Ther Adv Urol
(2012) 4(6) 279–301
DOI: 10.1177/1756287212463112

Evidence-based guidelines for the treatment of lower urinary tract symptoms related to uncomplicated benign prostatic hyperplasia in Italy: updated summary from AURO.it

Sebastiano Spatafora, Antonio Casarico, Andrea Fandella, Caterina Galetti, Rodolfo Hurle, Elisa Mazzini, Ciro Niro, Massimo Perachino, Roberto Sanseverino and Giovanni Luigi Pappagallo for the AURO.it BPH Guidelines Committee

Abstract:

Background: The first Italian national guidelines were developed by the Italian Association of Urologists and published in 2007. Since then, a number of new drugs or classes of drugs have emerged for the treatment of lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH), new data have emerged on medical therapy (monotherapies and combination therapies), new surgical techniques have come into practice, and our understanding of disease pathogenesis has increased. Consequently, a new update of the guidelines has become necessary.

Methods: A structured literature review was conducted to identify relevant papers published between 1 August 2006 and 12 December 2010. Publications before or after this timeframe were considered only if they were recognised as important milestones in the field or if the literature search did not identify publications within this timeframe. The quality of evidence and strength of recommendations were determined according to the Grading of Recommendations Assessment, Development and Evaluation framework.

Main findings: Decisions on therapeutic intervention should be based on the impact of symptoms on quality of life (QoL) rather than the severity of symptoms (International Prostate Symptom Score (IPSS) score). A threshold for intervention was therefore based on the IPSS Q8, with intervention recommended for patients with a score of at least 4. Several differences in clinical recommendations have emerged. For example, combination therapy with a 5α-reductase inhibitor plus α blocker is now the recommended option for the treatment of patients at risk of BPH progression. Other differences include the warning of potential worsening of cognitive disturbances with use of anticholinergics in older patients, the distinction between *Serenoa repens* preparations (according to the method of extraction), and the clearly defined threshold of prostate size for performing open surgery (>80 g). While the recommendations included in these guidelines are evidence based, clinical decisions should also be informed by patients' clinical and physical circumstances, as well as patients' preferences and actions.

Conclusions: These guidelines are intended to assist physicians and patients in the decision-making process regarding the management of LUTS/BPH, and support the process of continuous improvement of the quality of care and services to patients.

Keywords: benign prostatic hyperplasia, lower urinary tract symptoms, treatment guidelines

Correspondence to:
Sebastiano Spatafora, MD
Department of Surgery, Azienda Ospedaliera S. Maria Nuova, viale Risorgimento 80, 42100 Reggio Emilia, Italy
s.spatafora@me.com

Antonio Casarico, MD
E.O. Ospedali Galliera, Genoa, Italy

Andrea Fandella, MD
Casa di Cura Giovanni XXIII Monastier, Treviso, Italy

Caterina Galetti, MD
Az S. Orsola-Malpighi, Bologna, Italy

Rodolfo Hurle, MD
Humanitas Gavazzeni Hospital, Bergamo, Italy

Elisa Mazzini, MD
S. Maria Nuova Hospital, Reggio Emilia, Italy

Ciro Niro, MD
Italian Association of Family Doctors (AIMEF), Milano, Italy

Massimo Perachino, MD
Santo Spirito Hospital, Casale Monferrato, Italy

Roberto Sanseverino, MD
Hospital Umberto I, Salerno, Italy

Giovanni Luigi Pappagallo, MSc
P.F. Calvi Hospital, Noale, Italy

Introduction

Benign prostatic hyperplasia (BPH) is a complex pathological disease that is progressive in a large proportion of older men. BPH may be associated with bothersome lower urinary tract symptoms (LUTS), which can negatively impact quality of life (QoL) [Emberton *et al.* 2008]. LUTS/BPH are also associated with considerable healthcare costs [van Exel *et al.* 2006], and the economic impact is likely to increase in line with the aging of populations.

The Italian Association of Urologists (AURO.it) guidelines were previously updated in 2006 [Spatafora *et al.* 2007]. Since then, a number of new drugs or classes of drugs have emerged for the treatment of LUTS related to BPH, new data have emerged on medical therapy (monotherapies and combination therapies), new surgical techniques have come into practice, and our understanding of disease pathogenesis has increased. Consequently, a new update of the guidelines has become necessary. This article provides a summary of the updated guidelines. Only key studies are included, with the full list provided in the online version [AURO.it, 2011].

Scope and characteristics of the guidelines

The focus of the guidelines is LUTS that are considered to be related to BPH (LUTS/BPH); they do not cover LUTS that are secondary to other pathologies. LUTS secondary to BPH include symptoms associated with bladder storage and bladder voiding, and also the postmicturition period [Abrams *et al.* 2003]. The guidelines are intended to assist physicians and patients in the decision-making process regarding the management of LUTS/BPH, and support the process of continuous improvement of the quality of care and services to patients.

Target population

The target population is men with LUTS considered related to uncomplicated BPH.

Intended users

Intended users are clinicians involved in various aspects of LUTS/BPH management, including general practitioners, urologists, geriatricians, specialists in internal medicine, radiologists; members of organisations/health managers who are involved in the continuous improvement of the quality of care and patient empowerment; and decision makers in the public and private health service.

Development commission

Core panel comprising members of AURO.it (www.auro.it), in collaboration with the Italian Association of Family Physicians (www.aimef.org), individual geriatricians, radiologists and healthcare administrators.

Planned time of next update

The next update is planned to be carried out not more than 5 years from the current revision.

Methodology

The literature research was conducted in accordance with recommendations from the Centre for Reviews and Dissemination, University of York, UK. The quality of evidence and strength of recommendations was determined according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework [Guyatt *et al.* 2008a, 2008b, 2008c]. Lastly, the final report was prepared according to the recommendations of the Conference on Guidelines Standardization [Shiffman *et al.* 2003].

The commission defined the scope of the guidelines, the clinical questions, other relevant aspects (populations, interventions, outcomes, acceptable study designs), and literature search strategies. The following databases were searched: Medline, Embase, CRD database, NHS Economic Evaluation Database, Health Technology Assessment Database. Specific search strategies were defined for each of the following areas: risk factors for disease progression; watchful waiting (WW); lifestyle modifications; medical therapy with α blockers; medical therapy with 5α-reductase inhibitors (5ARIs); medical therapy with anticholinergics; medical therapy with phosphodiesterase-5 (PDE5) inhibitors; alternative medical therapies; combination therapies; surgical therapy; laser therapy; minimally invasive therapy; acute urinary retention; follow up following medical therapy; follow up following surgical therapy. Additional sources of information included Cochrane Library, European Association of Urology and American Urological Association (AUA) congress

Table 1. GRADE system used to rate the quality of evidence and grade the strength of recommendations.

Evidence levels	
High quality	Further research very unlikely to change confidence in estimate of effect
Moderate quality	Further research likely to have an important impact on confidence in estimate of effect and may change estimate
Low quality	Further research very likely to have an important impact on confidence in estimate of effect and likely to change estimate
Very low quality	Any estimate of effect is very uncertain
Strength of recommendations	
Strong positive	The examined treatment is the first-choice therapeutic option (favourable benefit/risk ratio)
Weak positive	Consider the examined therapeutic strategy as the first option, realising there are alternatives that could have similar or more appropriate indications in different settings
Weak negative	The examined treatment is not excluded, but its use is limited to carefully selected cases; the clinical decision must be thoroughly discussed and shared with the patient
Strong negative	The examined treatment should be avoided (unfavourable benefit/risk ratio or lack of scientific evidence)

Table 2. Definitions of the different benefit/risk ratios.

Benefit/risk ratio	Definition
Favourable	Benefits clearly outweigh risk and burdens
Uncertain	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced
Unfavourable	Risks clearly outweigh benefits and burdens

abstracts, ClinicalTrials.gov, and all literature reviewed for the production of the previous guidelines and revisions. Searches were restricted to the timeframe of 1 August 2006 to 12 December 2010. Publications before or after this timeframe were considered only if they were recognised as important milestones in the field or if the literature search did not identify publications within this timeframe. Each article identified was evaluated by two members of the commission, who applied an agreed checklist to select articles for further evaluation. Data on the effectiveness and adverse events (AEs) were extracted from selected records and summarised in an evidence profile. Extracted data and evidence profiles were reviewed by the commission for inclusion/exclusion; for included articles, the quality of evidence was assigned by the commission (evidence profiles are available in Italian in the extended online version of the guidelines [AURO.it, 2011]). The GRADE methodology framework was applied to rate the quality of evidence presented and grade the strength of treatment recommendations (Table 1) [Guyatt *et al.* 2008a, 2008b, 2008c]. Flow charts were defined for medical and surgical therapy that described the current standard therapeutic pathways at the commencement of work to update the guidelines; this enabled identification of decision points, and the definition of relevant clinical questions based on the PICOT (Population, Intervention, Comparison, Outcome of interest, Type of study) system. Outcomes were identified and their importance classified as important and essential (score 7–9), important but not essential (score 4–6), or not important (score 1–3) based on the votes of the core panel. On the basis of this classification, outcomes were given greater or lesser consideration in the literature review and subsequent formulation of recommendations. For each intervention, the commission voted on the strength of recommendation (applying previously published rules) [Schünemann *et al.* 2006] and also the benefit/risk ratio (see Table 2 for definitions). A total of 2328 papers/abstracts

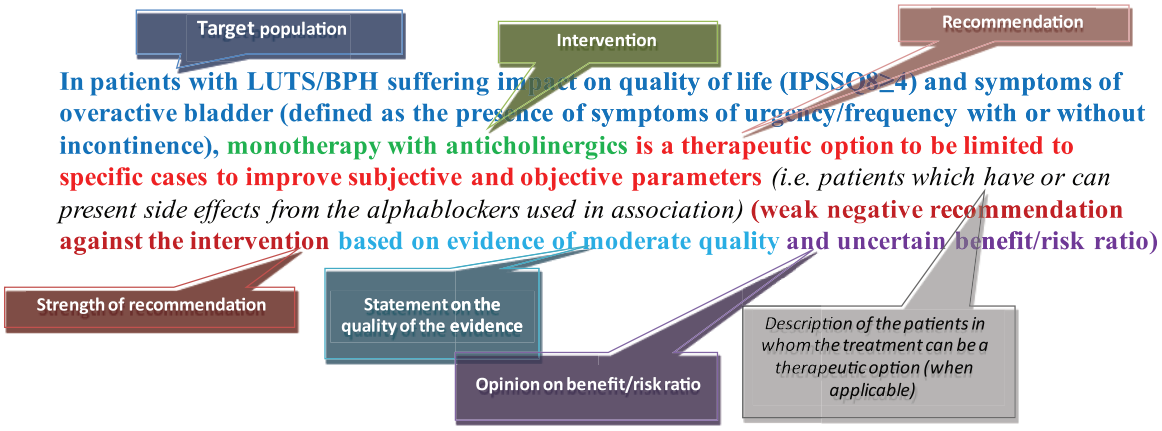

Figure 1. Structure of each recommendation.

were identified by the literature search: 1690 of these were extracted, 1357 were eliminated with reason, and 333 were assessed.

