/pubmed/30382600
578. Kaplan, S.A., *et al.* One-year outcomes after treatment with a drug-coated balloon catheter system for lower urinary tract symptoms related to benign prostatic hyperplasia. Prostate Cancer Prostatic Dis, 2021. 24: 1073.
https://www.ncbi.nlm.nih.gov/pubmed/33833379
579. Kaplan, S.A., *et al.* Long-term outcomes after treatment with Optilume BPH Four-year results from the EVEREST study. Can Urol Assoc J, 2024. 18: E319.
https://www.ncbi.nlm.nih.gov/pubmed/38976898
580. Kaplan, S.A., *et al.* The PINNACLE Study: A Double-blind, Randomized, Sham-controlled Study Evaluating the Optilume BPH Catheter System for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia. J Urol, 2023. 210: 500.
https://www.ncbi.nlm.nih.gov/pubmed/37555604
581. Sakalis, V.I., *et al.* Medical Treatment of Nocturia in Men with Lower Urinary Tract Symptoms: Systematic Review by the European Association of Urology Guidelines Panel for Male Lower Urinary Tract Symptoms. Eur Urol, 2017. 72: 757.
https://www.ncbi.nlm.nih.gov/pubmed/28666669
582. Hashim, H., *et al.* International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn, 2019. 38: 499.
https://www.ncbi.nlm.nih.gov/pubmed/30644584
583. Marshall, S.D., *et al.* Nocturia: Current Levels of Evidence and Recommendations From the International Consultation on Male Lower Urinary Tract Symptoms. Urology, 2015. 85: 1291.
https://www.ncbi.nlm.nih.gov/pubmed/25881866
584. Goessaert, A.S., *et al.* Nocturnal Polyuria: Excess of Nocturnal Urine Production, Excess of Definitions-Influence on Renal Function Profile. J Urol, 2016. 195: 670.
https://www.ncbi.nlm.nih.gov/pubmed/26410733
585. Cannon, A., *et al.* Desmopressin in the treatment of nocturnal polyuria in the male. BJU Int, 1999. 84: 20.
https://www.ncbi.nlm.nih.gov/pubmed/10444118
586. Han, J., *et al.* Desmopressin for treating nocturia in men. Cochrane Database Syst Rev, 2017. 10: CD012059.
https://www.ncbi.nlm.nih.gov/pubmed/29055129
587. Weiss, J.P., *et al.* Efficacy and safety of low dose desmopressin orally disintegrating tablet in men with nocturia: results of a multicenter, randomized, double-blind, placebo controlled, parallel group study. J Urol, 2013. 190: 965.
https://www.ncbi.nlm.nih.gov/pubmed/23454402
588. Sand, P.K., *et al.* Efficacy and safety of low dose desmopressin orally disintegrating tablet in women with nocturia: results of a multicenter, randomized, double-blind, placebo controlled, parallel group study. J Urol, 2013. 190: 958.
https://www.ncbi.nlm.nih.gov/pubmed/23454404
589. Juul, K.V., *et al.* Low-dose desmopressin combined with serum sodium monitoring can prevent clinically significant hyponatraemia in patients treated for nocturia. BJU Int, 2017. 119: 776.
https://www.ncbi.nlm.nih.gov/pubmed/27862898
590. Kurose, H., *et al.* Determining the optimal initial dose for Japanese patients with nocturnal polyuria using an initial dose of desmopressin 50 mug. Low Urin Tract Symptoms, 2023. 15: 89.
https://www.ncbi.nlm.nih.gov/pubmed/36755502
591. Cohn, J.A., *et al.* Desmopressin acetate nasal spray for adults with nocturia. Expert Rev Clin Pharmacol, 2017. 10: 1281.
https://www.ncbi.nlm.nih.gov/pubmed/29048257
592. Djavan, B., *et al.* The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: Preliminary results of a pilot study. Eur Urol Suppl, 2005. 4: 1119.
https://www.sciencedirect.com/science/article/abs/pii/S1569905604001277
593. Yokoyama, O., *et al.* Efficacy of fesoterodine on nocturia and quality of sleep in Asian patients with overactive bladder. Urology, 2014. 83: 750.
https://www.ncbi.nlm.nih.gov/pubmed/24518285
594. Yokoyama, O., *et al.* Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary. J Urol, 2011. 186: 170.
https://www.ncbi.nlm.nih.gov/pubmed/21575976

595. Johnson, T.M., 2nd, *et al.* The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. J Urol, 2007. 178: 2045.
https://www.ncbi.nlm.nih.gov/pubmed/17869295
596. Oelke, M., *et al.* Impact of dutasteride on nocturia in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): a pooled analysis of three phase III studies. World J Urol, 2014. 32: 1141.
https://www.ncbi.nlm.nih.gov/pubmed/24903347
597. Oelke, M., *et al.* Effects of tadalafil on nighttime voiding (nocturia) in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a *post hoc* analysis of pooled data from four randomized, placebo-controlled clinical studies. World J Urol, 2014. 32: 1127.
https://www.ncbi.nlm.nih.gov/pubmed/24504761
598. Drake, M.J., *et al.* Melatonin pharmacotherapy for nocturia in men with benign prostatic enlargement. J Urol, 2004. 171: 1199.
https://www.ncbi.nlm.nih.gov/pubmed/14767300
599. Reynard, J.M., *et al.* A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. Br J Urol, 1998. 81: 215.
https://www.ncbi.nlm.nih.gov/pubmed/9488061
600. Falahatkar, S., *et al.* Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. Urology, 2008. 72: 813.
https://www.ncbi.nlm.nih.gov/pubmed/18692876
601. Sigurdsson, S., *et al.* A parallel, randomized, double-blind, placebo-controlled study to investigate the effect of SagaPro on nocturia in men. Scand J Urol, 2013. 47: 26.
https://www.ncbi.nlm.nih.gov/pubmed/23323790
602. Fotovat, A., *et al.* The effect of Melatonin on Improving the benign Prostatic Hyperplasia Urinary Symptoms, a Randomized Clinical Trial. Urol J, 2022. 19: 406.
https://www.ncbi.nlm.nih.gov/pubmed/34746997
603. D'Ancona, C., *et al.* The International Continence Society (ICS) report on the terminology for adult male lower urinary tract and pelvic floor symptoms and dysfunction. Neurourol Urodyn, 2019. 38: 433.
https://www.ncbi.nlm.nih.gov/pubmed/30681183
604. Helfand, B.T., *et al.* Prevalence and Characteristics of Urinary Incontinence in a Treatment Seeking Male Prospective Cohort: Results from the LURN Study. J Urol, 2018. 200: 397.
https://www.ncbi.nlm.nih.gov/pubmed/29477718
605. Shamliyan, T.A., *et al.* Male urinary incontinence: prevalence, risk factors, and preventive interventions. Rev Urol, 2009. 11: 145.
https://www.ncbi.nlm.nih.gov/pubmed/19918340
606. Hester, A.G., *et al.* Male Incontinence: The Etiology or Basis of Treatment. Eur Urol Focus, 2017. 3: 377.
https://www.ncbi.nlm.nih.gov/pubmed/29249687
607. Herschorn, S., *et al.* A population-based study of urinary symptoms and incontinence: the Canadian Urinary Bladder Survey. BJU Int, 2008. 101: 52.
https://www.ncbi.nlm.nih.gov/pubmed/17908260
608. Espuna-Pons, M., *et al.* [Prevalence of urinary incontinence in Catalonia, Spain]. Med Clin (Barc), 2009. 133: 702.
https://www.ncbi.nlm.nih.gov/pubmed/19656535
609. Hampel, C., *et al.* [Epidemiology and etiology of male urinary incontinence]. Urologe A, 2010. 49: 481.
https://www.ncbi.nlm.nih.gov/pubmed/20376650
610. Hsu, L.N., *et al.* Metabolic Syndrome and Overactive Bladder Syndrome May Share Common Pathophysiologies. Biomedicines, 2022. 10.
https://www.ncbi.nlm.nih.gov/pubmed/36009505
611. Dumoulin C., *et al.*, Adult conservative managemen. Incontinence: 7th International Consultation on Incontinence (ICI) ed. t. ed. 2023, Bristol, UK.
https://www.ics.org/ici7
612. Sato, Y., *et al.* Simple and reliable predictor of urinary continence after radical prostatectomy: serial measurement of urine loss ratio after catheter removal. Int J Urol, 2014. 21: 647.
https://www.ncbi.nlm.nih.gov/pubmed/24612261
613. Shy, M., *et al.* Objective Evaluation of Overactive Bladder: Which Surveys Should I Use? Curr Bladder Dysfunct Rep, 2013. 8: 45.
https://www.ncbi.nlm.nih.gov/pubmed/23439804

