GUIDELINES ON MALE LOWER URINARY TRACT SYMPTOMS (LUTS), INCLUDING BENIGN PROSTATIC OBSTRUCTION (BPO)

(Text update February 2012)

M. Oelke (chair), A. Bachmann, A. Descazeaud, M. Emberton, S. Gravas, M.C. Michel, J. N'Dow, J. Nordling, J.J. de la Rosette

The EAU Guideline on Male LUTS is a symptom-orientated guideline that mainly reviews LUTS secondary to benign prostatic enlargement (BPE) or benign prostatic obstruction (BPO), detrusor overactivity or overactive bladder, and nocturia due to nocturnal polyuria in men aged 40 years or older. The multifactorial aetiology of LUTS is illustrated in Figure 1. An update of these guidelines will be presented in the course of 2013.

Assessment

Systematic diagnostic work-up is recommended (Figure 2). History, symptom and quality-of-life questionnaire, physical examination, urinalysis, blood analysis, ultrasonography (US) of the prostate, bladder and kidneys, as well as uroflowmetry and measurement of post-void residual urine are recommended in all patients. Optional tests are bladder diary in men with urinary frequency or nocturia; computer-urodynamic evaluation before surgical treatment should be performed in men who:

- cannot void ≥ 150 ml;
- have a maximum flow rate ≥ 15 mL/s;
- are < 50 or > 80 years of age;
- can void but have post-void residual urine > 300 mL;

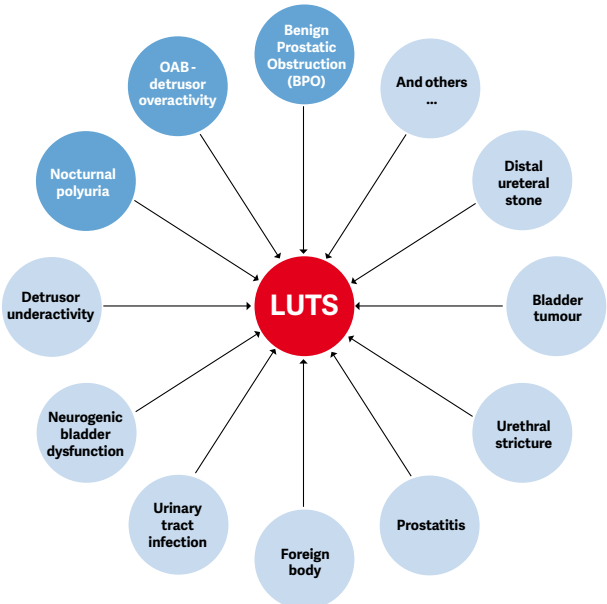

Figure 1: Causes of male lower urinary tract symptoms (LUTS)

- are suspicious of having neurogenic bladder dysfunction;
- have bilateral hydronephrosis;
- had radical pelvic surgery or;
- had previous unsuccessful (invasive) treatment.

Note that only the diagnosis of nocturnal polyuria (> 33% of the 24-hour urine excretion over night) can be made by the bladder diary, whereas the diagnosis of all other forms of non-neurogenic benign forms of LUTS in men aged 40 years or older is mainly made by exclusion.

Treatment

The level of evidence and the grade of recommendation (according to the Oxford Centre for Evidence-Based Medicine