Discrepancies between current clinical practice and scientific evidence, and any controversies identified in the literature, were discussed and voted on at a consensus conference in June 2011 attended by 69 delegates (including urologists, geriatricians, health decision makers, general practitioners, epidemiologists, methodologists, representatives of complementary medicine, patient representatives and a judge). The outcomes of the discussions and consensus votes were considered by the commission when developing/revising draft guidelines. The guidelines underwent revision by a multidisciplinary group of professionals (recognised as experts in their respective fields) who had not participated in their development, including urologists, geriatricians, general practitioners and health economists.

The commission felt strongly that decisions on therapeutic intervention should be based on the impact of symptoms on QoL rather than the severity of symptoms (International Prostate Symptom Score (IPSS) score). A threshold for intervention was therefore set based on the IPSS Q8, with intervention recommended for patients with an IPSS Q8 score of at least 4. The commission also regarded it as important that recommendations were written in such a way as to include information on the following parameters (Figure 1): target population; intervention; recommendation; description of patients in whom the treatment can be a therapeutic option (when applicable); strength of recommendation; statement on the quality of evidence; opinion of the benefit/risk ratio.

Progression of lower urinary tract symptoms/benign prostatic hyperplasia

The commission defined BPH progression *a priori* as the appearance of one of the events considered to be an index of its progression. The indices of progression are: worsening of symptoms (increase of three points in the IPSS); any deterioration of QoL score; acute urinary retention (AUR); recurrent urinary tract infection; urinary incontinence; formation of calcium deposits in the bladder; obstructive renal insufficiency; BPH-related surgery.

Based on the quality of evidence found in the literature, the commission suggests the following in relation to progression of LUTS/BPH. Prostate-specific antigen (PSA), prostate volume and age can be considered as risk factors for progression, and should be taken into consideration when making therapeutic choices (quality of evidence, low). Maximal urinary flow rate (Q_{max}), symptom severity, postvoiding residual urine volume and prostate inflammation should not be considered as risk factors for BPH progression (quality of evidence, low). The commission was unable to express a judgement on the use of other parameters as risk factors for BPH progression due to lack of evidence.

Conservative treatment of lower urinary tract symptoms/benign prostatic hyperplasia

Watchful waiting

In a study comparing WW and transurethral resection of the prostate (TURP) in men with moderate BPH symptoms (n = 556), those who underwent surgery had improved bladder function compared with the WW group [Flanigan *et al.* 1998]. At the 5-year follow-up, 26% of the WW group had

therapeutic failure, 4% had severe symptoms and 5.8% had AUR; in the TURP group, 10% had therapeutic failure, 0.3% had severe symptoms and 0.4% had AUR. A second study compared WW with a program of lifestyle changes in men with moderate to severe LUTS and compromised QoL [Brown *et al.* 2007]. Lifestyle changes significantly reduced the frequency of treatment failure and severity of urinary symptoms.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, WW should not be considered as a treatment for improving subjective and objective parameters (strength of recommendation, strong negative; quality of evidence, very low; unfavourable benefit/risk ratio).

Lifestyle changes

A multidisciplinary panel developed a self-management program of lifestyle and behavioural interventions for men with uncomplicated LUTS/BPH [Brown *et al.* 2004]. This program has been compared with WW in a randomised, controlled trial, and was shown to be associated with significantly reduced frequency of treatment failure and improvement in urinary symptoms [Brown *et al.* 2007].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, changes in lifestyle are a therapeutic option that might be taken into consideration for the improvement of subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, low; favourable benefit/risk ratio).

Medical (drug) treatment of lower urinary tract symptoms/benign prostatic hyperplasia

α Blockers

All α blockers have similar efficacy for improving symptoms, QoL and Q_{max} when used at appropriate doses [AUA, 2010; Chapple *et al.* 2011]. Long-term studies show that α blockers significantly reduce the risk of symptom deterioration, but have no effect on other BPH progression events such as AUR or BPH-related surgery [McConnell *et al.* 2003; Roehrborn *et al.* 2010; Lepor, 2007; Roehrborn, 2008].

The major AEs associated with α blockers are orthostatic hypotension, dizziness, headache, asthenia, nasal congestion and ejaculation problems; vasodilating effects appear to be more common with doxazosin and terazosin than with other α blockers [Oelke *et al.* 2011; Roehrborn, 2009]. Ejaculation problems appear to be more common with tamsulosin and silodosin (Table 3).

Table 3. Ejaculation disorders reported for tamsulosin and silodosin.

Study	Number of events EjD	Number of patients	% (CI)
Tamsulosin			
Chapple *et al.* [1996]	17	381	4.4
Chapple *et al.* [2005]	16	1069	1.5
Kaplan *et al.* [2006]	4	215	1.8
Narayan and Tewari [1998]	27	248	10.1
Roehrborn *et al.* [2008b]	68	1610	4.2
Chapple *et al.* [2011]	8	384	2.1
Total	140	4013	2.97 (2.56–3.45)
Silodosin			
Kawabe *et al.* [2006]	39	175	22.3
Marks *et al.* [2009]	108	347	31.1
Miyakita *et al.* [2010]	7	46	8.7
Total	154	790	19.5 (16.9–22.4)

EjD, ejaculatory dysfunction.

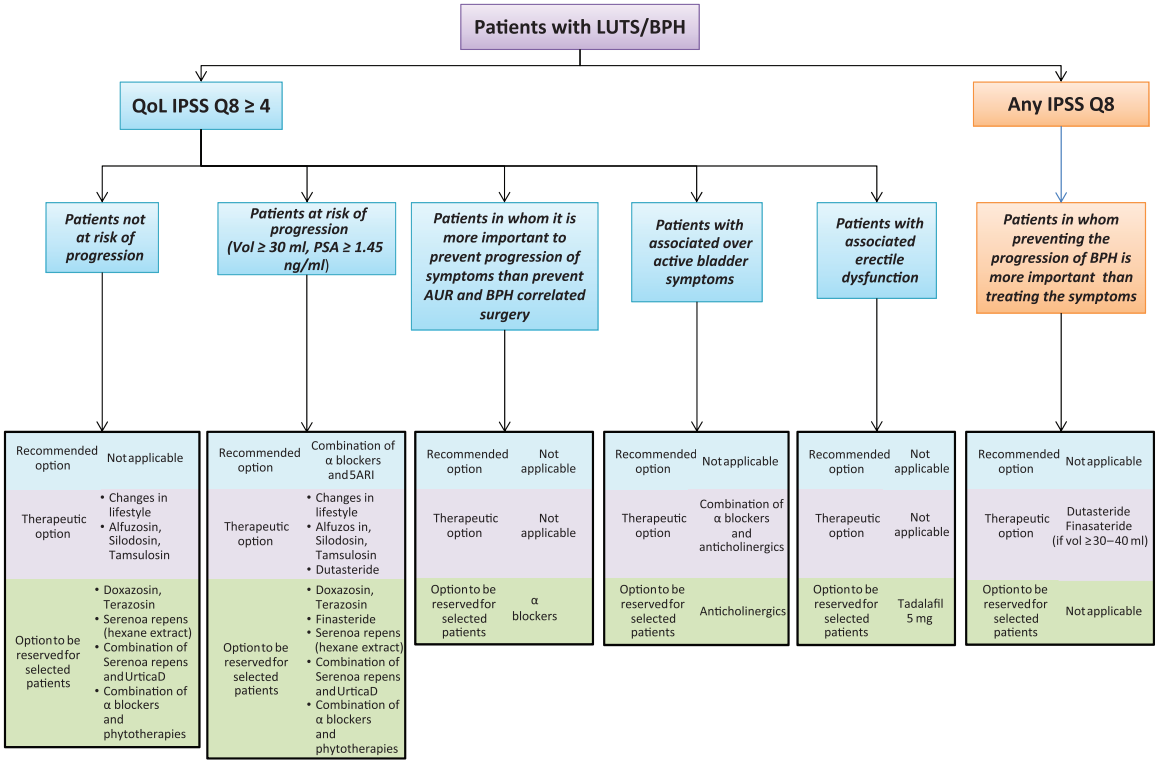

Figure 2. Treatment algorithm for medical therapy.
5ARI, 5α-reductase inhibitor; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; QoL, quality of life.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with tamsulosin, alfuzosin, or silodosin is an option that can be taken into consideration for the improvement of subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, high; favourable benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with α blockers is a therapeutic option that should be reserved for particular cases in order to reduce the risk of AUR, BPH-related surgery, worsening of QoL and worsening of symptoms (i.e. patients in whom only the reduction of worsening of symptoms is important) (strength of recommendation, weak negative; quality of evidence, high; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with doxazosin or terazosin is a therapeutic option that should be limited to specific patients (i.e. those in whom possible hypotensive effects will not cause clinical problems) (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Recommendation Due to incompleteness of literature data, the commission is unable to express a judgement on the differences in benefit/risk between the different α blockers (strength of recommendation, not applicable; quality of available evidence, moderate/high; uncertain benefit/risk ratio).