614. Arcila-Ruiz, M., *et al.* The Role of Urodynamics in Post-Prostatectomy Incontinence. Curr Urol Rep, 2018. 19: 21.
https://www.ncbi.nlm.nih.gov/pubmed/29479637
615. Bruschini, H., *et al.* Urinary incontinence following surgery for BPH: the role of aging on the incidence of bladder dysfunction. Int Braz J Urol, 2011. 37: 380.
https://www.ncbi.nlm.nih.gov/pubmed/21756386
616. Porena, M., *et al.* Voiding dysfunction after radical retropubic prostatectomy: more than external urethral sphincter deficiency. Eur Urol, 2007. 52: 38.
https://www.ncbi.nlm.nih.gov/pubmed/17403565
617. Al-Zahrani, A.A., *et al.* Association of symptoms with urodynamic findings in men with overactive bladder syndrome. BJU Int, 2012. 110: E891.
https://www.ncbi.nlm.nih.gov/pubmed/22928556
618. Clement, K.D., *et al.* Urodynamic studies for management of urinary incontinence in children and adults. Cochrane Database Syst Rev, 2013. 2013: CD003195.
https://www.ncbi.nlm.nih.gov/pubmed/24166676
619. Gacci, M., *et al.* Latest Evidence on Post-Prostatectomy Urinary Incontinence. J Clin Med, 2023. 12.
https://www.ncbi.nlm.nih.gov/pubmed/36769855
620. Moore, K.C., *et al.* Management of male urinary incontinence. Indian J Urol, 2010. 26: 236.
https://www.ncbi.nlm.nih.gov/pubmed/20877603
621. Soljanik, I., *et al.* [Imaging for urinary incontinence]. Urologe A, 2015. 54: 963.
https://www.ncbi.nlm.nih.gov/pubmed/26162272
622. Wyman, J.F., *et al.* Practical aspects of lifestyle modifications and behavioural interventions in the treatment of overactive bladder and urgency urinary incontinence. Int J Clin Pract, 2009. 63: 1177.
https://www.ncbi.nlm.nih.gov/pubmed/19575724
623. Breyer, B.N., *et al.* Intensive lifestyle intervention reduces urinary incontinence in overweight/obese men with type 2 diabetes: results from the Look AHEAD trial. J Urol, 2014. 192: 144.
https://www.ncbi.nlm.nih.gov/pubmed/24533998
624. Imamura, M., *et al.* Lifestyle interventions for the treatment of urinary incontinence in adults. Cochrane Database Syst Rev, 2015. 2015: CD003505.
https://www.ncbi.nlm.nih.gov/pubmed/26630349
625. Townsend, M.K., *et al.* Fluid intake and risk of stress, urgency, and mixed urinary incontinence. Am J Obstet Gynecol, 2011. 205: 73 e1.
https://www.ncbi.nlm.nih.gov/pubmed/21481835
626. Hashim, H., *et al.* Management of fluid intake in patients with overactive bladder. Curr Urol Rep, 2009. 10: 428.
https://www.ncbi.nlm.nih.gov/pubmed/19863853
627. Hannestad, Y.S., *et al.* Are smoking and other lifestyle factors associated with female urinary incontinence? The Norwegian EPINCONT Study. BJOG, 2003. 110: 247.
https://www.ncbi.nlm.nih.gov/pubmed/12628262
628. Bryant, C.M., *et al.* Caffeine reduction education to improve urinary symptoms. Br J Nurs, 2002. 11: 560.
https://www.ncbi.nlm.nih.gov/pubmed/11979209
629. Chughtai, B., *et al.* Prevalence of and Risk Factors for Urinary Incontinence in Home Hospice Patients. Eur Urol, 2019. 75: 268.
https://www.ncbi.nlm.nih.gov/pubmed/30482670
630. Held, F., *et al.* Polypharmacy in older adults: Association Rule and Frequent-Set Analysis to evaluate concomitant medication use. Pharmacol Res, 2017. 116: 39.
https://www.ncbi.nlm.nih.gov/pubmed/27988385
631. Schnelle, J.F., *et al.* A controlled trial of an intervention to improve urinary and fecal incontinence and constipation. J Am Geriatr Soc, 2010. 58: 1504.
https://www.ncbi.nlm.nih.gov/pubmed/20653804
632. Brazzelli, M., *et al.* Absorbent products for containing urinary and/or fecal incontinence in adults. J Wound Ostomy Continence Nurs, 2002. 29: 45.
https://www.ncbi.nlm.nih.gov/pubmed/11810074
633. Fader, M., *et al.* Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product designs. Health Technol Assess, 2008. 12: iii.
https://www.ncbi.nlm.nih.gov/pubmed/18547500
634. Prieto, J.A., *et al.* Intermittent catheter techniques, strategies and designs for managing long-term bladder conditions. Cochrane Database Syst Rev, 2021. 10: CD006008.
https://www.ncbi.nlm.nih.gov/pubmed/34699062

635. Jahn, P., *et al.* Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database Syst Rev, 2012. 10: CD004997.
https://www.ncbi.nlm.nih.gov/pubmed/23076911
636. Hunter, K.F., *et al.* Long-term bladder drainage: Suprapubic catheter versus other methods: a scoping review. Neurourol Urodyn, 2013. 32: 944.
https://www.ncbi.nlm.nih.gov/pubmed/23192860
637. Macaulay, M., *et al.* A trial of devices for urinary incontinence after treatment for prostate cancer. BJU Int, 2015. 116: 432.
https://www.ncbi.nlm.nih.gov/pubmed/25496354
638. Eustice, S., *et al.* Prompted voiding for the management of urinary incontinence in adults. Cochrane Database Syst Rev, 2000. 2000: CD002113.
https://www.ncbi.nlm.nih.gov/pubmed/10796861
639. Flanagan, L., *et al.* Systematic review of care intervention studies for the management of incontinence and promotion of continence in older people in care homes with urinary incontinence as the primary focus (1966-2010). Geriatr Gerontol Int, 2012. 12: 600.
https://www.ncbi.nlm.nih.gov/pubmed/22672329
640. Ostaszkiewicz, J., *et al.* Habit retraining for the management of urinary incontinence in adults. Cochrane Database Syst Rev, 2004. 2004: CD002801.
https://www.ncbi.nlm.nih.gov/pubmed/15106179
641. Rai, B.P., *et al.* Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults. Cochrane Database Syst Rev, 2012. 12: CD003193.
https://www.ncbi.nlm.nih.gov/pubmed/23235594
642. Anderson, C.A., *et al.* Conservative management for postprostatectomy urinary incontinence. Cochrane Database Syst Rev, 2015. 1: CD001843.
https://www.ncbi.nlm.nih.gov/pubmed/25602133
643. Kannan, P., *et al.* Effectiveness of Pelvic Floor Muscle Training Alone and in Combination With Biofeedback, Electrical Stimulation, or Both Compared to Control for Urinary Incontinence in Men Following Prostatectomy: Systematic Review and Meta-Analysis. Phys Ther, 2018. 98: 932.
https://www.ncbi.nlm.nih.gov/pubmed/30137629
644. Sciarra, A., *et al.* A biofeedback-guided programme or pelvic floor muscle electric stimulation can improve early recovery of urinary continence after radical prostatectomy: A meta-analysis and systematic review. Int J Clin Pract, 2021. 75: e14208.
https://www.ncbi.nlm.nih.gov/pubmed/33811418
645. Goonewardene, S.S., *et al.* A systematic review of PFE pre-prostatectomy. J Robot Surg, 2018. 12: 397.
https://www.ncbi.nlm.nih.gov/pubmed/29564692
646. Marchioni, M., *et al.* Conservative management of urinary incontinence following robot-assisted radical prostatectomy. Minerva Urol Nefrol, 2020. 72: 555.
https://www.ncbi.nlm.nih.gov/pubmed/32432436
647. Gomes, C.S., *et al.* The effects of Pilates method on pelvic floor muscle strength in patients with post-prostatectomy urinary incontinence: A randomized clinical trial. Neurourol Urodyn, 2018. 37: 346.
https://www.ncbi.nlm.nih.gov/pubmed/28464434
648. Heydenreich, M., *et al.* Does trunk muscle training with an oscillating rod improve urinary incontinence after radical prostatectomy? A prospective randomized controlled trial. Clin Rehabil, 2020. 34: 320.
https://www.ncbi.nlm.nih.gov/pubmed/31858823
649. Soto Gonzalez, M., *et al.* Early 3-month treatment with comprehensive physical therapy program restores continence in urinary incontinence patients after radical prostatectomy: A randomized controlled trial. Neurourol Urodyn, 2020. 39: 1529.
https://www.ncbi.nlm.nih.gov/pubmed/32442334
650. Farzinmehr, A., *et al.* A Comparative Study of Whole Body Vibration Training and Pelvic Floor Muscle Training on Women's Stress Urinary Incontinence: Three- Month Follow- Up. J Family Reprod Health, 2015. 9: 147.
https://www.ncbi.nlm.nih.gov/pubmed/27047560
651. Wang, C., *et al.* Extended nursing for the recovery of urinary functions and quality of life after robot-assisted laparoscopic radical prostatectomy: a randomized controlled trial. Support Care Cancer, 2018. 26: 1553.
https://www.ncbi.nlm.nih.gov/pubmed/29196816