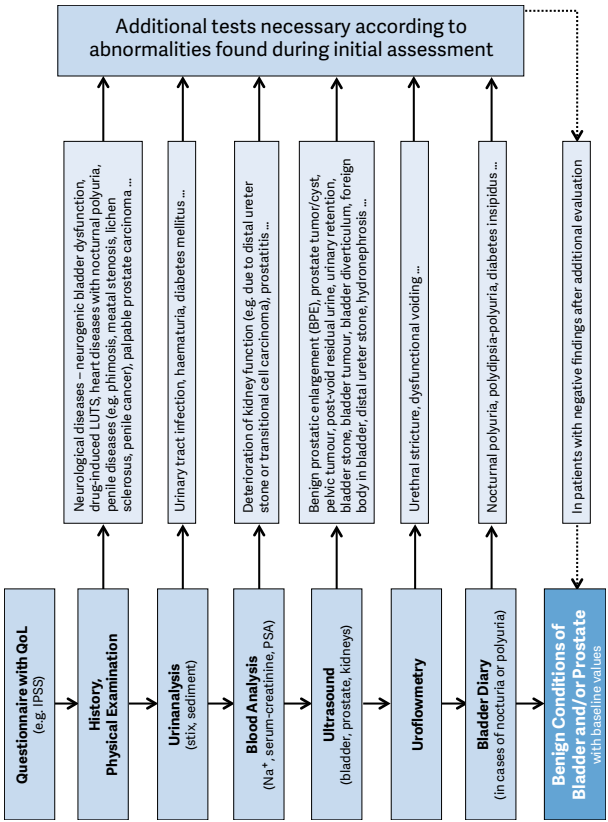

Figure 2: Assessment algorithm of LUTS in men aged 40 years or older

[CEBM]) for each treatment option are summarised in Table 1.

Conservative treatment

Watchful waiting (WW) is suitable for mild-to-moderate uncomplicated LUTS. It includes education, re-assurance, life-style advice, and periodic monitoring.

Drug treatment

Drugs used for the treatment of various forms of male LUTS are listed in Table 2.

Table 2: Key pharmacokinetic properties and standard doses of drugs licensed in Europe for the treatment of LUTS

Drug (class)	t_{max} [hours]	t½ [hours]	Recommended daily dose
α_1-adrenoceptor antagonists (for treating symptoms of "BPH")			
Alfuzosin IR	1.5	4-6	3 x 2.5 mg
Alfuzosin SR	3	8	2 x 5 mg
Alfuzosin XL	9	11	1 x 10 mg
Doxazosin IR	2-3	20	1 x 2-8 mg
Doxazosin GITS	8-12	20	1 x 4-8 mg
Silodosin	2.5	11-18	1 x 4-8 mg
Tamsulosin MR	6	10-13	1 x 0.4 mg
Tamsulosin OCAS	4-6	14-15	1 x 0.4 mg
Terazosin	1-2	8-14	1 x 5-10 mg
5α-reductase inhibitors (for treating benign prostatic enlargement due to BPH)			
Dutasteride	1-3	3-5 weeks	1 x 0.5 mg
Finasteride	2	6-8	1 x 5 mg

Antimuscarinic drugs (for treating OAB/storage symptoms)			
Darifenacin	7	13 - 19	1 x 7.5-15 mg
Fesoterodine	5	7	1 x 4-8 mg
Oxybutynin IR	0.5 - 1	2 - 4	3-4 x 2.5-5 mg
Oxybutynin ER	5	16	2-3 x 5 mg
Propiverine	2.5	13 - 20	2-3 x 15 mg
Propiverine ER	7	20	1 x 30 mg
Solifenacin	4 - 6	45 - 68	1 x 5-10 mg
Tolterodine IR	1 - 3	2-10	2 x 1-2 mg
Tolterodine ER	4	6 - 10	1 x 4 mg
Trospium chloride	4 - 6	5 - 15	3 x 10-15 mg or 2 x 10-20 mg
Antidiuretic (for treating nocturnal polyuria)			
Desmopressin	1-2	3	1 x 0.1-0.4 mg orally before sleeping
Phosphodiesterase 5 Inhibitors (for treating erectile dysfunction ± male LUTS [experimental])			
Sildenafil	1 (0.5-2) *	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1 (0.5-2) *	4-5	2 x 10 mg

*ER = extended release; GITS = gastrointestinal therapeutic system; IR = immediate release; MR = modified release; OCAS = oral controlled absorption system; SR = sustained release; t_{max} = time to maximum plasma concentration; t½ = elimination half-life. *dependent on food intake (i.e. slower resorption of the drug and an increase in t_{max} by approximately 1 hour after a fatty meal).*

α_1-adrenoceptor antagonists (α_1-blockers) are often the first-line drug treatment of male LUTS because of their rapid onset of action and good efficacy. They are also used intermittently in LUTS of fluctuating symptom intensity. The main

α_1-blockers are alfuzosin, doxazosin, tamsulosin and terazosin. All α_1-blockers have a similar efficacy in mild, moderate, or severe LUTS and in different age groups. Efficacy may be better with smaller prostates (< 40 mL). Some patients still require surgical treatment because α_1-blockers do not reduce prostate size or prevent acute urinary retention. α_1-blocker efficacy is maintained over at least 4 years. The commonest side effects of α_1-blockers are asthenia, dizziness and (orthostatic) hypotension.