5α-reductase inhibitors

In placebo-controlled studies, finasteride improved symptom scores by 0.6–2.2 points, and improved Q_{max} by 0.2–1.7 ml/s [Gormley *et al.* 1992; Tammela and Konturri, 1995; Andersen *et al.* 1995; Nickel *et al.* 1996; Marberger, 1998; McConnell *et al.* 1998]. These benefits of finasteride are greater in men with larger prostate volumes (≥30–40 ml) and higher PSA levels (>1.4 ng/ml), with the greatest effects after 12 months of treatment [Boyle *et al.* 1996; Roehrborn *et al.* 1999; Kaplan *et al.* 2011]. Fewer data exist on QoL benefits, with reported improvements

modest and at the limit of significance [Bruskewitz *et al.* 1999; Lepor *et al.* 1998; Lowe *et al.* 2003]. After 2–4 years' treatment, finasteride reduced the risk of AUR by 34–57% and the risk of BPH surgery by 40–55%, with the magnitude of benefit related to treatment duration and risk factors for BPH progression (prostate volume and PSA) [Marberger, 1998; McConnell *et al.* 1998].

In a combined analysis of three randomised, placebo-controlled trials in men with prostate volume at least 30 ml and PSA at least 1.5 ng/ml, dutasteride significantly improved symptoms, QoL (BPH impact index), and Q_{max} compared with placebo [Roehrborn *et al.* 2002; O'Leary *et al.* 2003]. Compared with placebo, dutasteride reduces the relative risk of AUR and BPH-related surgery by 57% and 48% (both $p < 0.001$). For both outcomes, the risk reduction appears to be greater in men with prostate volume greater than 40 ml than in men with prostate volume of 30–40 ml [Gittelman *et al.* 2006].

5ARIs are associated with sexual adverse effects (altered libido, erectile dysfunction, reduced ejaculation volume), particularly during the first year of treatment [Lowe *et al.* 2003; Wessels *et al.* 2003; Andriole and Kirby, 2003; Debruyne *et al.* 2004].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with finasteride is a therapeutic option that should be limited to selected cases to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio); it is a therapeutic option that can be taken into consideration to reduce the risk of AUR, BPH-related surgery, worsening of QoL and/or worsening of symptoms in men with prostate volume greater than 30–40 ml (strength of recommendation, weak positive; quality of evidence, moderate; favourable benefit/risk ratio).

Recommendation In patients with LUTS/BPH, IPSS Q8 of at least 4 and prostate volume greater than 30 ml, monotherapy with dutasteride is a therapeutic option that can be taken into consideration to improve subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, high; uncertain benefit/risk ratio), and to reduce the risk of AUR, BPH-related surgery, worsening of QoL and/or worsening of symptoms in men with prostate volume greater than 30–40 ml (strength of recommendation, weak positive; quality of evidence, high; favourable benefit/risk ratio).

Recommendation Due to the absence of reliable data, the commission is unable to express a judgement on the differences in benefit/risk between the different 5ARIs.

Anticholinergics

A randomised, placebo-controlled trial was identified that assessed tolterodine extended release (ER), tamsulosin or both in men with LUTS (IPSS ≥ 12) and overactive bladder [Kaplan *et al.* 2006]. In this study, monotherapy with tolterodine ER was not significantly different to placebo in terms of changes in IPSS total score, IPSS Q8 score or Q_{max}. The most common AE with tolterodine monotherapy was xerostomia.

Other studies have reported a potential worsening of cognitive disturbances in older patients treated with anticholinergics [Schiefe and Takeda, 2005; Landi *et al.* 2007; Ancelin *et al.* 2006]. On the basis of these reports, an anticholinergic with low haematoencephalic barrier permeability should be considered for the treatment of older patients.

Recommendation In patients with LUTS/BPH, IPSS Q8 of at least 4 and symptoms of overactive bladder (defined as the presence of symptoms of urgency/frequency with or without incontinence), monotherapy with an anticholinergic is a therapeutic option to be limited to specific cases to improve subjective and objective parameters (i.e. patients who have or are at risk of side effects from α blockers used in association) (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Phytotherapies

In a double-blind, randomised, placebo-controlled trial ($n = 85$), *Serenoa repens* (hexane extracted) resulted in a statistically significant improvement in urinary symptom score (4.4 *versus* 2.2, $p = 0.038$) but had no measurable effect on urinary flow rate [Gerber *et al.* 2001]. A meta-analysis of all available published trials did show a significant improvement in Q_{max} (2.2 ml/s *versus* 1.2 ml/s, $p = 0.042$) compared with placebo [Boyle *et al.* 2004]; trials included in this analysis were considered to be of low or very low quality. In another double-blind, randomised,

placebo-controlled trial (n = 225), *S. repens* (CO_2 extracted) did not improve symptoms or objective measures of BPH [Bent *et al.* 2006].

A meta-analysis of studies of *Pygeum africanum* concluded that it may be a useful treatment option for men with BPH/LUTS, although the quality of included studies was very low [Wilt *et al.* 2002]. Men treated with *P. africanum* were more likely to report symptom improvement than those who received placebo; episodes of nocturia, residual urine volume and Q_{max} were also improved.

A low-quality randomised, double-blind, parallel-group study of mepartricin has indicated improvements compared with placebo in symptom and QoL scores, and Q_{max} [Denis *et al.* 1998]. However, at 6 months the improvements in objective parameters with mepartricin were not statistically significant compared with placebo.

The combination of *S. repens* (other extracts) and *Urtica dioica* has been shown to significantly improve symptom score compared with placebo in a randomised, double-blind study [Lopatkin *et al.* 2005]. This study was considered to be of low quality due to limited internal validity.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with *S. repens* (hexane extracted) is a treatment option to be limited to specific cases to improve subjective and objective parameters (e.g. patients who wish to be treated with phytotherapy) (strength of recommendation, weak negative; quality of evidence, very low; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with *S. repens* (other extracts) is a treatment option that should not be taken into consideration to improve subjective and objective parameters (strength of recommendation, strong negative; quality of evidence, high; unfavourable benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with *P. africanum* and mepartricin should not be considered a treatment to improve subjective and objective parameters (strength of recommendation, strong negative; quality of evidence, low to very low; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, the combination of *S. repens* (other extracts) and *U. dioica* is a treatment option that should be limited to selected cases (e.g. patients who wish to be treated with phytotherapy) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Phosphodiesterase-5 inhibitors

In a 12-week dose-finding study, tadalafil significantly improved LUTS, erectile function and QoL compared with placebo [Roehrborn *et al.* 2008a]. The frequency of AEs was dose dependent, and tadalafil 5 mg provided the best risk–benefit profile. Vardenafil and sildenafil have also been shown to significantly improve LUTS, erectile function, and QoL in 8- and 12-week randomised, double-blind, placebo-controlled studies respectively [Steif *et al.* 2008; McVary *et al.* 2007]; these studies were considered to be of low quality. AEs were higher with both vardenafil and sildenafil (13.7% and 32% respectively) compared with placebo. None of these studies showed a significant effect of PDE5 inhibitors on Q_{max}.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with tadalafil 5 mg is a treatment option that should be limited to selected cases to improve subjective and objective parameters (e.g. patients with LUTS/BPH and erectile dysfunction who wish to simultaneously treat both conditions) (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monotherapy with vardenafil or sildenafil should not be considered a treatment to improve subjective and objective parameters (strength of recommendation, strong negative; quality of evidence, low; uncertain benefit/risk ratio).

Combination therapy: α blockers and 5α-reductase inhibitors

In the Medical Therapy of Prostatic Symptoms (MTOPS) study, combination therapy (finasteride plus doxazosin) significantly improved symptom score and Q_{max} compared with placebo, and also compared with either monotherapy [McConnell *et al.* 2003]; it was not reported whether these improvements had an impact on QoL. The Combination of Avodart and

Table 4. Combination therapy (5α-reductase inhibitor plus α blocker) *versus* monotherapies: incidence and relative risk of benign prostatic hyperplasia progression events.

	Combination		5ARI		α blocker		RR combination *versus* 5ARI		RR combination *versus* α blocker	
	Events	Patients	Events	Patients	Events	Patients	% (CI)	*p*	% (CI)	*p*
Worsening ≥4 points IPSS	177	2396	277	2391	284	2367	37 (24, 47)	<0.001	39 (27, 49)	<0.001
AUR	30		43		91		34 (–10, 56)	<0.15	67 (51, 78)	<0.001
BPH-related surgery	50		70		152		28 (–2, 50)	<0.08	67 (56, 76)	<0.001

Source data: McConnell *et al.* [2003]; Roehrborn *et al.* [2010].
5ARI, 5α-reductase inhibitor; AUR, acute urinary retention; BPH, benign prostatic hyperplasia; CI, confidence interval; IPSS, International Prostate Symptom Score; RR, relative risk.

Tamsulosin (CombAT) study specifically included men at increased risk of BPH progression (prostate volume ≥ 30 ml and PSA ≥ 1.5 ng/ml). The combination of dutasteride plus tamsulosin provided significant improvements in symptom score and Q_{max} compared with either monotherapy; these improvements were reflected in significant improvements in QoL measures with combination therapy compared with either monotherapy [Roehrborn *et al.* 2010; Montorsi *et al.* 2010].

Across both the MTOPS and CombAT studies, combination therapy with 5ARI plus an α blocker was more effective for preventing disease progression events (symptom progression, AUR, BPH-related surgery) compared with either monotherapy (Table 4); the reduction in risk of AUR and BPH-related surgery with combination therapy was not statistically significant compared with 5ARI monotherapy. However, the number of progression events was low in MTOPS and in the subgroup of patients with prostate volume less than 40 ml in CombAT [McConnell *et al.* 2003; Roehrborn *et al.* 2011].