652. Fernandez, R.A., *et al.* Improvement of continence rate with pelvic floor muscle training post-prostatectomy: a meta-analysis of randomized controlled trials. Urol Int, 2015. 94: 125.
https://www.ncbi.nlm.nih.gov/pubmed/25427689
653. Goode, P.S., *et al.* Behavioral therapy with or without biofeedback and pelvic floor electrical stimulation for persistent postprostatectomy incontinence: a randomized controlled trial. JAMA, 2011. 305: 151.
https://www.ncbi.nlm.nih.gov/pubmed/21224456
654. Dubbelman, Y., *et al.* The recovery of urinary continence after radical retropubic prostatectomy: a randomized trial comparing the effect of physiotherapist-guided pelvic floor muscle exercises with guidance by an instruction folder only. BJU Int, 2010. 106: 515.
https://www.ncbi.nlm.nih.gov/pubmed/20201841
655. Moore, K.N., *et al.* Return to continence after radical retropubic prostatectomy: a randomized trial of verbal and written instructions versus therapist-directed pelvic floor muscle therapy. Urology, 2008. 72: 1280.
https://www.ncbi.nlm.nih.gov/pubmed/18384853
656. Russo, F., *et al.* Effects of a home-based pelvic floor muscle training with and without action and cue observation on urinary incontinence after prostatectomy: A randomized controlled trial. Clin Rehabil, 2025. 39: 295.
https://www.ncbi.nlm.nih.gov/pubmed/39881606
657. Ouchi, M., *et al.* Physiotherapy for continence and muscle function in prostatectomy: a randomised controlled trial. BJU Int, 2024. 134: 398.
https://www.ncbi.nlm.nih.gov/pubmed/38658057
658. Gerlegiz, E.N.A., *et al.* Lifestyle recommendations and pelvic floor muscle training with Knack maneuver for post-prostatectomy urinary incontinence: a randomized controlled trial. Support Care Cancer, 2025. 33: 132.
https://www.ncbi.nlm.nih.gov/pubmed/39888446
659. Glazener, C., *et al.* Urinary incontinence in men after formal one-to-one pelvic-floor muscle training following radical prostatectomy or transurethral resection of the prostate (MAPS): two parallel randomised controlled trials. Lancet, 2011. 378: 328.
https://www.ncbi.nlm.nih.gov/pubmed/21741700
660. Anan, G., *et al.* Preoperative pelvic floor muscle exercise for early continence after holmium laser enucleation of the prostate: a randomized controlled study. BMC Urol, 2020. 20: 3.
https://www.ncbi.nlm.nih.gov/pubmed/31973706
661. Lim, R., *et al.* Efficacy of electromagnetic therapy for urinary incontinence: A systematic review. Neurourol Urodyn, 2015. 34: 713.
https://www.ncbi.nlm.nih.gov/pubmed/25251335
662. Wallace, P.A., *et al.* Sacral nerve neuromodulation in patients with underlying neurologic disease. Am J Obstet Gynecol, 2007. 197: 96 e1.
https://www.ncbi.nlm.nih.gov/pubmed/17618775
663. Yang, J.M., *et al.* Effect of pelvic floor muscle training on urinary incontinence after radical prostatectomy: An umbrella review of meta-analysis and systematic review. Clin Rehabil, 2023. 37: 494.
https://www.ncbi.nlm.nih.gov/pubmed/36305082
664. Pane-Alemany, R., *et al.* Efficacy of transcutaneous perineal electrostimulation versus intracavitary anal electrostimulation in the treatment of urinary incontinence after a radical prostatectomy: Randomized controlled trial. Neurourol Urodyn, 2021. 40: 1761.
https://www.ncbi.nlm.nih.gov/pubmed/34224598
665. Berghmans, B., *et al.* Electrical stimulation with non-implanted electrodes for urinary incontinence in men. Cochrane Database Syst Rev, 2013. 2013: CD001202.
https://www.ncbi.nlm.nih.gov/pubmed/23740763
666. Civic, D., *et al.* Re: Randomized trial of percutaneous tibial nerve stimulation versus sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial: K. M. Peters, D. J. Carrico, R. A. Perez-Marrero, A. U. Khan, L. S. Wooldridge, G. L. Davis and S. A. MacDiarmid J Urol 2010; 183: 1438-1443. J Urol, 2011. 185: 362; author reply 362.
https://www.ncbi.nlm.nih.gov/pubmed/21092997
667. Ramirez-Garcia, I., *et al.* Efficacy of transcutaneous stimulation of the posterior tibial nerve compared to percutaneous stimulation in idiopathic overactive bladder syndrome: Randomized control trial. Neurourol Urodyn, 2019. 38: 261.
https://www.ncbi.nlm.nih.gov/pubmed/30311692

668. Booth, J., *et al.* The effectiveness of transcutaneous tibial nerve stimulation (TTNS) for adults with overactive bladder syndrome: A systematic review. Neurourol Urodyn, 2018. 37: 528.
https://www.ncbi.nlm.nih.gov/pubmed/28731583
669. Wang, M., *et al.* Percutaneous tibial nerve stimulation for overactive bladder syndrome: a systematic review and meta-analysis. Int Urogynecol J, 2020. 31: 2457.
https://www.ncbi.nlm.nih.gov/pubmed/32681345
670. Chapple, C., *et al.* Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial. BJU Int, 2014. 114: 418.
https://www.ncbi.nlm.nih.gov/pubmed/24552358
671. Kaplan, S.A., *et al.* Efficacy and safety of fesoterodine 8 mg in subjects with overactive bladder after a suboptimal response to tolterodine ER. Int J Clin Pract, 2014. 68: 1065.
https://www.ncbi.nlm.nih.gov/pubmed/24898471
672. Bianco, F.J., *et al.* A randomized, double-blind, solifenacin succinate versus placebo control, phase 4, multicenter study evaluating urinary continence after robotic assisted radical prostatectomy. J Urol, 2015. 193: 1305.
https://www.ncbi.nlm.nih.gov/pubmed/25281778
673. Yang, R., *et al.* Efficacy of solifenacin in the prevention of short-term complications after laparoscopic radical prostatectomy. J Int Med Res, 2017. 45: 2119.
https://www.ncbi.nlm.nih.gov/pubmed/28661264
674. Chapple, C.R., *et al.* Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability. Neurourol Urodyn, 2014. 33: 17.
https://www.ncbi.nlm.nih.gov/pubmed/24127366
675. Maman, K., *et al.* Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol, 2014. 65: 755.
https://www.ncbi.nlm.nih.gov/pubmed/24275310
676. MacDiarmid, S., *et al.* Mirabegron as Add-On Treatment to Solifenacin in Patients with Incontinent Overactive Bladder and an Inadequate Response to Solifenacin Monotherapy: Responder Analyses and Patient-Reported Outcomes from the BESIDE Study [corrected]. J Urol, 2016. 196: 809.
https://www.ncbi.nlm.nih.gov/pubmed/27063854
677. Su, S., *et al.* The efficacy and safety of mirabegron on overactive bladder induced by benign prostatic hyperplasia in men receiving tamsulosin therapy: A systematic review and meta-analysis. Medicine (Baltimore), 2020. 99: e18802.
https://www.ncbi.nlm.nih.gov/pubmed/31977871
678. Kotecha, P., *et al.* Use of Duloxetine for Postprostatectomy Stress Urinary Incontinence: A Systematic Review. Eur Urol Focus, 2021. 7: 618.
https://www.ncbi.nlm.nih.gov/pubmed/32605820
679. Toia, B., *et al.* Bulking for stress urinary incontinence in men: A systematic review. Neurourol Urodyn, 2019. 38: 1804.
https://www.ncbi.nlm.nih.gov/pubmed/31321804
680. Imamoglu, M.A., *et al.* The comparison of artificial urinary sphincter implantation and endourethral macroplastique injection for the treatment of postprostatectomy incontinence. Eur Urol, 2005. 47: 209.
https://www.ncbi.nlm.nih.gov/pubmed/15661416
681. Sacco E, B.R.G.C.V.L.B.P. 43rd Annual Congress of the Italian Urodynamic Society, Rome, Italy, 13th-15th June 2019. Neurourol Urodyn, 2019. 38 Suppl 2: S4.
https://www.ncbi.nlm.nih.gov/pubmed/31179575
682. Nguyen, L., *et al.* The use of urethral bulking injections in post-prostatectomy stress urinary incontinence: A narrative review of the literature. Neurourol Urodyn, 2019. 38: 2060.
https://www.ncbi.nlm.nih.gov/pubmed/31432568
683. Choiniere, R., *et al.* Evaluation of Benefits and Harms of Surgical Treatments for Post-radical Prostatectomy Urinary Incontinence: A Systematic Review and Meta-analysis. Eur Urol Focus, 2022. 8: 1042.
https://www.ncbi.nlm.nih.gov/pubmed/34563480
684. Kowalik, C.R., *et al.* Results of an innovative bulking agent in patients with stress urinary incontinence who are not optimal candidates for mid-urethral sling surgery. Neurourol Urodyn, 2018. 37: 339.
https://www.ncbi.nlm.nih.gov/pubmed/28452427
685. Stothers, L., *et al.* Delayed hypersensitivity and systemic arthralgia following transurethral collagen