5α-reductase inhibitors should only be considered in men with bothersome moderate-to-severe LUTS and enlarged prostates (prostate volume > 40 mL) or elevated PSA concentration (> 1.4-1.6 µg/L). 5α-reductase inhibitors are only suitable for long-term treatment (over many years) because of their slow onset of action. Dutasteride and finasteride are equally effective. Symptom reduction may not be better than placebo in patients with prostates < 40 mL. 5α-reductase inhibitors reduce LUTS more slowly than α_1-blockers and, in finasteride, less effectively. The greater the baseline prostate volume (or serum PSA concentration), the faster and more pronounced the symptomatic benefit of dutasteride. 5α-reductase inhibitors, but not α_1-blockers, reduce the long-term (> 1 year) risk of acute urinary retention or need for surgery. The most relevant side effects include reduced libido, erectile dysfunction and ejaculation disorders. About 1-2% of patients develop gynaecomastia (breast enlargement with breast or nipple tenderness).

Muscarinic receptor antagonists may benefit men with smaller PSA levels (smaller prostates). Tolterodine significantly reduced urgency incontinence, daytime or 24-hour frequency, and urgency-related voiding compared to placebo. Nocturia, urgency and the International Prostate Symptom Score (IPSS) were also reduced, though without statistical significance.

Although studies have been carried out with tolterodine or fesoterodine, other antimuscarinic agents are likely to show similar effects. Muscarinic receptor antagonists are generally well tolerated. Adverse effects include dry mouth, constipation, micturition difficulties, nasopharyngitis and dizziness. An increase in post-void residual (PVR) urine in men without BPO is minimal. Antimuscarinic drugs are not recommended in men with BPO because of a theoretical decrease in bladder strength, which might be associated with PVR or urinary retention. However, short-term treatment with antimuscarinic drugs in men with BPO is safe. There are no published long-term studies addressing efficacy. On this basis, antimuscarinic drugs, especially in men with BPO, should be prescribed with caution, and regular re-evaluations of IPSS and PVR are advised.

Plant extracts (phytotherapy): no specific recommendations can be made about phytotherapy in male LUTS because of product heterogeneity, lack of regulatory framework, and research methodological problems.

Desmopressin is a synthetic analogue of the antidiuretic hormone, arginine vasopressin, which plays a key role in body water homoeostasis and urine production. Desmopressin is used to treat nocturia due to nocturnal polyuria in adults. The clinical effects (urine volume decrease, increase in urine osmolality) last about 8-12 hours. The most frequent adverse events are headache, nausea, diarrhoea, abdominal pain, dizziness, dry mouth, and hyponatremia (serum sodium concentration <130 mmol/L). Peripheral oedema and hypertension were reported with long-term treatment. Serum sodium concentration should be monitored regularly to detect hyponatremia. The risk of hyponatremia increases with age, lower serum sodium concentration at baseline, and higher basal 24-hour urine volume per bodyweight.

Combination therapies

α_1-blocker + 5α-reductase inhibitor are best prescribed long term (> 12 months) to men with moderate-to-severe LUTS at risk of disease progression (e.g. higher prostate volume, higher PSA concentration, advanced age). Combination treatment is better than monotherapy at reducing symptoms and improving Q_{max}, and better than α_1-blockers at reducing the risk of acute urinary retention and the need for surgery. The α_1-blocker may be discontinued after 6 months in men with moderate LUTS at baseline, but longer-term combination therapy is beneficial in severe LUTS (IPSS > 20). Adverse events of both drug classes have been reported.

α_1-blocker + muscarinic receptor antagonist are more efficacious in reducing voiding frequency, nocturia, or IPSS than α_1-blockers or placebo alone. Furthermore, combination treatment significantly reduced urgency urinary incontinence episodes and urgency and increased quality of life. Persistent LUTS during α_1-blocker treatment can be reduced by the addition of a muscarinic receptor antagonist (tolterodine) especially if there is detrusor overactivity. Adverse events of both drug classes are reported. PVR measurement is recommended during combination treatment to assess increased PVR or urinary retention.

Phosphodiesterase 5 inhibitors (PDE5Is) are still experimental and should not be used routinely.

Summary conservative and/or medical treatment

Behavioural with or without medical treatments are usually the first choice of therapy. A flowchart illustrating conservative and medical treatment choices according to evidence-based medicine and patients' profiles is provided in Figure 3.