In patients at risk of progression, dutasteride plus tamsulosin was significantly superior to tamsulosin monotherapy at reducing the relative risk of AUR or BPH-related surgery (68% and 71%, respectively; $p < 0.001$); the reduction in risk of AUR and BPH-related surgery with combination therapy was not statistically significant compared with dutasteride monotherapy [Roehrborn *et al.* 2010]. Combination therapy was also significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression. Symptom progression was reduced by 35% and 41% respectively compared with dutasteride and α-blocker monotherapy [Roehrborn *et al.* 2010]. The cumulative incidence of progression events (7–14%) and the absolute risk reductions (4–6%) in CombAT were clinically relevant.

AEs with combination therapy were generally similar to those for each drug alone. A combined analysis of all randomised controlled trials of 5ARI plus α-blocker combination therapy showed that differences in incidences of AEs are low, ranging from –0.2% to +2.4% for cardiovascular AEs and from +0.3% to +3% for sexual AEs (Table 5).

Two studies were identified that assessed the impact of α-blocker withdrawal following a period of combination therapy [Barkin *et al.* 2003; Nickel *et al.* 2008], but were deemed to have limitations in design and methodology that impeded assessment of benefit/risk profile.

Recommendation In the general population of patients with LUTS/BPH and IPSS Q8 of at least 4, the combination of α blockers and 5ARI is a treatment option to be limited to selected cases to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio); this combination should not be considered as a therapeutic option to reduce the risk of AUR, BPH-related surgery, worsening of QoL, or worsening of symptoms (strength of recommendation, strong negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH, IPSS Q8 of at least 4 and risk of progression

Table 5. Combination therapy (5α-reductase inhibitor plus α blocker) *versus* monotherapies: cumulative incidence and relative risk of adverse events.

	Combination			5ARI					α blocker				
	Events	Patients	%	Events	Patients	%	Δ C *versus* 5ARI, %	RR C *versus* 5ARI, % CI	Events	Patients	%	Δ C *versus* α blocker, %	RR C *versus* α blocker, % (CI)
Postural hypotension	41	1730	2.4	15	1686	0.8	+1.6	2.69 (1.50–4.82)	45	1694	2.6	–0.2	NS
Dizziness	144	3340	4.3	64	3309	1.9	+2.4	2.20 (1.66–2.91)	159	3306	4.8	–0.5	NS
Asthenia	75	1730	4.3	36	1686	2.1	+2.2	2.02 (1.38–2.95)	61	1683	3.6	+0.7	NS
Reduced libido	86	3340	2.6	76	3309	2.3	+0.3	NS	49	3305	1.5	+1.1	1.74 (1.23–2.46)
EjD	102	3340	3.0	29	3323	0.9	+2.1	3.50 (2.33–5.26)	21	3305	0.6	+2.4	4.75 (2.99–7.53)
ED	180	3031	5.9	138	2999	4.6	+1.3	NS	89	3000	3.0	+2.9	2.01 (1.57–2.58)

Source data: McConnell *et al.* [2003]; Roehrborn *et al.* [2008b]; Lepor *et al.* [1996]; Debruyne *et al.* [1998]; Kirby *et al.* [2003].
5ARI, 5α-reductase inhibitor; C, combination; CI, confidence interval; ED, erectile dysfunction; EjD, ejaculatory dysfunction; NS, nonsignificant; RR, relative risk.

(defined as prostate volume > 30 ml and PSA > 1.5 ng/ml), the combination of α blockers and 5ARI is a therapeutic option recommended to improve subjective and objective parameters (strength of recommendation, strong positive; quality of evidence, high; favourable benefit/risk ratio), and to reduce the risk of AUR, BPH-related surgery, worsening of QoL or worsening of symptoms (strength of recommendation, strong positive; quality of evidence, high; favourable benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, the suspension of α blockers after a period of combination therapy is a therapeutic option that should be limited to selected cases (e.g. patients in whom control of symptoms is less important than reducing the risk of AUR and BPH-related surgery) (strength of recommendation, weak negative; quality of evidence, very low; uncertain benefit/risk ratio).

Combination therapy: α blockers and anticholinergics

Two studies were identified that assessed the combination of α blocker plus anticholinergic in patients with LUTS/BPH and overactive bladder. In one study, significantly more patients who received tolterodine ER plus tamsulosin reported treatment benefit by week 12 than patients who received placebo, tolterodine ER monotherapy, or tamsulosin monotherapy [Kaplan *et al.* 2006]. Significant improvements for combination therapy compared with placebo in IPSS and QoL item score were also reported. In the other study, tamsulosin combined with ER oxybutynin resulted in significantly greater improvements in IPSS (–6.9 *versus* –5.3; $p = 0.006$) and QoL (IPSS Q8: –1.3 *versus* – 0.8; $p < 0.01$) at 12 weeks compared with tamsulosin plus placebo [MacDiarmid *et al.* 2008]. In both studies the most frequent AE was xerostomia. As indicated previously, other studies have indicated a worsening of cognitive disturbances in older patients treated with anticholinergics [Scheife and Takeda, 2005; Landi *et al.* 2007; Ancelin *et al.* 2006].

Recommendation In patients with LUTS/BPH, IPSS Q8 of at least 4 and symptoms of overactive bladder (defined as symptoms of urgency/frequency with or without incontinence), the combination of an α blocker and anticholinergic is a therapeutic option that can be taken into consideration to improve subjective and objective

parameters (strength of recommendation, weak positive; quality of evidence, high; uncertain benefit/risk ratio).

Combination therapy: α blockers and phytotherapies

Two studies were identified that have assessed the combination of tamsulosin and *S. repens*; one was a prospective observational study [Hizli and Uygur, 2007] and one a double-blind randomised trial [Glemain *et al.* 2002]. Neither showed any additional benefit of adding phytotherapy to tamsulosin. Despite the absence of data to show a benefit of this combination, it is widely used in Italy. The benefit/risk ratio was considered as uncertain/favourable by 43% of experts at the consensus conference, while 44.5% considered it to be uncertain/unfavourable.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, the combination of α blocker and phytotherapies is a therapeutic option that should be limited to selected cases to improve subjective and objective parameters (e.g. patients in receipt of α blockers who also wish to be treated with phytotherapies) (strength of recommendation, weak negative; quality of evidence, very low; uncertain benefit/risk ratio).

Surgical treatment of lower urinary tract symptoms/benign prostatic hyperplasia

Open surgery

Open surgery is associated with QoL improvements of 2–2.8 points at 18–24 months post operation [Naspro *et al.* 2006; Skolarikos *et al.* 2008]. Studies of patients with an average prostatic weight of approximately 80 g show that open surgery improves the IPSS by 11–20 points after 12 months' follow up [Skolarikos *et al.* 2008; Ou *et al.* 2010; Suer *et al.* 2008; Gacci *et al.* 2003]; one randomised study showed an improvement of 18 points at 5-year follow-up [Kuntz *et al.* 2008]. A rate of early complications of 17.3% has been reported [Gratzke *et al.* 2007], and the technique is associated with long hospitalisation and recovery times.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, open surgery is a therapeutic option to be limited to selected cases (i.e. patients with prostates > 80 g; this value was established from the literature analysis and the opinions of experts at the consensus conference) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, very low; uncertain benefit/risk ratio).

Transurethral resection of the prostate

In randomised studies, monopolar and bipolar TURP provided similar improvements in QoL and symptom scores [Yang *et al.* 2004; Singh *et al.* 2005; Seckiner *et al.* 2006; Iori *et al.* 2008; Autorino *et al.* 2009; Kong *et al.* 2009; Singhania *et al.* 2010; Nuhoğlu *et al.* 2006; Patankar *et al.* 2006; Erturhan *et al.* 2007; Ho *et al.* 2007; Yoon *et al.* 2006; Chen *et al.* 2010; Bhansali *et al.* 2009]. In observational studies, QoL improvements of 2.4–4.4 points have been reported for monopolar TURP after 12 years' follow up [Mishriki *et al.* 2008; Masumoiri *et al.* 2010]. Complication rates are slightly higher with monopolar TURP than with the bipolar procedure [Ahyai *et al.* 2010].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monopolar TURP is a therapeutic option that can be taken into consideration to improve subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, low; favourable benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, bipolar TURP is a therapeutic option that can be taken into consideration to improve subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, low; favourable benefit/risk ratio).

Transurethral incision of the prostate

QoL and symptom improvements with transurethral incision of the prostate (TUIP) have been shown in randomised trials (average prostatic weight approximately 30 g) to be not significantly different to those with monopolar TURP [Tkocz and Prajsner, 2002; Larsen *et al.* 1987; Dørflinger *et al.* 1992; Riehmann *et al.* 1995; Saporta *et al.* 1996; Jahnson *et al.* 1998]. Intra- and postoperative complication rates with TUIP are generally similar to those with TURP; reintervention rate is significantly higher with TUIP than with TURP, while ejaculatory dysfunction is significantly lower [Lourenco *et al.* 2010].