injection for stress urinary incontinence. J Urol, 1998. 159: 1507.
https://www.ncbi.nlm.nih.gov/pubmed/9554343
686. Malizia, A.A., Jr., *et al.* Migration and granulomatous reaction after periurethral injection of polytef (Teflon). JAMA, 1984. 251: 3277.
https://www.ncbi.nlm.nih.gov/pubmed/6374180
687. Pannek, J., *et al.* Particle migration after transurethral injection of carbon coated beads for stress urinary incontinence. J Urol, 2001. 166: 1350.
https://www.ncbi.nlm.nih.gov/pubmed/11547072
688. Cornu, J.N., *et al.* Mid-term evaluation of the transobturator male sling for post-prostatectomy incontinence: focus on prognostic factors. BJU Int, 2011. 108: 236.
https://www.ncbi.nlm.nih.gov/pubmed/20955265
689. Cornel, E.B., *et al.* Can advance transobturator sling suspension cure male urinary postoperative stress incontinence? J Urol, 2010. 183: 1459.
https://www.ncbi.nlm.nih.gov/pubmed/20172561
690. Zeif, H.-J., *et al.* The Male Sling for Post-Radical Prostatectomy Urinary Incontinence: Urethral Compression versus Urethral Relocation or What is Next? Brit J Med Surg Urol, 2010. 3: 134.
http://www.sciencedirect.com/science/article/pii/S1875974210000248
691. Bole, R., *et al.* Narrative review of male urethral sling for post-prostatectomy stress incontinence: sling type, patient selection, and clinical applications. Transl Androl Urol, 2021. 10: 2682.
https://www.ncbi.nlm.nih.gov/pubmed/34295753
692. Chen, Y.C., *et al.* Surgical treatment for urinary incontinence after prostatectomy: A meta-analysis and systematic review. PLoS One, 2017. 12: e0130867.
https://www.ncbi.nlm.nih.gov/pubmed/28467435
693. Guacheta Bomba, P.L., *et al.* Effectiveness of surgical management with an adjustable sling versus an artificial urinary sphincter in patients with severe urinary postprostatectomy incontinence: a systematic review and network meta-analysis. Ther Adv Urol, 2019. 11: 1756287219875581.
https://www.ncbi.nlm.nih.gov/pubmed/31632464
694. Abrams, P., *et al.* Outcomes of a Noninferiority Randomised Controlled Trial of Surgery for Men with Urodynamic Stress Incontinence After Prostate Surgery (MASTER). Eur Urol, 2021. 79: 812.
https://www.ncbi.nlm.nih.gov/pubmed/33551297
695. Grabbert, M., *et al.* Extended follow-up of the AdVance XP male sling in the treatment of male urinary stress incontinence after 48 months: Results of a prospective and multicenter study. Neurourol Urodyn, 2019. 38: 1973.
https://www.ncbi.nlm.nih.gov/pubmed/31297894
696. Husch, T., *et al.* The AdVance and AdVanceXP male sling in urinary incontinence: is there a difference? World J Urol, 2018. 36: 1657.
https://www.ncbi.nlm.nih.gov/pubmed/29728764
697. Malval, B., *et al.* Long-term outcomes of I-Stop TOMS male sling implantation for post-prostatectomy incontinence management. Prog Urol, 2017. 27: 1084.
https://www.ncbi.nlm.nih.gov/pubmed/29097039
698. Silva, L.A.D., *et al.* Adjustable sling for the treatment of post-prostatectomy urinary incontinence: systematic review and meta-analysis. Einstein (Sao Paulo), 2019. 17: eRW4508.
https://www.ncbi.nlm.nih.gov/pubmed/31553360
699. Bauer, R.M., *et al.* Results of the AdVance transobturator male sling after radical prostatectomy and adjuvant radiotherapy. Urology, 2011. 77: 474.
https://www.ncbi.nlm.nih.gov/pubmed/21167563
700. Wright, H.C., *et al.* Transobturator sling for post-prostatectomy incontinence: radiation's effect on efficacy/satisfaction. Can J Urol, 2017. 24: 8998.
https://www.ncbi.nlm.nih.gov/pubmed/28971786
701. Meisterhofer, K., *et al.* Male Slings for Postprostatectomy Incontinence: A Systematic Review and Meta-analysis. Eur Urol Focus, 2020. 6: 575.
https://www.ncbi.nlm.nih.gov/pubmed/30718160
702. Abrams, P., *et al.* Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. Neurourol Urodyn, 2010. 29: 213.
https://www.ncbi.nlm.nih.gov/pubmed/20025020
703. Gill, B.C., *et al.* Patient perceived effectiveness of a new male sling as treatment for post-prostatectomy incontinence. J Urol, 2010. 183: 247.
https://www.ncbi.nlm.nih.gov/pubmed/19913826