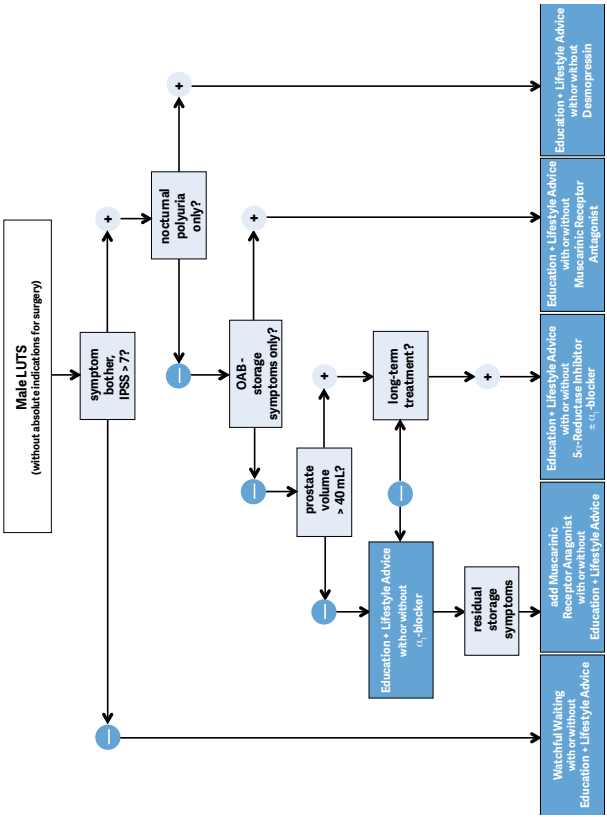

Figure 3: Treatment algorithm of male LUTS using medical and/or conservative treatment options. Treatment decisions depend on results assessed during initial evaluation (◊).The absence ("-") or presence of the condition ("+") are indicated in circles (○).

Surgical treatment

Prostate surgery is usually required when patients have experienced recurrent or refractory urinary retention, overflow incontinence, recurrent urinary tract infections, 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 had insufficient relief in LUTS or PVR after conservative or medical treatments (relative operation indications).

Transurethral Resection (TURP) or Transurethral Incision of the Prostate (TUIP): TUIP reduces BPO by splitting the bladder outlet without tissue removal and TURP removes tissue from the prostatic transition zone to reduce BPO and, secondly LUTS. The choice between TURP and TUIP is based on prostate volume with prostates < 30 mL suitable for TUIP and prostates of 30-80 mL for TURP. Urinary tract infections should be treated prior to surgery. Bipolar TURP is an alternative to monopolar TURP in moderate-to-severe LUTS secondary to BPO. It has similar efficacy but lower morbidity.

Open prostatectomy is the oldest surgical treatment modality for moderate-to-severe LUTS secondary to BPO. Removal of prostatic tissue resolves BPO and, secondarily, LUTS. Efficacy is maintained > 5 years. Perioperative complications include mortality and blood transfusion. Long-term complications are urinary incontinence and bladder neck stenosis or urethral stricture. Open prostatectomy is the most invasive, but also the most effective and durable procedure for treating LUTS/BPO. Only Holmium enucleation (HoLEP) delivers similar results, but with less morbidity. In the absence of a Holmium laser, open prostatectomy is the surgical treatment of choice for men with prostates > 80 mL.

Transurethral Microwave Therapy (TUMT) emits microwave radiation through an intra-urethral antenna to deliver heat into the prostate, which leads to tissue destruction, apoptosis, and denervation of α-receptors reducing BPO and LUTS. Treatment is well tolerated, although most patients experience perineal discomfort and urinary urgency and require pain medication prior to or during therapy. TUMT is an outpatient procedure and an alternative for older patients with co-morbidities and those at risk for anaesthesia or otherwise unsuitable for invasive treatment. Baseline parameters predicting an unfavourable outcome include small prostates, mild-to-moderate BOO, and low energy delivered during treatment.

Transurethral Needle Ablation (TUNA™) of the prostate delivers low-level radiofrequency energy to the prostate via needles inserted transurethrally into the prostatic parenchyma. The energy induces coagulation necroses in the prostatic transition zone resulting in prostate volume reduction and resolution of BPO. TUNA™ is unsuitable for prostates > 75 mL or isolated bladder neck obstruction. TUNA™ can be performed as a day-case procedure and is associated with fewer side effects than TURP (e.g. bleeding, erectile dysfunction, urinary incontinence).