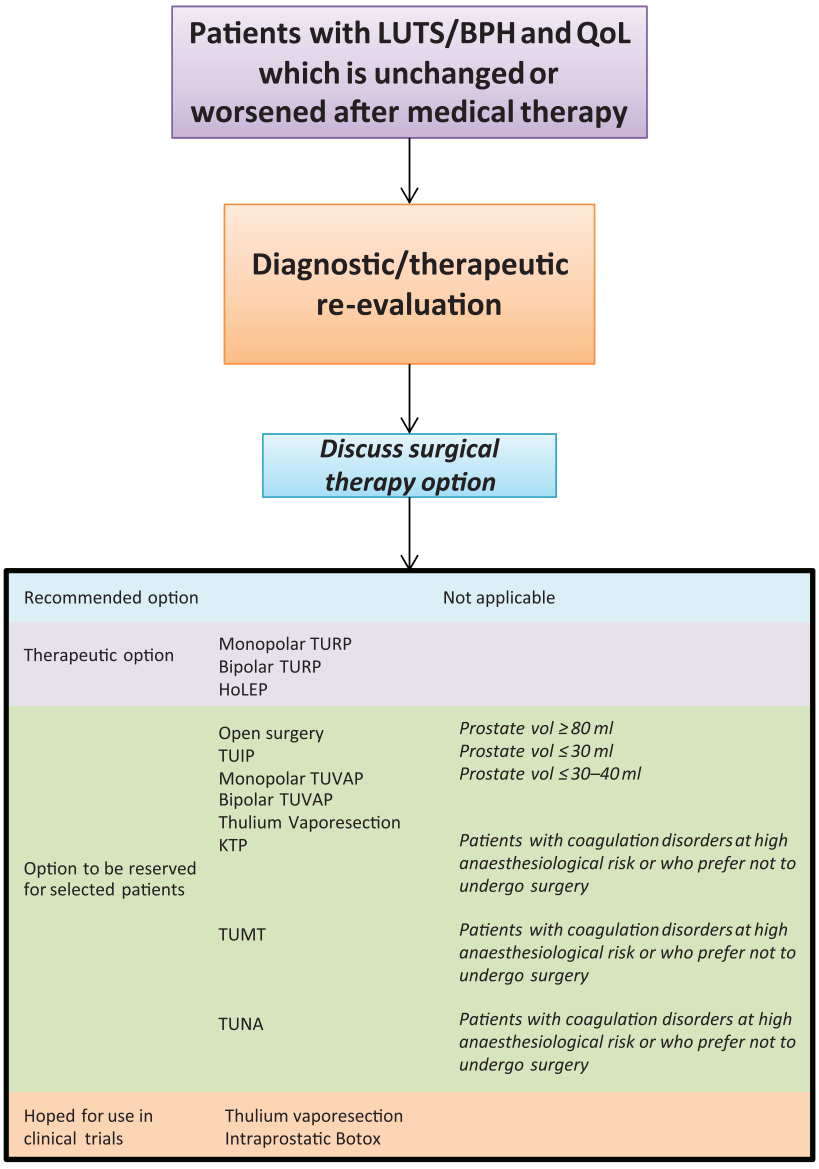

Figure 3. Treatment algorithm for surgical therapy.
BPH, benign prostatic hyperplasia; HoLEP, holmium laser enucleation of the prostate; KTP, potassium titanyl-phosphate; LUTS, lower urinary tract symptoms; QoL, quality of life; TUIP, transurethral incision of the prostate; TUMT, transurethral microwave thermotherapy; TUNA, transurethral needle ablation; TURP, transurethral resection of the prostate; TUVAP, transurethral electrovaporisation of the prostate.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, TUIP is a therapeutic option that should be limited to selected cases (i.e. patients with prostates < 30 g; this value was established from the literature analysis and the opinions of experts at the consensus conference) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Transurethral electrovaporisation of the prostate

Three randomised trials comparing monopolar transurethral electrovaporisation of the prostate (TUVAP) and TURP in patients with prostate size 30–40 g were identified [Hammadeh *et al.* 2003; Gallucci *et al.* 1998; Nuhoğlu *et al.* 2005]. The two procedures provided similar improvements in QoL and symptom score, and rates of complications and reintervention for BPH were

also generally similar (except for AUR due to clotting, which was significantly lower with TUVAP than with TURP).

Four randomised studies comparing bipolar TUVAP and TURP were identified; across all the studies the maximum prostate size was 80 g [Geavlete *et al.* 2010; Hoekstra *et al.* 2010; Hon *et al.* 2006; Kaya *et al.* 2007]. Improvements in QoL score and IPSS were similar for the two procedures. Rates of complications and reintervention for BPH were also similar, except for significantly lower rates of capsule perforation and AUR due to clotting with TUVAP. There are, as yet, insufficient data to determine the medium- to long-term benefits of bipolar TUVAP. A potential issue with bipolar TUVAP is the risk of urethral stenosis due to the use of high-calibre endoscopic instruments.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, monopolar TUVAP is a therapeutic option that should be limited to certain cases (i.e. patients with small- to medium-volume prostates (<30–40 g); this value was established from the literature analysis and the opinions of the commission) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, bipolar TUVAP is a therapeutic option that should be limited to selected cases (e.g. patients with prostates of 60–80 g (this value was established from the literature analysis and the opinions of the commission) or patients with coagulation problems or taking anticoagulant medication) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Laser treatment of lower urinary tract symptoms/benign prostatic hyperplasia

Holmium laser enucleation of the prostate

Holmium laser enucleation of the prostate (HoLEP) provides similar improvements in QoL score (2.6- to 3.6-point improvement compared with baseline) to open surgery and TURP over 2 years' follow up [Naspro *et al.* 2006; Wilson *et al.* 2006], and similar improvements in IPSS over 5–6 years [Kuntz 2006]. Complication rates with HoLEP are generally similar to rates with open surgery or TURP; catheterisation time and duration of hospital stay appear to be shorter with HoLEP [Naspro *et al.* 2006; Kuntz *et al.* 2008; Wilson *et al.* 2006; Neill *et al.* 2006; Ahyai *et al.* 2007]. Despite favourable results obtained with HoLEP, relatively few centres are competent in what is a technically challenging procedure.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, HoLEP is a therapeutic option to be taken into consideration to improve subjective and objective parameters (strength of recommendation, weak positive; quality of evidence, moderate; favourable benefit/risk ratio).

Thulium laser

A single, prospective randomised study was identified that compared thulium vaporesection and standard TURP in patients with symptomatic BPH, with follow up of 12 months [Xia *et al.* 2008]. No differences were observed between the two treatments in terms of symptom improvement and urodynamic findings. Thulium laser resection was associated with significantly shorter catheterisation times and duration of hospital stay, while the rate of late complications was similar in the two groups. An observational study (deemed to be very low quality) has indicated that the benefits of thulium vaporesection are maintained over a follow-up period greater than 12 months [Bach *et al.* 2010].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, thulium vaporesection is a therapeutic option that should be limited to selected cases (e.g. patients treated in centres highly trained in the technique) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Recommendation The commission and consensus conference agree that currently available data are limited and of very low quality. Based on this, and the uncertain benefit/risk ratio, the commission is unable to express a clinical recommendation for the use of thulium laser vapoenucleation to improve subjective and objective parameters in patients with LUTS/BPH; it is hoped that more data on the procedure will be provided by future randomised clinical trials

(quality of evidence, very low; uncertain benefit/risk ratio).

Potassium titanyl-phosphate laser

Data from randomised clinical trials indicate that improvements in QoL and symptom scores with potassium titanyl-phosphate (KTP) laser treatment are similar to those with open surgery and monopolar TURP [Skolarikos *et al.* 2008; Bouchier-Hayes *et al.* 2009; Al-Ansari *et al.* 2010]. Improvements in symptom scores and QoL appear to be maintained during follow up of up to 3 years [Al-Ansari *et al.* 2010]. KTP laser treatment results in shorter catheterisation times and duration of hospital stay compared with open surgery or TURP, although the reported reintervention rate is higher with the laser therapy [Skolarikos *et al.* 2008; Bouchier-Hayes *et al.* 2009; Al-Ansari *et al.* 2010; Horasanli *et al.* 2008; Tugcu *et al.* 2008].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, the KTP laser is a therapeutic option that should be limited to selected cases (e.g. patients with blood coagulation disorders, or at high cardiovascular and anaesthesiologic risk) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, low; uncertain benefit/risk ratio).

Minimally invasive therapies for lower urinary tract symptoms/benign prostatic hyperplasia

Transurethral microwave thermotherapy

Improvements in QoL with transurethral microwave thermotherapy (TUMT) may be lower than with TURP, especially with longer-term follow up [D'Ancona *et al.* 1998; de la Rosette *et al.* 2003; Mattiasson *et al.* 2007]. Data on symptom improvement are inconsistent, with one study showing similar improvements with TUMT and TURP and another suggesting greater benefit with TURP [D'Ancona *et al.* 1998; de la Rosette *et al.* 2003]. Reported rates of postoperative complications such as AUR and urinary tract infection are higher with TUMT than with TURP, as is the reintervention rate [D'Ancona *et al.* 1998; de la Rosette *et al.* 2003; Mattiasson *et al.* 2007].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, TUMT is a therapeutic option that should be limited to selected cases (e.g. patients with blood coagulation disorders, at high anaesthesiologic risk or who prefer not to undergo surgery) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Transurethral needle ablation

Long-term (5- and 7-year follow-up) data are available from prospective, randomised trials comparing transurethral needle ablation (TUNA) and TURP [Hill *et al.* 2004; Chandraskar *et al.* 2003]. These studies indicate good durability of improvement in symptom score and QoL with TUNA. Although the improvements appear to be less than those obtained with TURP, TUNA is associated with a lower risk of AEs. TUNA is also associated with a shorter duration of hospitalisation than TURP, although the reintervention rate is higher [Hill *et al.* 2004; Chandraskar *et al.* 2003].

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, TUNA is a therapeutic option that should be limited to selected cases (e.g. patients with blood coagulation disorders, at high anaesthesiologic risk or who prefer not to undergo surgery) to improve subjective and objective parameters (strength of recommendation, weak negative; quality of evidence, moderate; uncertain benefit/risk ratio).

Intraprostatic Botox

A review of seven studies of Botox, deemed to be of very low quality, suggests QoL and symptom score improvements of 1.3 and 11 points respectively after 11 months' follow up compared with preoperative scores [Chartier-Kastler *et al.* 2011]. The rate of postoperative AUR was reported as 10%.

Recommendation The commission is unable to make a recommendation due to the lack of available data; randomised clinical studies are urgently needed.