704. Rehder, P., *et al.* The 1 year outcome of the transobturator retroluminal repositioning sling in the treatment of male stress urinary incontinence. BJU Int, 2010. 106: 1668.
https://www.ncbi.nlm.nih.gov/pubmed/20518761
705. Navalon-Monllor, V., *et al.* Long-term follow-up for the treatment of male urinary incontinence with the Remeex system. Actas Urol Esp, 2016. 40: 585.
https://www.ncbi.nlm.nih.gov/pubmed/27237411
706. Shamout, S., *et al.* Short-term evaluation of the adjustable bulbourethral male sling for post-prostatectomy urinary incontinence. Low Urin Tract Symptoms, 2019. 11: O111.
https://www.ncbi.nlm.nih.gov/pubmed/29869450
707. Esquinas, C., *et al.* Effectiveness of Adjustable Transobturator Male System (ATOMS) to Treat Male Stress Incontinence: A Systematic Review and Meta-Analysis. Adv Ther, 2019. 36: 426.
https://www.ncbi.nlm.nih.gov/pubmed/30560525
708. Lima, J.P., *et al.* Argus T(R) versus Advance(R) Sling for postprostatectomy urinary incontinence: A randomized clinical trial. Int Braz J Urol, 2016. 42: 531.
https://www.ncbi.nlm.nih.gov/pubmed/27286117
709. Kim, J. Abstracts of the 35th Annual Congress of the Italian Urodynamics Society. June 9011, 2011. Turin, Italy. Neurourol Urodyn, 2011. 30 Suppl 1: 1.
https://www.ncbi.nlm.nih.gov/pubmed/21661030
710. Bochove-Overgaauw, D.M., *et al.* An adjustable sling for the treatment of all degrees of male stress urinary incontinence: retrospective evaluation of efficacy and complications after a minimal followup of 14 months. J Urol, 2011. 185: 1363.
https://www.ncbi.nlm.nih.gov/pubmed/21334683
711. Dalpiaz, O., *et al.* Mid-term complications after placement of the male adjustable suburethral sling: a single center experience. J Urol, 2011. 186: 604.
https://www.ncbi.nlm.nih.gov/pubmed/21684559
712. Loertzer, H., *et al.* Retropubic vs transobturator Argus adjustable male sling: Results from a multicenter study. Neurourol Urodyn, 2020. 39: 987.
https://www.ncbi.nlm.nih.gov/pubmed/32125722
713. Angulo, J.C., *et al.* Systematic review and meta-analysis comparing Adjustable Transobturator Male System (ATOMS) and Adjustable Continence Therapy (ProACT) for male stress incontinence. PLoS One, 2019. 14: e0225762.
https://www.ncbi.nlm.nih.gov/pubmed/31790490
714. Hubner, W.A., *et al.* Adjustable bulbourethral male sling: experience after 101 cases of moderate-to-severe male stress urinary incontinence. BJU Int, 2011. 107: 777.
https://www.ncbi.nlm.nih.gov/pubmed/20964801
715. Muhlstadt, S., *et al.* Five-year experience with the adjustable transobturator male system for the treatment of male stress urinary incontinence: a single-center evaluation. World J Urol, 2017. 35: 145.
https://www.ncbi.nlm.nih.gov/pubmed/27156092
716. Cestari, A., *et al.* Retropubic Intracorporeal Placement of a Suburethral Autologous Sling During Robot-Assisted Radical Prostatectomy to Improve Early Urinary Continence Recovery: Preliminary Data. J Endourol, 2015. 29: 1379.
https://www.ncbi.nlm.nih.gov/pubmed/26131781
717. Kojima, Y., *et al.* Bladder neck sling suspension during robot-assisted radical prostatectomy to improve early return of urinary continence: a comparative analysis. Urology, 2014. 83: 632.
https://www.ncbi.nlm.nih.gov/pubmed/24387929
718. Cestari, A., *et al.* Simple vs six-branches autologous suburethral sling during robot-assisted radical prostatectomy to improve early urinary continence recovery: prospective randomized study. J Robot Surg, 2017. 11: 415.
https://www.ncbi.nlm.nih.gov/pubmed/28078523
719. Nguyen, H.G., *et al.* A Randomized Study of Intraoperative Autologous Retropubic Urethral Sling on Urinary Control after Robotic Assisted Radical Prostatectomy. J Urol, 2017. 197: 369.
https://www.ncbi.nlm.nih.gov/pubmed/27693447
720. Kretschmer, A., *et al.* Surgical Treatment of Male Postprostatectomy Incontinence: Current Concepts. Eur Urol Focus, 2017. 3: 364.
https://www.ncbi.nlm.nih.gov/pubmed/29174616
721. Ostrowski, I., *et al.* Preliminary outcomes of the European multicentre experience with the ZSI 375 artificial urinary sphincter for treatment of stress urinary incontinence in men. Cent European J Urol, 2019. 72: 263.
https://www.ncbi.nlm.nih.gov/pubmed/31720028

722. Lima, S.V.C., *et al.* Artificial sphincter "BR - SL - AS 904" in the treatment of urinary incontinence after radical prostatectomy: efficacy, practicality and safety in a prospective and multicenter study. Int Braz J Urol, 2018. 44: 1215.
https://www.ncbi.nlm.nih.gov/pubmed/30325613
723. Suh, Y.S., *et al.* Long-term outcomes of primary implantation and revisions of artificial urinary sphincter in men with stress urinary incontinence. Neurourol Urodyn, 2017. 36: 1930.
https://www.ncbi.nlm.nih.gov/pubmed/28169469
724. Collado Serra, A., *et al.* Prospective follow-up study of artificial urinary sphincter placement preserving the bulbospongiosus muscle. Neurourol Urodyn, 2017. 36: 1387.
https://www.ncbi.nlm.nih.gov/pubmed/27654121
725. Viers, B.R., *et al.* Long-Term Quality of Life and Functional Outcomes among Primary and Secondary Artificial Urinary Sphincter Implantations in Men with Stress Urinary Incontinence. J Urol, 2016. 196: 838.
https://www.ncbi.nlm.nih.gov/pubmed/26997310
726. Leon, P., *et al.* Long-term functional outcomes after artificial urinary sphincter implantation in men with stress urinary incontinence. BJU Int, 2015. 115: 951.
https://www.ncbi.nlm.nih.gov/pubmed/24958004
727. Trigo Rocha, F., *et al.* A prospective study evaluating the efficacy of the artificial sphincter AMS 800 for the treatment of postradical prostatectomy urinary incontinence and the correlation between preoperative urodynamic and surgical outcomes. Urology, 2008. 71: 85.
https://www.ncbi.nlm.nih.gov/pubmed/18242371
728. Lai, H.H., *et al.* Urodynamic testing in evaluation of postradical prostatectomy incontinence before artificial urinary sphincter implantation. Urology, 2009. 73: 1264.
https://www.ncbi.nlm.nih.gov/pubmed/19371935
729. Queissert, F., *et al.* High/low-volume center experience predicts outcome of AMS 800 in male stress incontinence: Results of a large middle European multicenter case series. Neurourol Urodyn, 2020. 39: 1856.
https://www.ncbi.nlm.nih.gov/pubmed/32567709
730. Dosanjh, A., *et al.* A national study of artificial urinary sphincter and male sling implantation after radical prostatectomy in England. BJU Int, 2020. 125: 467.
https://www.ncbi.nlm.nih.gov/pubmed/31755624
731. Llorens, C., *et al.* Urinary artificial sphincter ZSI 375 for treatment of stress urinary incontinence in men: 5 and 7 years follow-up report. Urologia, 2017. 84: 263.
https://www.ncbi.nlm.nih.gov/pubmed/28525665
732. Srivastava, A., *et al.* Causes of Artificial Urinary Sphincter Failure and Strategies for Surgical Revision: Implications of Device Component Survival. Eur Urol Focus, 2019. 5: 887.
https://www.ncbi.nlm.nih.gov/pubmed/29545058
733. Dupuis, H.G.A., *et al.* Early Efficacy and Safety Outcomes of Artificial Urinary Sphincter for Stress Urinary Incontinence Following Radical Prostatectomy or Benign Prostatic Obstruction Surgery: Results of a Large Multicentric Study. Eur Urol Focus, 2022. 8: 1053.
https://www.ncbi.nlm.nih.gov/pubmed/34548254
734. Van der Aa, F., *et al.* The artificial urinary sphincter after a quarter of a century: a critical systematic review of its use in male non-neurogenic incontinence. Eur Urol, 2013. 63: 681.
https://www.ncbi.nlm.nih.gov/pubmed/23219375
735. Queissert, F., *et al.* Artificial Urinary Sphincter Cuff Size Predicts Outcome in Male Patients Treated for Stress Incontinence: Results of a Large Central European Multicenter Cohort Study. Int Neurourol J, 2019. 23: 219.
https://www.ncbi.nlm.nih.gov/pubmed/31607101
736. Kaiho, Y., *et al.* Surgical and Patient Reported Outcomes of Artificial Urinary Sphincter Implantation: A Multicenter, Prospective, Observational Study. J Urol, 2018. 199: 245.
https://www.ncbi.nlm.nih.gov/pubmed/28823767
737. Sacco, E., *et al.* Artificial urinary sphincter significantly better than fixed sling for moderate post-prostatectomy stress urinary incontinence: a propensity score-matched study. BJU Int, 2021. 127: 229.
https://www.ncbi.nlm.nih.gov/pubmed/32744793
738. Bentellis, I., *et al.* Prevalence and Risk Factors of Artificial Urinary Sphincter Revision in Nonneurological Male Patients. J Urol, 2021. 206: 1248.
https://www.ncbi.nlm.nih.gov/pubmed/34184925