Holmium Laser Enucleation (HoLEP) or Holmium Laser Resection of the Prostate (HoLRP): the holmium:yttrium-aluminum-garnet (Ho:YAG) laser with a wavelength of 2140 nm is a pulsed, solid-state laser. Resection is usually performed in prostates < 60 mL, while enucleation is used for larger glands. Patients using anticoagulant medication and those with urinary retention can be treated safely. Dysuria is the most common peri-operative complication.

Laser vaporisation of prostate (KTP, "Greenlight") leads to immediate removal of prostatic tissue, relief of BPO and,

secondarily, reduction of LUTS. Because no tissue for pathological examination can be harvested, screening for prostate cancer, if indicated, should be carried out before the laser operation. The treatment choice of tissue ablation depends on the availability of the armamentarium, patient's choice, concomitant morbidity or drug use, and experience of the surgeon.

Prostate stents are an alternative to catheterisation for men unfit for surgery. Stents require a functioning detrusor. Insertion is usually performed in an outpatient setting under local anaesthesia. Placement is confirmed by abdominal US or cystoscopy. Antibiotic prophylaxis is only necessary with a positive urine culture.

Ethanol or botulinum toxin injections into the prostate are still experimental.

Summary surgical treatment

The choice of the surgical technique depends primarily on prostate size, co-morbidities of the patient, and the ability to have anaesthesia but also on patients' preferences, willingness to accept surgery-associated side effects, availability of the surgical armamentarium, and experience of the surgeon with these operation techniques. A flowchart illustrating surgical treatment choices according to patients' profiles is provided in Figure 4.

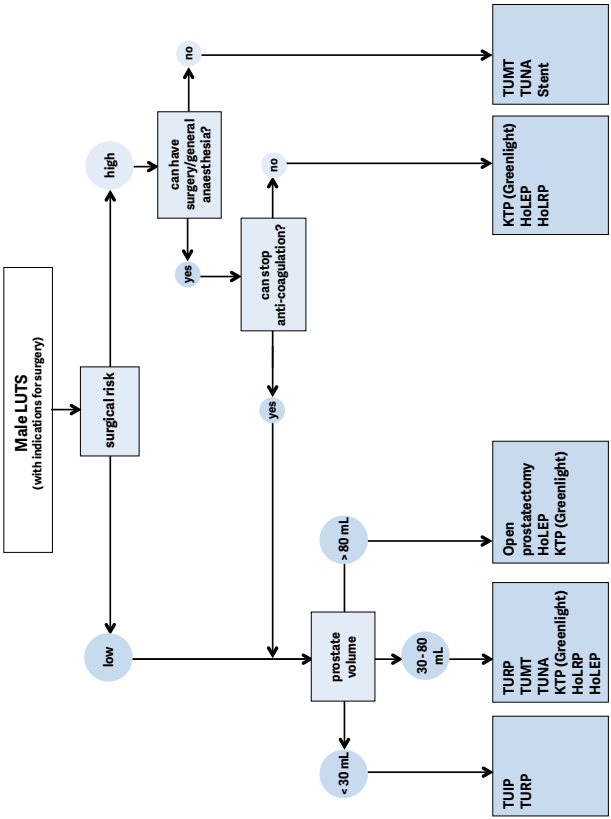

Figure 4: Treatment algorithm of bothersome LUTS refractory to conservative/medical treatment or in cases of absolute operation indications. The flowchart was stratified by the patient's ability to have anaesthesia, cardiovascular risk, and prostate size.

Follow-up

The below listed follow-up strategy is recommended:

- Patients with WW should be reviewed at 6 months and then annually, provided symptoms do not deteriorate or absolute indications develop for surgical treatment.
- Patients receiving α_1-blockers, muscarinic receptor antagonists, or a combination of α_1-blockers + 5α-reductase inhibitors or muscarinic receptor antagonists should be reviewed 4-6 weeks after drug initiation. If patients gain symptomatic relief in the absence of troublesome adverse events, drug therapy may be continued. Patients should be reviewed at 6 months and then annually, provided symptoms do not deteriorate or absolute indications develop for surgical treatment.
- Patients receiving 5α-reductase inhibitor monotherapy should be reviewed after 12 weeks and 6 months to determine their response and adverse events.
- In patients receiving desmopressin, serum sodium concentration should be measured at day 3 and 7 as well as after 1 month and, if serum sodium concentration has remained normal, every 3 months subsequently; the follow-up sequence should be re-started after dose escalation.
- Patients after prostate surgery should be reviewed 4-6 weeks after catheter removal to evaluate treatment response and adverse events. If patients have symptomatic relief and are without adverse events further re-assessment is not necessary.