Prostatic stent

Two systematic reviews are available that have assessed use of an epithelialising stent [Armitage *et al.* 2007] and a thermo-expandable metallic stent [Armitage *et al.* 2006]. In both reviews,

Table 6. Proposed follow-up schedule for patients treated with medical therapy.

	Lifestyle changes	Phytotherapies	α blockers	Anticholinergics + α blockers	PDE5 inhibitors	5ARIs	5ARI + α blocker
4–6 weeks	x		x	x	x		x
3 months		x				x	
6 months	x		x	x	x		x
12 months	x	x	x	x	x	x	x

5ARI, 5α-reductase inhibitor; PDE5, phosphodiesterase 5.

Table 7. Proposed follow-up schedule for patients treated with invasive therapy.

	All treatments
4–6 weeks	x
3 months	
6 months	x
12 months	X (end of follow up)

improvements in symptoms and Q_{max} were noted, however high rates of failures and stent removal were reported.

Recommendation In patients with LUTS/BPH and IPSS Q8 of at least 4, prostatic stents are a therapeutic option that should not be taken into consideration to improve subjective and objective parameters (strength of recommendation, strong negative; quality of evidence, very low; unfavourable benefit/risk ratio).

Follow up of patients treated for lower urinary tract symptoms/benign prostatic hyperplasia

Patients on medical (drug) therapy

There are limited, very low quality data available on which to base recommendations about the optimal follow-up process for patients receiving drug treatment for LUTS/BPH. A schedule of follow-up appointments has been proposed by the commission and approved by the consensus conference of experts (Table 6).

Patients undergoing invasive therapy

There is a lack of information in the literature on which to base recommendations for the follow up of patients who have received invasive therapy. A schedule of follow-up appointments has therefore been proposed by the commission and approved by the consensus conference of experts (Table 7).

Management of acute urinary retention

Data were assessed from three randomised, controlled trials of α blockers in men with AUR secondary to BPH who had been catheterised [Lucas *et al.* 2005; McNeill and Hargreave, 2004; Prieto *et al.* 2008]. Across the three studies, 53% of men who also received an α blocker had a successful trial without catheter, compared with 39% of men who were catheterised without the addition of an α blocker (Table 8). Compared with catheterisation alone, the relative risk of spontaneous micturition recovery in men who also received an α blocker was 1.4 (95% confidence interval 1.14–1.68, $p < 0.001$). Across the studies, there was wide variation in the duration of catheterisation and α-blocker treatment such that no conclusions can be drawn on the ideal length of each treatment.

Table 8. Catheter *versus* catheter plus α blockers: relative risk of recatheterisation.

Intervention	No. patients	Spontaneous micturition recovery	Recatheterisation	RR (CI)
Catheter	215	83	132	1.4 (1.14–1.68)
Catheter + α blocker	332	177	55	

CI, confidence interval; RR, relative risk.

Recommendation Combining bladder catheterisation and α-blocker therapy is an option that can be taken into consideration to manage BPH-related AUR (strength of recommendation, weak positive; quality of evidence, very low; favourable benefit/risk ratio).

Recommendation Bladder catheterisation alone is a therapeutic option that should be limited to selected cases, such as patients who are unable to tolerate α-blocker therapy (strength of recommendation, weak negative; quality of evidence, very low; uncertain benefit/risk ratio).

Summary

These updated guidelines reflect the emergence in recent years of new drugs or classes of drugs for the treatment of LUTS related to BPH, new data on medical therapies (monotherapies and combination therapies), and new surgical techniques. As with our previous recommendations [Spatafora *et al.* 2007], decisions on therapeutic intervention are based on the impact of symptoms on QoL, rather than the severity of symptoms. Unlike our previous recommendations, a threshold for intervention was set based on the IPSS Q8, with intervention recommended for patients with an IPSS Q8 score of at least 4. This represents a divergence from other LUTS/BPH guidelines, which recommend interventions on the basis of symptom severity [AUA, 2010; Oelke *et al.* 2011].

Another distinction between the present update and our previous update is the application of the GRADE methodology framework to rate the quality of evidence presented and grade the strength of treatment recommendations [Guyatt *et al.* 2008a–c]. GRADE is considered to be the best methodology for the development of clinical practice guidelines, and the most widely used by major scientific/medical associations around the world.

In addition to differences in the philosophy and methodology behind our guidelines compared with others in the field, there are a number of differences in clinical recommendations that have emerged due to interpretation of the literature or availability of new information. For example, combination therapy with a 5ARI plus an α blocker is the recommended option for the treatment of patients at risk of BPH progression, rather than just a therapeutic option. This is based on greater improvement in QoL compared with monotherapies, and the commission's belief that the absolute reduction in the risk of AUR or BPH-related surgery is clinically relevant in the group of patients with enlarged prostates. Other differences in clinical recommendations include the warning of potential worsening of cognitive disturbances with use of anticholinergics in older patients, the distinction between *S. repens* preparations (according to the method of extraction), and the clearly defined threshold of prostate size for performing open surgery (>80 g).

While the recommendations included in these guidelines are evidence based, there are also other factors to consider when making treatment decisions. In addition to the research evidence, clinical decisions should be informed by patients' clinical and physical circumstances, as well as patients' preferences and actions [Haynes *et al.* 2002]. Clinical expertise is also needed to bring these three aspects together and recommend a treatment that is acceptable to the patient.

Implementation of any guidelines can present challenges, and will require a collective effort. Previous experience suggests that small-group local meetings between general practitioners and urologists, in which best practice is discussed and shared, can be useful in promoting at least some changes to clinical practice. As previously described [Spatafora *et al.* 2007], collaboration between local administrators and all clinicians involved in BPH management in each local health unit will also be central to facilitating adoption of these guidelines.

Acknowledgements

Medical writing support for the development of this manuscript was provided by Tony Reardon of Spirit Medical Communications. We are grateful to the following members for their participation in the development of the guidelines.

Consultants: Nunzio Costa, general practitioner, Stornarella-FG; Federica Marchesotti, urologist, Casale Monferrato-AL; Giorgio Mazzi, health decision maker, Reggio Emilia; Giorgio Napodano, urologist, Nocera Inferiore-SA; Afro Salsi, geriatrician, Bologna; Domenico Viola, urologist, Reggio Emilia.

Reviewers: Carlo Adriano Biagini, geriatrician, Pistoia; Massimo Brunetti, health economist, Modena; Salvatore Campo, general practitioner, Palermo; Giario Conti, urologist, Como; Paolo

Gontero, urologist, Turin; Giovanni Muto, urologist, Turin; Arcangelo Pagliarulo, urologist, Bari; Furio Pirozzi Farina, urologist, Sassari; Tommaso Prayer Galletti, urologist, Padua; Domenico Prezioso, urologist, Naples; Paolo Puppo, urologist, Genoa; Alessandro Sciarra, urologist, Rome; Andrea Tubaro, urologist, Rome.

Funding

The preparation of these guidelines was supported by an unrestricted educational grant from GlaxoSmithKline. Funding for medical writing support for the development of this manuscript was provided by the Italian Association of Urologists.

Conflict of interest statement

SS has received consulting fees from GSK and Nycomed, and support for congress participation from GSK; AC has received consulting fees from Eli Lilly and Pfizer, and support for congress participation from GSK and Astellas; AF has received consulting fees from GSK, and support for congress participation from Sigma Tau and Pierre Fabre; CG has received support for congress participation from Sanofi-Aventis; RH has received support for congress participation from GSK; EM and CN have no relevant conflicts to declare; MP has received consulting fees from GSK and Nycomed, and support for congress participation from GSK, Nycomed and Bayer; RS has received consulting fees from GSK and Nycomed, research funding from Janssen-Cilag, and support for congress participation from GSK, Nycomed, Teleflex, Johnson & Johnson and Pierre Fabre; GLP has received consulting fees from Pfizer, Merck-Sorono, Bayer, Eli Lilly and IBSA, and support for congress participation from GSK.

References

Abrams, P., Cardozo, L., Fall, M., Griffiths, D., Rosier, P., Ulmsten, U. *et al.* (2003) The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology* 61: 37–49.

Ahyai, S., Gilling, P., Kaplan, S., Kuntz, R., Madersbacher, S., Montorsi, F. *et al.* (2010) Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. *Eur Urol* 58: 384–397.

Ahyai, S., Lehrich, K. and Kuntz, R. (2007) Holmium laser enucleation versus transurethral resection of the prostate: 3-year follow-up results of a randomized clinical trial. *Eur Urol* 52: 1456–1463.

Al-Ansari, A., Younes, N., Sampige, V., Al-Rumaihi, K., Ghafouri, A., Gul, T. *et al.* (2010) 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* 58: 349–355.

Ancelin, M., Artero, D., Portet, F., Dupuy, A., Touchon, J. and Ritchie, K. (2006) Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 332: 455–459.

Andersen, J., Ekman, P., Wolf, H., Beisland, H., Johansson, J., Kontturi, M. *et al.* (1995) Can finasteride reverse the progress of benign prostatic hyperplasia? A two-year placebo-controlled study. *Urology* 46: 631–637.

Andriole, G. and Kirby, R. (2003) Safety and tolerability of the dual 5alpha-reductase inhibitor dutasteride in the treatment of benign prostatic hyperplasia. *Eur Urol* 44: 82–88.

Armitage, J., Cathcart, P., Rashidian, A., De Nigris, E., Emberton, M. and van der Meulen, J. (2007) Epithelializing stent for benign prostatic hyperplasia: a systematic review of the literature. *J Urol* 177: 1619–1624.

Armitage, J., Rashidian, A., Cathcart, P., Emberton, M. and van der Meulen, J. (2006) The thermo-expandable metallic stent for managing benign prostatic hyperplasia: a systematic review. *BJU Int* 98: 806–810.

AUA (American Urological Association) (2010) *Management of BPH* (revised 2010). Available from: http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=bph (accessed 17 July 2012).

AURO.it (2011) Guidelines. Available from: http://www.auro.it/linee-guida-su-luts-correlati-alliperplasia-prostatica-benigna/ (accessed 17 July 2012).