739. Lenfant, L., *et al.* Artificial Urinary Sphincter Implants in Men: A National Health Care Data System-Based Study to Assess Reinterventions in France. J Urol, 2025. 213: 217.
https://www.ncbi.nlm.nih.gov/pubmed/39401342
740. Heesakkers, J., *et al.* Results at 1 Year from SATURN, A European, Prospective, Multicenter Registry for Male Stress Urinary Incontinence Surgery. Eur Urol Focus, 2024. 10: 818.
https://www.ncbi.nlm.nih.gov/pubmed/38627124
741. Larson, T., *et al.* Adjustable continence therapy (ProACT) for the treatment of male stress urinary incontinence: A systematic review and meta-analysis. Neurourol Urodyn, 2019. 38: 2051.
https://www.ncbi.nlm.nih.gov/pubmed/31429982
742. Crivellaro, S., *et al.* Adjustable continence therapy (ProACT) and bone anchored male sling: Comparison of two new treatments of post prostatectomy incontinence. Int J Urol, 2008. 15: 910.
https://www.ncbi.nlm.nih.gov/pubmed/18761534
743. Martens, F.M., *et al.* ProACT for stress urinary incontinence after radical prostatectomy. Urol Int, 2009. 82: 394.
https://www.ncbi.nlm.nih.gov/pubmed/19506404
744. Roupret, M., *et al.* Management of stress urinary incontinence following prostate surgery with minimally invasive adjustable continence balloon implants: functional results from a single center prospective study. J Urol, 2011. 186: 198.
https://www.ncbi.nlm.nih.gov/pubmed/21575974
745. Tricard, T., *et al.* Adjustable continence therapy (proACT) for the treatment of male stress urinary incontinence post-prostatectomy: a systematic review and meta-analysis (2023 update). World J Urol, 2023. 41: 1793.
https://www.ncbi.nlm.nih.gov/pubmed/37311990
746. Herschorn, S., *et al.* Surgical treatment of stress incontinence in men. Neurourol Urodyn, 2010. 29: 179.
https://www.ncbi.nlm.nih.gov/pubmed/20025026
747. Gilling, P.J., *et al.* An adjustable continence therapy device for treating incontinence after prostatectomy: a minimum 2-year follow-up. BJU Int, 2008. 102: 1426.
https://www.ncbi.nlm.nih.gov/pubmed/18564132
748. Hubner, W.A., *et al.* Treatment of incontinence after prostatectomy using a new minimally invasive device: adjustable continence therapy. BJU Int, 2005. 96: 587.
https://www.ncbi.nlm.nih.gov/pubmed/16104915
749. Magistro, G., *et al.* New intraprostatic injectables and prostatic urethral lift for male LUTS. Nat Rev Urol, 2015. 12: 461.
https://www.ncbi.nlm.nih.gov/pubmed/26195444
750. Duthie, J.B., *et al.* Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev, 2011. 2011: CD005493.
https://www.ncbi.nlm.nih.gov/pubmed/22161392
751. Mangera, A., *et al.* Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). Eur Urol, 2011. 60: 784.
https://www.ncbi.nlm.nih.gov/pubmed/21782318
752. Nitti, V.W., *et al.* OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol, 2013. 189: 2186.
https://www.ncbi.nlm.nih.gov/pubmed/23246476
753. Drake, M.J., *et al.* Comparative assessment of the efficacy of onabotulinumtoxinA and oral therapies (anticholinergics and mirabegron) for overactive bladder: a systematic review and network meta-analysis. BJU Int, 2017. 120: 611.
https://www.ncbi.nlm.nih.gov/pubmed/28670786
754. Chughtai, B., *et al.* Randomized, double-blind, placebo controlled pilot study of intradetrusor injections of onabotulinumtoxinA for the treatment of refractory overactive bladder persisting following surgical management of benign prostatic hyperplasia. Can J Urol, 2014. 21: 7217.
https://www.ncbi.nlm.nih.gov/pubmed/24775575
755. Faure Walker, N.A., *et al.* Onabotulinum toxin A Injections in Men With Refractory Idiopathic Detrusor Overactivity. Urology, 2019. 123: 242.
https://www.ncbi.nlm.nih.gov/pubmed/30266377
756. Bels, J., *et al.* Long-term Follow-up of Intravesical Onabotulinum Toxin-A Injections in Male Patients with Idiopathic Overactive Bladder: Comparing Surgery-naive Patients and Patients After Prostate Surgery. Eur Urol Focus, 2021. 7: 1424.
https://www.ncbi.nlm.nih.gov/pubmed/32919951

757. Herschorn, S., *et al.* The Efficacy and Safety of OnabotulinumtoxinA or Solifenacin Compared with Placebo in Solifenacin Naive Patients with Refractory Overactive Bladder: Results from a Multicenter, Randomized, Double-Blind Phase 3b Trial. J Urol, 2017. 198: 167.
https://www.ncbi.nlm.nih.gov/pubmed/28161352
758. Lozano-Ortega, G., *et al.* The Relative Efficacy and Safety of Mirabegron and OnabotulinumtoxinA in Patients With Overactive Bladder who Have Previously Been Managed With an Antimuscarinic: A Network Meta-analysis. Urology, 2019. 127: 1.
https://www.ncbi.nlm.nih.gov/pubmed/30790650
759. Cui, Y., *et al.* Botulinum toxin-A injections for idiopathic overactive bladder: a systematic review and meta-analysis. Urol Int, 2013. 91: 429.
https://www.ncbi.nlm.nih.gov/pubmed/23970316
760. Mateu Arrom, L., *et al.* Treatment Response and Complications after Intradetrusor OnabotulinumtoxinA Injection in Male Patients with Idiopathic Overactive Bladder Syndrome. J Urol, 2020. 203: 392.
https://www.ncbi.nlm.nih.gov/pubmed/31479408
761. He, Q., *et al.* Treatment for refractory overactive bladder: a systematic review and meta-analysis of sacral neuromodulation and onabotulinumtoxinA. Int Urogynecol J, 2021. 32: 477.
https://www.ncbi.nlm.nih.gov/pubmed/32661556
762. Tutolo, M., *et al.* Efficacy and Safety of Sacral and Percutaneous Tibial Neuromodulation in Non-neurogenic Lower Urinary Tract Dysfunction and Chronic Pelvic Pain: A Systematic Review of the Literature. Eur Urol, 2018. 73: 406.
https://www.ncbi.nlm.nih.gov/pubmed/29336927
763. Venn, S.N., *et al.* Long-term results of augmentation cystoplasty. Eur Urol, 1998. 34 Suppl 1: 40.
https://www.ncbi.nlm.nih.gov/pubmed/9705554
764. Awad, S.A., *et al.* Long-term results and complications of augmentation ileocystoplasty for idiopathic urge incontinence in women. Br J Urol, 1998. 81: 569.
https://www.ncbi.nlm.nih.gov/pubmed/9598629
765. El-Azab, A.S., *et al.* The satisfaction of patients with refractory idiopathic overactive bladder with onabotulinumtoxinA and augmentation cystoplasty. Arab J Urol, 2013. 11: 344.
https://www.ncbi.nlm.nih.gov/pubmed/26558103
766. Cody, J.D., *et al.* Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy. Cochrane Database Syst Rev, 2012. 2012: CD003306.
https://www.ncbi.nlm.nih.gov/pubmed/22336788
767. Hoen, L., *et al.* Long-term effectiveness and complication rates of bladder augmentation in patients with neurogenic bladder dysfunction: A systematic review. Neurourol Urodyn, 2017. 36: 1685.
https://www.ncbi.nlm.nih.gov/pubmed/28169459
768. Chapple, C.R., *et al.* The underactive bladder: a new clinical concept? Eur Urol, 2015. 68: 351.
https://www.ncbi.nlm.nih.gov/pubmed/25770481
769. Kuo, H.C. Videourodynamic analysis of pathophysiology of men with both storage and voiding lower urinary tract symptoms. Urology, 2007. 70: 272.
https://www.ncbi.nlm.nih.gov/pubmed/17826488
770. Wang, C.C., *et al.* Videourodynamics identifies the causes of young men with lower urinary tract symptoms and low uroflow. Eur Urol, 2003. 43: 386.
https://www.ncbi.nlm.nih.gov/pubmed/12667720
771. Abarbanel, J., *et al.* Impaired detrusor contractility in community-dwelling elderly presenting with lower urinary tract symptoms. Urology, 2007. 69: 436.
https://www.ncbi.nlm.nih.gov/pubmed/17382138
772. Thomas, A.W., *et al.* The natural history of lower urinary tract dysfunction in men: minimum 10-year urodynamic follow-up of untreated detrusor underactivity. BJU Int, 2005. 96: 1295.
https://www.ncbi.nlm.nih.gov/pubmed/16287448
773. Groen, J., *et al.* Summary of European Association of Urology (EAU) Guidelines on Neuro-Urology. Eur Urol, 2016. 69: 324.
https://www.ncbi.nlm.nih.gov/pubmed/26304502
774. Osman, N.I., *et al.* Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. Eur Urol, 2014. 65: 389.
https://www.ncbi.nlm.nih.gov/pubmed/24184024
775. Vale, L., *et al.* Pathophysiological mechanisms in detrusor underactivity: Novel experimental findings. Low Urin Tract Symptoms, 2019. 11: 92.
https://www.ncbi.nlm.nih.gov/pubmed/30864243