Table 1: Level of Evidence (LE) and Grade of Recommendation (GR) of various treatments of male LUTS and follow-up			
		LE	**GR**
Conservative treatment – Watchful Waiting			
	Suitable for men with mild symptoms.	1b	A
	Men with LUTS should be offered lifestyle advice prior to or concurrent with treatment.	1b	A
Drug treatment			
1.	α_1-blockers should be offered to men with moderate-to-severe LUTS.	1a	A
2.	5α-reductase inhibitors should be offered to men who have moderate-to-severe LUTS and an enlarged prostate (> 40 mL). 5α-reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery.	1b	A
3.	Muscarinic receptor antagonists might be considered in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms. Caution is advised in men with bladder outlet obstruction (BOO).	1b 4	B C
4.	Desmopressin can be used for the treatment of nocturia due to nocturnal polyuria.	1b	A

5.	Combination treatment with an α_1-blocker together with a 5α-reductase inhibitor should be offered to men with bothersome moderate-to-severe LUTS, enlarged prostates, and reduced Q_{max} (men likely to develop disease progression). Combination treatment is not recommended for short-term therapy (< 1 year).	1b	A
6.	Combination treatment with an α_1-blocker together with a muscarinic receptor antagonists might be considered in patients with bothersome moderate-to-severe LUTS if symptom relief has been insufficient with the monotherapy of either drug. Combination treatment should cautiously be prescribed in men with suspected BOO.	1b 2b	B B
7.	PDE5Is reduce moderate-to-severe male LUTS but are experimental and restricted to men with erectile dysfunction, pulmonary arterial hypertension, or to those who have bothersome LUTS in clinical trials.	1b	A
Surgical treatment			
1.	Monopolar TURP is the current surgical standard procedure for men with prostate sizes of 30-80 mL and bothersome moderate-to-severe LUTS secondary of BPO. Monopolar TURP provides subjective and objective improvement rates superior to medical or minimally invasive treatments.	1a	A
	Bipolar TURP achieves short-term results comparable to monopolar TURP.	1a	A

	TUIP is the surgical therapy of choice for men with prostate sizes < 30 mL, without a middle lobe, and bothersome moderate-to-severe LUTS secondary to BPO.	1a	A
2.	Open prostatectomy is the first choice of surgical treatment in men with prostate sizes > 80 mL, bothersome moderate-to-severe LUTS secondary to BPO, and LUTS refractory to drugs in the absence of a Holmium laser.	1b	A
	Open prostatectomy is the most invasive surgical method with significant morbidity.	1b	A
3.	TUMT achieves symptom improvement comparable to TURP, but is associated with decreased morbidity and lower flow improvements.	1a	A
	Durability is in favour of TURP with lower re-treatment rates compared to TUMT.	1a	A
4.	TUNA™ is an alternative to TURP for patients who wish to defer/avoid (complications of) TURP, but patients should be aware of significant re-treatment rates and less improvement in symptoms and quality of life.	1a	A
5.	HoLEP and 532 nm laser vaporisation of the prostate are minimally invasive alternatives to TURP in men with moderate-to-severe LUTS due to BPO. Laser operations lead to immediate, objective and subjective improvements comparable to TURP.	1b	A

	With regard to intra-operative safety, 532 nm laser vaporisation is superior to TURP and should be considered in patients receiving anticoagulant medication or with high cardiovascular risk.	3	B
	With regard to long-term complication rates, results are only available for HoLEP and are comparable to TURP.	1b	A
6.	Prostatic stents are an alternative to catheterisation for men unfit for surgery. Stents may have a role in the temporary relief of LUTS/BPO after minimally invasive treatment.	3	C
7.	Intra-prostatic ethanol injections for men with moderate-to-severe LUTS secondary to BPO are still experimental and should be performed only in clinical trials.	3	C
8.	Intra-prostatic BTX injections for men with bothersome moderate-to-severe LUTS secondary to BPO or men in urinary retention are still experimental and should be performed only in clinical trials.	3	C
Follow-up			
1.	Follow-up for all conservative, medical or operative treatment modalities is based on empirical data or theoretical considerations but not on evidence based studies.	3-4	C

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 978-90-79754-83-0), available to all members of the European Association of Urology at their website, http://www.uroweb.org.