Autorino, R., Damiano, R., Di Lorenzo, G., Quarto, G., Perdonà, S., D'Armiento, M. *et al.* (2009) Four-year outcome of a prospective randomised trial comparing bipolar plasmakinetic and monopolar transurethral resection of the prostate. *Eur Urol* 55: 922–929.

Bach, T., Netsch, C., Haecker, A., Michel, M., Hermann, T. and Gross, A. (2010) Thulium:YAG laser enucleation (VapoEnucleation) of the prostate: safety and durability during intermediate-term follow-up. *World J Urol* 28: 39–43.

Barkin, J., Guimaraes, M., Jacobi, G., Pushkar, D., Taylor, S. and van Vierssen Trip, O. (2003) Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. *Eur Urol* 44: 461–466.

Bent, S., Kane, C., Shinohara, K., Neuhaus, J., Hudes, E., Goldberg, H. *et al.* (2006) Saw palmetto for benign prostatic hyperplasia. *N Engl J Med* 354: 557–566.

Bhansali, M., Patankar, S., Dobhada, S. and Khaladkar, S. (2009) Management of large (>60 g) prostate gland: PlasmaKinetic Superpulse (bipolar) versus conventional (monopolar) transurethral resection of the prostate. *J Endourol* 23: 141–145.

Bouchier-Hayes, G., Van Appledorn, S., Bugeja, P., Corwe, H., Challacombe, B. and Costello, A. (2009) A randomized trial of photoselective vaporization of the prostate using the 80-W potassium-titanyl-phosphate laser vs transurethral prostatectomy, with a 1-year follow-up. *BJU Int* 105: 964–969.

Boyle, P., Gould, A. and Roehrborn, C. (1996) Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 48: 398–405.

Boyle, P., Robertson, C., Lowe, F. and Roehrborn, C. (2004) Updated meta-analysis of clinical trials of Serenoa repens extract in the treatment of symptomatic benign prostatic hyperplasia. *BJU Int* 93: 751–756.

Brown, C., van der Meulen, J., Mundy, A., O'Flynn, E. and Emberton, M. (2004) Defining the components of a self-management programme for men with uncomplicated lower urinary tract symptoms: a consensus approach. *Eur Urol* 46: 254–262.

Brown, C., Yap, T., Cromwell, D., Rixon, L., Steed, L., Mulligan, K. *et al.* (2007) Self management for men with lower urinary tract symptoms: randomised controlled trial. *BMJ* 334: 25.

Bruskewitz, R., Girman, C., Fowler, J., Rigby, O., Sullivan, M., Bracken, R. *et al.* (1999) Effect of finasteride on bother and other health-related quality of life aspects associated with benign prostatic hyperplasia. PLESS Study Group. Proscar Long-term Efficacy and Safety Study. *Urology* 54: 670–678.

Chandraskar, P., Virdi, J. and Kapasi, F. (2003) Transurethral needle ablation of the prostate (TUNA) in the treatment of benign prostatic hyperplasia; a prospective randomized study, long term results. *J Urol* 169(Suppl.): 468.

Chapple, C., Al Shukri, S., Gattegno, B., Holmes, S., Martinez-Sagarra, J. and Scarpa, R. (2005) Tamsulosin oral controlled absorption system (OCAS) in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH): efficacy and tolerability in a placebo and active comparator controlled phase IIIA study. *Eur Urol Suppl* 4(2): 33–44.

Chapple, C., Montorsi, F., Tammela, T., Wirth, M., Koldewijn, E. and Fernandez, E. for the European Silodosin Study Group (2011) 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* 59: 342–352.

Chapple, C., Wyndaele, J., Nordling, J., Boeminghaus, F., Ypma, A. and Abrams, P. (1996) Tamsulosin, the first prostate-selective alpha1A-adrenoceptor antagonist. A meta-analysis of two randomized, placebo-controlled, multicentre studies in patients with benign prostatic obstruction (symptomatic BPH). *Eur Urol* 29: 155–167.

Chartier-Kastler, E., Mehnert, U., Denys, P. and Giuliano, F. (2011) Botulinum neurotoxin A for male lower urinary tract symptoms. *Curr Opin Urol* 21: 13–21.

Chen, Q., Zhang, L., Fan, Q., Zhou, J., Peng, Y. and Wang, Z. (2010) 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* 106: 1339–1343.

D'Ancona, F., Francisca, E., Witjes, W., Welling, L., Debruyne, F. and de la Rosette, J. (1998) Transurethral resection of the prostate vs high-energy thermotherapy of the prostate in patients with benign prostatic hyperplasia: long-term results. *BJU Int* 81: 259–264.

Debruyne, F., Barkin, J., van Erps, P., Reis, M., Tammela, T. and Roehrborn, C.; ARIA3001, ARIA3002 and ARIB3003 Study Investigators (2004) Efficacy and safety of long-term treatment with the dual 5 alpha-reductase inhibitor dutasteride in men with symptomatic benign prostatic hyperplasia. *Eur Urol* 46: 488–495.

Debruyne, F., Jardin, A., Colloi, D., Resel, L., Witjes, W., Delauche-Cavallier, M. *et al.* (1998) European ALFIN Study Group. Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. *Eur Urol* 34: 169–175.

de la Rosette, J., Laguan, M., Gravas, S. and de Wildt, M. (2003) Transurethral microwave thermotherapy: the gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? *J Endourol* 17: 245–251.

Denis, L., Pagano, F., Nonis, A., Robertson, C., Romano, P. and Boyle, P. (1998) Double-blind,

placebo-controlled trial to assess the efficacy and tolerability of mepartricin in the treatment of BPH. *Prostate* 37: 246–252.

Dørflinger, T., Jensen, F., Krarup, T. and Walter, S. (1992) Transurethral prostatectomy compared with incision of the prostate in the treatment of prostatism caused by small benign prostate glands. *Scand J Urol Nephrol* 26: 333–338.

Emberton, M., Cornel, E., Bassi, P., Fourcade, R., Gómez, J. and Castro, R. (2008) Benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. *Int J Clin Pract* 62: 1076–1086.

Erturhan, S., Erbagci, A., Seckiner, I., Yagci, F. and Ustun, A. (2007) Plasmakinetic resection of the prostate versus standard transurethral resection of the prostate: a prospective randomized trial with 1-year follow-up. *Prostate Cancer Prostatic Dis* 10: 97–100.

Flanigan, R., Reda, D., Wasson, J., Anderson, R., Abdellatif, M. and Bruskewitz, R. (1998) 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* 160: 12–17.

Gacci, M., Bartoletti, R., Figlioli, S., Sarti, E., Eisner, B., Boddi, V. *et al.* (2003) Urinary symptoms, quality of life and sexual function in patients with benign prostatic hypertrophy before and after prostatectomy: a prospective study. *BJU Int* 91: 196–200.

Gallucci, M., Puppo, P., Perachino, M., Fortunato, P., Muto, G., Breda, G. *et al.* (1998) Transurethral electrovaporization of the prostate vs. transurethral resection. Results of a multicentric, randomized clinical study on 150 patients. *Eur Urol* 33: 359–364.

Geavlete, B., Multescu, R., Dragutescu, M., Jecu, M., Georgescu, D. and Geavlete, P. (2010) 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* 106: 1695–1699.

Gerber, G., Kuznetsov, D., Johnson, B. and Burstein, J. (2001) Randomized, double-blind, placebo-controlled trial of saw palmetto in men with lower urinary tract symptoms. *Urology* 58: 960–965.

Gittelman, M., Ramsdell, J., Young, J. and McNicholas, T. (2006) Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. *J Urol* 176: 1045–1050.

Glemain, P., Coulange, C., Billebaud, T., Gattegno, B., Muszynski, R. and Loeb, G. for the Groupe de l'essai OCOS (2002) [Tamsulosin with or without Serenoa repens in benign prostatic hyperplasia: the OCOS trial]. *Prog Urol* 12: 395–404 (in French).

Gormley, G., Stoner, E., Bruskewitz, R., Imperator-McGinley, J., Walsh, P., McConnell, J. *et al.* (1992) The effect of finasteride in men with benign prostatic hyperplasia. *N Engl J Med* 327: 1185–1191.

Gratzke, C., Schlenker, B., Seitz, M., Karl, A., Hermanek, P., Lack, N. *et al.* (2007) Complications and early postoperative outcome after open prostatectomy in patients with benign prostatic enlargement: results of a prospective multicenter study. *J Urol* 177: 1419–1422.

Guyatt, G., Oxman, A., Kunz, R., Falck-Ytter, Y., Vist, G., Liberati, A. *et al.* for the GRADE Working Group (2008a) Going from evidence to recommendations. *BMJ* 336: 1049–1051.

Guyatt, G., Oxman, A., Kunz, R., Vist, G., Falck-Ytter, Y. and Schünemann, H. for the GRADE Working Group (2008b) What is 'quality of evidence' and why is it important to clinicians? *BMJ* 336: 995–998.

Guyatt, G., Oxman, A., Vist, G., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P. *et al.* for the GRADE Working Group (2008c) GRADE: an emerging consensus on rating quality of evidence and strengths of recommendations. *BMJ* 336: 924–926.

Hammadeh, M., Madaan, S., Hines, J. and Philip, T. (2003) 5-year outcome of a prospective randomized trial to compare transurethral electrovaporization of the prostate and standard transurethral resection. *Urology* 61: 1166–1171.

Haynes, R., Devereaux, P. and Guyatt, G. (2002) Physicians' and patients' choices in evidence based practice. *BMJ* 324: 1350.

Hill, B., Belville, W., Bruskewitz, R., Issa, M., Perez-Marrero, R., Roehrborn, C. *et al.* (2004) Transurethral needle ablation versus transurethral resection of the prostate for the treatment of symptomatic benign prostatic hyperplasia: 5-year results of a prospective, randomized, multicenter clinical trial. *J Urol* 171: 2336–2340.