776. Fusco, F., *et al.* Progressive bladder remodeling due to bladder outlet obstruction: a systematic review of morphological and molecular evidences in humans. BMC Urol, 2018. 18: 15.
https://www.ncbi.nlm.nih.gov/pubmed/29519236
777. Osman, N.I., *et al.* Detrusor Underactivity and the Underactive Bladder: A Systematic Review of Preclinical and Clinical Studies. Eur Urol, 2018. 74: 633.
https://www.ncbi.nlm.nih.gov/pubmed/30139634
778. Gammie, A., *et al.* Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies. Eur Urol, 2016. 69: 361.
https://www.ncbi.nlm.nih.gov/pubmed/26318706
779. Matsukawa, Y., *et al.* Development of an artificial intelligence diagnostic system for lower urinary tract dysfunction in men. Int J Urol, 2021. 28: 1143.
https://www.ncbi.nlm.nih.gov/pubmed/34342055
780. Namitome, R., *et al.* A Prediction Model of Detrusor Underactivity Based on Symptoms and Noninvasive Test Parameters in Men with Lower Urinary Tract Symptoms: An Analysis of a Large Group of Patients undergoing Pressure-Flow Studies. J Urol, 2020. 203: 779.
https://www.ncbi.nlm.nih.gov/pubmed/31647388
781. Kim, A., *et al.* Novel symptom questionnaire for the differential diagnosis of detrusor underactivity and bladder outlet obstruction in men. Aging Male, 2019. 22: 150.
https://www.ncbi.nlm.nih.gov/pubmed/29985721
782. Lee, K.S., *et al.* Does uroflowmetry parameter facilitate discrimination between detrusor underactivity and bladder outlet obstruction? Investig Clin Urol, 2016. 57: 437.
https://www.ncbi.nlm.nih.gov/pubmed/27847918
783. Wada, N., *et al.* Uroflowmetry pattern in detrusor underactivity and bladder outlet obstruction in male patients with lower urinary tract symptoms. Low Urin Tract Symptoms, 2021. 13: 361.
https://www.ncbi.nlm.nih.gov/pubmed/33648017
784. Rademakers, K.L., *et al.* Ultrasound detrusor wall thickness measurement in combination with bladder capacity can safely detect detrusor underactivity in adult men. World J Urol, 2017. 35: 153.
https://www.ncbi.nlm.nih.gov/pubmed/27447991
785. van Koeveringe, G.A., *et al.* Detrusor underactivity: a plea for new approaches to a common bladder dysfunction. Neurourol Urodyn, 2011. 30: 723.
https://www.ncbi.nlm.nih.gov/pubmed/21661020
786. Smith, P.P., *et al.* Detrusor underactivity and the underactive bladder: Symptoms, function, cause-what do we mean? ICI-RS think tank 2014. Neurourol Urodyn, 2016. 35: 312.
https://www.ncbi.nlm.nih.gov/pubmed/26872574
787. Donkelaar, S.C., *et al.* Comparison of three methods to analyze detrusor contraction during micturition in men over 50 years of age. Neurourol Urodyn, 2017. 36: 2153.
https://www.ncbi.nlm.nih.gov/pubmed/28346712
788. Jeong, S.J., *et al.* How do we diagnose detrusor underactivity? Comparison of diagnostic criteria based on an urodynamic measure. Investig Clin Urol, 2017. 58: 247.
https://www.ncbi.nlm.nih.gov/pubmed/28681034
789. Moran, E., *et al.* Evolution of male patients with detrusor underactivity and conservative treatment. Five-year follow-up. Actas Urol Esp (Engl Ed), 2021. 45: 83.
https://www.ncbi.nlm.nih.gov/pubmed/33012591
790. Fowler, C.J., *et al.* The neural control of micturition. Nat Rev Neurosci, 2008. 9: 453.
https://www.ncbi.nlm.nih.gov/pubmed/18490916
791. Ladi-Seyedian, S., *et al.* Management of non-neuropathic underactive bladder in children with voiding dysfunction by animated biofeedback: a randomized clinical trial. Urology, 2015. 85: 205.
https://www.ncbi.nlm.nih.gov/pubmed/25444633
792. Bates, T.S., *et al.* Is the conservative management of chronic retention in men ever justified? BJU Int, 2003. 92: 581.
https://www.ncbi.nlm.nih.gov/pubmed/14511038
793. Liao, L., *et al.* Randomized controlled trial of intravesical electrical stimulation for underactive bladder. BJU Int, 2023. 131: 321.
https://www.ncbi.nlm.nih.gov/pubmed/36084065
794. Huber, E.R., *et al.* [The value of intravesical electrostimulation in the treatment of acute prolonged bladder overdistension]. Urologe A, 2007. 46: 662.
https://www.ncbi.nlm.nih.gov/pubmed/17356837

795. Shen, Y.C., *et al.* Prospective, Randomized, Double-blind, Placebo-controlled, Pilot Study of Extracorporeal Shock Wave Therapy for Detrusor Underactivity/Underactive Bladder. Eur Urol Focus, 2023. 9: 524.
https://www.ncbi.nlm.nih.gov/pubmed/36437222
796. Coolen, R.L., *et al.* Transcutaneous Electrical Nerve Stimulation and Percutaneous Tibial Nerve Stimulation to Treat Idiopathic Nonobstructive Urinary Retention: A Systematic Review. Eur Urol Focus, 2021. 7: 1184.
https://www.ncbi.nlm.nih.gov/pubmed/33268327
797. Moro, C., *et al.* The effectiveness of parasympathomimetics for treating underactive bladder: A systematic review and meta-analysis. Neurourol Urodyn, 2022. 41: 127.
https://www.ncbi.nlm.nih.gov/pubmed/34816481
798. Barendrecht, M.M., *et al.* Is the use of parasympathomimetics for treating an underactive urinary bladder evidence-based? BJU Int, 2007. 99: 749.
https://www.ncbi.nlm.nih.gov/pubmed/17233798
799. Yamanishi, T., *et al.* Combination of a cholinergic drug and an alpha-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with underactive detrusor. Int J Urol, 2004. 11: 88.
https://www.ncbi.nlm.nih.gov/pubmed/14706012
800. Buckley, B.S., *et al.* Drugs for treatment of urinary retention after surgery in adults. Cochrane Database Syst Rev, 2010: CD008023.
https://www.ncbi.nlm.nih.gov/pubmed/20927768
801. Hindley, R.G., *et al.* Prostaglandin E2 and bethanechol in combination for treating detrusor underactivity. BJU Int, 2004. 93: 89.
https://www.ncbi.nlm.nih.gov/pubmed/14678375
802. Santos-Pereira, M., *et al.* Understanding underactive bladder: a review of the contemporary literature. Porto Biomed J, 2020. 5: e070.
https://www.ncbi.nlm.nih.gov/pubmed/32734011
803. Onur, R., *et al.* Sacral neuromodulation in patients with detrusor underactivity: Is biological sex an indicator? Neurourol Urodyn, 2022. 41: 847.
https://www.ncbi.nlm.nih.gov/pubmed/35181913
804. Paick, J.S., *et al.* Influence of bladder contractility on short-term outcomes of high-power potassium-titanyl-phosphate photoselective vaporization of the prostate. Urology, 2007. 69: 859.
https://www.ncbi.nlm.nih.gov/pubmed/17482922
805. Monoski, M.A., *et al.* Urodynamic predictors of outcomes with photoselective laser vaporization prostatectomy in patients with benign prostatic hyperplasia and preoperative retention. Urology, 2006. 68: 312.
https://www.ncbi.nlm.nih.gov/pubmed/16904443
806. Lee, K.H., *et al.* Recovery of Voiding Efficiency and Bladder Function in Male Patients With Non-neurogenic Detrusor Underactivity After Transurethral Bladder Outlet Surgery. Urology, 2019. 123: 235.
https://www.ncbi.nlm.nih.gov/pubmed/30308261
807. Mitchell, C.R., *et al.* Efficacy of holmium laser enucleation of the prostate in patients with non-neurogenic impaired bladder contractility: results of a prospective trial. Urology, 2014. 83: 428.
https://www.ncbi.nlm.nih.gov/pubmed/24231217
808. Zhu, Y., *et al.* Detrusor underactivity influences the efficacy of TURP in patients with BPO. Int Urol Nephrol, 2021. 53: 835.
https://www.ncbi.nlm.nih.gov/pubmed/33386583
809. Choi, S.W., *et al.* 120 W Greenlight HPS Laser Photoselective Vaporization of the Prostate for Treatment of Benign Prostatic Hyperplasia in Men with Detrusor Underactivity. Korean J Urol, 2011. 52: 824.
https://www.ncbi.nlm.nih.gov/pubmed/22216394
810. Jeong, H.J., *et al.* Effect of detrusor underactivity on surgical outcomes of holmium laser enucleation of the prostate. BJU Int, 2024. 133: 770.
https://www.ncbi.nlm.nih.gov/pubmed/38520132
811. van Kerrebroeck, P.E., *et al.* Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol, 2007. 178: 2029.
https://www.ncbi.nlm.nih.gov/pubmed/17869298

812. Chan, G., *et al.* Evaluation of pre-operative bladder contractility as a predictor of improved response rate to a staged trial of sacral neuromodulation in patients with detrusor underactivity. World J Urol, 2021. 39: 2113.
https://www.ncbi.nlm.nih.gov/pubmed/32725304
813. Chen, S.F., *et al.* Will detrusor acontractility recover after medical or surgical treatment? A longitudinal long-term urodynamic follow-up. Neurourol Urodyn, 2021. 40: 228.
https://www.ncbi.nlm.nih.gov/pubmed/33053242
814. Creta, M., *et al.* Management of Primary Bladder Neck Obstruction and Dysfunctional Voiding in Young Men: A Systematic Review and Meta-analysis. Eur Urol Focus, 2025.
https://www.ncbi.nlm.nih.gov/pubmed/39965997
815. Boyle, P., *et al.* The prevalence of lower urinary tract symptoms in men and women in four centres. The UrEpik study. BJU Int, 2003. 92: 409.
https://www.ncbi.nlm.nih.gov/pubmed/12930430
816. Kaplan, S.A., *et al.* Etiology of voiding dysfunction in men less than 50 years of age. Urology, 1996. 47: 836.
https://www.ncbi.nlm.nih.gov/pubmed/8677573
817. Nitti, V.W., *et al.* Lower urinary tract symptoms in young men: videourodynamic findings and correlation with noninvasive measures. J Urol, 2002. 168: 135.
https://www.ncbi.nlm.nih.gov/pubmed/12050507
818. Gupta, N.K., *et al.* Role of videourodynamics in the identification of causes of lower urinary tract symptoms and low uroflow in young men. Urol Ann, 2022. 14: 332.
https://www.ncbi.nlm.nih.gov/pubmed/36505983
819. Poulsen, E.U., *et al.* Symptomatology and urodynamic findings in younger males with bladder neck dysfunction. Scand J Urol Nephrol Suppl, 1989. 125: 59.
https://www.ncbi.nlm.nih.gov/pubmed/2633320
820. El Khoury, J., *et al.* Primary bladder neck obstruction in men: The importance of urodynamic assessment and cystourethrography in measuring its severity. Neurourol Urodyn, 2024. 43: 874.
https://www.ncbi.nlm.nih.gov/pubmed/38390751
821. Yani, M.S., *et al.* Impaired Ability to Relax Pelvic Floor Muscles in Men With Chronic Prostatitis/ Chronic Pelvic Pain Syndrome. Phys Ther, 2022. 102.
https://www.ncbi.nlm.nih.gov/pubmed/35576002
822. Schifano, N., *et al.* Patients presenting with lower urinary tract symptoms who most deserve to be investigated for primary bladder neck obstruction. Sci Rep, 2021. 11: 4167.
https://www.ncbi.nlm.nih.gov/pubmed/33603071
823. Jeong, S.J., *et al.* Chronic lower urinary tract symptoms in young men without symptoms of chronic prostatitis: urodynamic analyses in 308 men aged 50 years or younger. Korean J Urol, 2014. 55: 341.
https://www.ncbi.nlm.nih.gov/pubmed/24868339
824. Kaplan, S.A., *et al.* Pseudodyssynergia (contraction of the external sphincter during voiding) misdiagnosed as chronic nonbacterial prostatitis and the role of biofeedback as a therapeutic option. J Urol, 1997. 157: 2234.
https://www.ncbi.nlm.nih.gov/pubmed/9146624
825. Di Girolamo, M., *et al.* MRI and MR voiding cystourethrography in the evaluation of male primary bladder neck obstruction: preliminary experience. Abdom Radiol (NY), 2022. 47: 746.
https://www.ncbi.nlm.nih.gov/pubmed/34870729
826. Trockman, B.A., *et al.* Primary bladder neck obstruction: urodynamic findings and treatment results in 36 men. J Urol, 1996. 156: 1418.
https://www.ncbi.nlm.nih.gov/pubmed/8808886
827. Cornel, E.B., *et al.* The effect of biofeedback physical therapy in men with Chronic Pelvic Pain Syndrome Type III. Eur Urol, 2005. 47: 607.
https://www.ncbi.nlm.nih.gov/pubmed/15826751
828. Sureka, S.K., *et al.* Clinical and Urodynamic Predictors for Failure of Medical Management with Alpha Blockers in PBNO: A Retrospective Cohort Analysis. Urology, 2023. 179: 101.
https://www.ncbi.nlm.nih.gov/pubmed/37348659
829. Sudrania, M.K., *et al.* Urodynamic outcomes of tamsulosin in the treatment of primary bladder neck obstruction in men. Indian J Urol, 2018. 34: 34.
https://www.ncbi.nlm.nih.gov/pubmed/29343910
830. Mittal, A., *et al.* Evaluating the Optimal Approach: Effectiveness of Medical vs. Surgical Treatment for Primary Bladder Neck Obstruction in Young Males. Cureus, 2025. 17: e81072.
https://www.ncbi.nlm.nih.gov/pubmed/40271312

831. Sacco, E., *et al.* OnabotulinumtoxinA injection therapy in men with LUTS due to primary bladder-neck dysfunction: objective and patient-reported outcomes. Neurourol Urodyn, 2014. 33: 142. https://www.ncbi.nlm.nih.gov/pubmed/23868794

8. CONFLICT OF INTEREST

All members of the EAU Non-neurogenic MLUTS Guidelines Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is reported below and is also publicly accessible through the European Association of Urology website: http://uroweb.org/guidelines.

Disclosures: The EAU Guidelines Office certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following:

Jean-Nicolas Cornu certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g. employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received or pending), are the following:

M. Baboudjian reported serving as a company consultant to Coloplast; receiving company speaker honoraria from Ambu A/S and Accord Healthcare; and receiving honoraria or consultation fees from Rocamed and Boston Scientific. M. Creta reported participating in company-sponsored speaker's training events with Medac Pharma S.r.l. J.-N. Cornu reported serving as a company consultant to STIMULI Technology (French), AbbVie, Boston Scientific, Coloplast, B. Braun Medical, Stimuli Technology, Medtronic France S.A.S. Stimuli Technology and Boston Scientific. C. De Nunzio reported receiving company speaker honoraria from Accord, Bayern Ferring, Janssen, Pierre fabre, Sanophy and Ipsen; receiving fellowship and travel grants from Ipsen, AB Medica, Biostylogit, Pierre fabre, Janssen, Idipharma; and participating in trials for Stimuli Technology, Janssen, Ipsen, Bayer, Teleflex and Pierre fabre. D. Elterman reported serving as a company consultant to Boston Scientific, Medi-Tate Ltd., Olympus Corporation, Procept Biorobotics, Zenflow, Inc., Urotronic, Medtronic Inc. and Laborie Medical Technologies Europe B.V; and receiving company speaker honoraria from Atellas Pharma. H. Hashim reported serving as a company consultant to Astellas, Boston Scientific, Medtronic and Tensi +; receiving company speaker honoraria from Astellas and Medtronic; serving as Co-Chair of the International Continence Society (ICS), and as Journal Associate Editor for Neurourology and Urodynamics and BJUI Compass; and participating in clinical trials with Astellas, Medtronic, and Boston. T.R.W. Herrmann reported serving as a company consultant to Karl Storz SE & Co. KG. S. Malde reported receiving honoraria or consultation fees from Medtronic. C. Netsch reported serving as a company consultant to Lisa Laser, Olympus, KLS-Martin, Biolitec, and Richard Wolf GmbH; receiving company speaker honoraria from Richard Wolf GmbH and Richard Wolf; and receiving honoraria or consultation fees from Boston Scientific. M. Rieken reported serving as company consultant to Schwabe Pharma and received speaker honoraria from Astellas Pharma, Boston Scientific and Schwabe Pharma. V. Sakalis reported serving as a company consultant to Ipsen Epe; receiving fellowship or travel grants from Anastasios Mavrogenis S.A. and Ariti S.A.; and receiving grants or research support from Demo Pharmaceutical Industry. M. Tutolo reported receiving company speaker honoraria from Pierre Fabre. M. Karavitakis, M.B. Duran, L. Moris, and N. Pyrgidis have nothing to declare.

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

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