Hizli, F. and Uygur, C. (2007) A prospective study of Serenoa repens, tamsulosin and Serenoa repens plus tamsulosin treatment for patients with benign prostatic hyperplasia. *Int Urol Nephrol* 39: 879–886.

Ho, H., Yip, S., Lim, K., Fook, S., Foo, K. and Cheng, C. (2007) A prospective randomized study comparing monopolar and bipolar transurethral resection of prostate using transurethral resection in saline (TURIS) system. *Eur Urol* 52: 517–522.

Hoekstra, R., Van Melick, H., Kok, E. and Ruud Bosch, J. (2010) A 10-year follow-up after transurethral resection of the prostate, contact laser prostatectomy and electrovaporization in men with benign prostatic hyperplasia; long-term results of a randomized controlled trial. *BJU Int* 106: 822–826.

Hon, N., Brathwaite, D., Hussain, Z., Ghiblawi, S., Brace, H., Hayne, D. *et al.* (2006) 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* 176: 205–209.

Horasanli, K., Silay, M., Altay, B., Tanriverdi, O., Sarica, K. and Miroglu, C. (2008) Photoselective potassium titanyl phosphate (KTP) laser vaporization versus transurethral resection of the prostate for prostates larger than 70 mL: a short-term prospective randomized trial. *Urology* 71: 247–251.

Iori, F., Franco, G., Leonardo, C., Laurenti, V., Tubaro, A., D-Amico, F. *et al.* (2008) Bipolar transurethral resection of prostate: clinical and urodynamic evaluation. *Urology* 71: 252–255.

Jahnson, S., Dalén, M., Gustavsson, G. and Pedersen, J. (1998) Transurethral incision versus resection of the prostate for small to medium benign prostatic hyperplasia. *Br J Urol* 81: 276–281.

Kaplan, S., Lee, J., Meehan, A. and Kusek, J. for the MTOPS Research Group (2011) Long-term treatment with finasteride improves clinical progression of benign prostatic hyperplasia in men with an enlarged versus a smaller prostate: data from the MTOPS trial. *J Urol* 185: 1369–1373.

Kaplan, S., Roehrborn, C., Rovner, E., Carlsson, M., Bavendam, T. and Guan, Z. (2006) Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. *JAMA* 269: 2319–2328.

Kawabe, K., Yoshida, M. and Homma, Y. (2006) Silodosin, a new alpha1A-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. *BJU Int* 98: 1019–1024.

Kaya, C., Ilktac, A., Gokmen, E., Ozturk, M. and Karaman, I. (2007) The long-term results of transurethral vaporization of the prostate using plasmakinetic energy. *BJU Int* 99: 845–848.

Kirby, R., Roehrborn, C., Boyle, P., Bartsch, G., Jardin, A., Cary, M. *et al.* (2003) Prospective European Doxazosin and Combination Therapy Study Investigators. 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* 61: 119–126.

Kong, C., Ibrahim, M. and Zainuddin, Z. (2009) A prospective, randomized clinical trial comparing bipolar plasma kinetic resection of the prostate versus conventional monopolar transurethral resection of the prostate in the treatment of benign prostatic hyperplasia. *Ann Saudi Med* 26: 429–432.

Kuntz, R. M. (2006) Current role of lasers in the treatment of benign prostatic hyperplasia (BPH). *Eur Urol* 49: 961–969.

Kuntz, R., Lehrich, K. and Ahyai, S. (2008) 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* 53: 160–166.

Landi, F., Russo, A., Liperoti, R., Cesari, M., Barillaro, C., Pahor, M. *et al.* (2007) Anticholinergic drugs and physical function among frail elderly population. *Clin Pharmacol Ther* 81: 235–241.

Larsen, E., Dørflinger, T., Gasser, T., Graversen, P. and Bruskewitz, R. (1987) Transurethral incision versus transurethral resection of the prostate for the treatment of benign prostatic hypertrophy. A preliminary report. *Scand J Urol Nephrol Suppl* 104: 83–86.

Lepor, H. (2007) Alpha blockers for the treatment of benign prostatic hyperplasia. *Rev Urol* 9: 181–190.

Lepor, H., Williford, W., Barry, M., Brawer, M., Dixon, C., Gormley, G. *et al.* (1996) The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N Engl J Med* 335: 533–539.

Lepor, H., Williford, W., Barry, M., Haakenson, C. and Jones, K. (1998) The impact of medical therapy on bother due to symptoms, quality of life and global outcome, and factors predicting response. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group *J Urol* 160: 1358–1367.

Lopatkin, N., Sivkov, A., Walther, C., Schläfke, S., Medvedev, A., Avdeichuk, J. *et al.* (2005) Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms – a placebo-controlled, double-blind, multicenter trial. *World J Urol* 23: 139–146.

Lourenco, R., Shaw, M., Fraser, C., MacLennan, G., N'Dow, J. and Pickard, R. (2010) The clinical effectiveness of transurethral incision of the prostate: a systematic review of randomised controlled trials. *World J Urol* 28: 23–32.

Lowe, F., McConnell, J., Hudson, P., Romas, N., Boake, R., Lieber, M. *et al.* for the Finasteride Study Group (2003) Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. *Urology* 61: 791–796.

Lucas, M., Stephenson, T. and Nargund, V. (2005) Tamsulosin in the management of acute urinary retention from benign prostatic hyperplasia. *BJU Int* 95: 354–357.

MacDiarmid, S., Peters, K., Chen, A., Armstrong, R., Orman, C., Aquilina, J. *et al.* (2008) 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* 83: 1002–1010.

Marberger, M. (1998) Long-term effects of finasteride in patients with benign prostatic hyperplasia: a double-blind, placebo-controlled, multicenter study. *Urology* 51: 677–686.

Marks, L., Gittelman, M., Hill, L., Volinn, W. and Hoel, G. (2009) Silodosin in the treatment of the signs and symptoms of benign prostatic hyperplasia: a 9-month, open-label extension study. *Urology* 74: 1318–1322.

Masumoiri, N., Furuya, R., Tanaka, Y., Furuya, S., Ogura, H. and Tasukamoto, T. (2010) The 12-year symptomatic outcome of transurethral resection of the prostate for patients with lower urinary tract symptoms suggestive of benign prostatic obstruction compared to the urodynamic findings before surgery. *BJU Int* 105: 1429–1433.

Mattiasson, A., Wagrell, L., Schelin, S., Nordling, J., Richthoff, J., Magnusson, B. *et al.* (2007) Five-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology* 69: 91–97.

McConnell, J., Bruskewitz, R., Walsh, P., Andriole, G., Lieber, M., Holtgrewe, H. *et al.* (1998) The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 338: 557–563.

McConnell, J., Roehrborn, C., Bautista, O., Andriole, G., Dixon, C., Kusek, J. *et al.* for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group (2003) The long-term effect of doxazosin, finasteride and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 349: 2385–2396.

McNeill, S. and Hargreave, T. (2004) Alfuzosin once daily facilitates return to voiding in patients in acute urinary retention. *J Urol* 171: 2316–2320.

McVary, K., Monnig, W., Camps, J. Jr, Young, J., Tseng, L. and van den Ende, G. (2007) Sildenafil citrate improves erectile function and urinary symptoms in men with erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia: a randomized, double-blind trial. *J Urol* 177: 1071–1077.

Mishriki, S., Grimsley, S., Nabi, G., Martindale, A. and Cohen, N. (2008) Improved quality of life and enhanced satisfaction after TURP: prospective 12-year follow-up study. *Urology* 72: 322–328.

Miyakita, H., Yokoyama, E., Onodera, Y., Utsonomiya, T., Tokunaga, M., Tojo, T. *et al.* (2010) Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Int J Urol* 17: 869–875.

Montorsi, F., Henkel, T., Geboers, A., Mirone, V., Arrosagaray, P., Morrill, B. *et al.* (2010) Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study. *Int J Clin Pract* 64: 1042–1051.

Narayan, P. and Tewari, A. (1998) A second phase III multicenter placebo-controlled study of two dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. *J Urol* 160: 1701–1706.

Naspro, R., Suardi, N., Salonia, A., Scattoni, V., Guazzoni, G., Colombo, R. *et al.* (2006) Holmium laser enucleation of the prostate versus open prostatectomy for prostates >70 g: 24-month follow-up. *Eur Urol* 50: 563–568.

Neill, M., Gilling, P., Kennett, K., Frampton, C., Westenberg, A., Fraundorfer, M. *et al.* (2006) Randomized trial comparing holmium laser enucleation of prostate with plasmakinetic enucleation of prostate for treatment of benign prostatic hyperplasia. *Urology* 68: 1020–1024.

Nickel, J., Barkin, J., Koch, C., Dupont, C. and Elhilali, M. (2008) Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. *Can Urol Assoc J* 2: 16–21.

Nickel, J., Fradet, Y., Boake, R., Pommerville, P., Perreault, J., Afridi, S. *et al.* (1996) 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* 155: 1251–1259.

Nuhoğlu, B., Ayyildiz, A., Fidan, V., Ersoy, E., Huri, E. and Germiyanoğu, C. (2005) Transurethral electrovaporization of the prostate: is it any better than standard transurethral prostatectomy? 5-year follow-up. *J Endourol* 19: 79–82.

Nuhoğlu, B., Ayyildiz, A., Karagüzel, E., Cebeci, O. and Germiyanoğlu, C. (2006) Plasmakinetic prostate resection in the treatment of benign prostate hyperplasia: results of 1-year follow up. *Int J Urol* 13: 21–24.

Oelke, M., Bachmann, A., Descazeaud, A., Emberton, M., Gravas, S., Michel, M. et al. (2011) Guidelines on the treatment of non-neurogenic male LUTS. Update March 2011. Available from: http://www.uroweb.org/gls/pdf/12_Male_LUTS.pdf (accessed 17 July 2012).

O'Leary, M., Roehrborn, C., Andriole, G., Nickel, J., Boyle, P. and Hoefner, K. (2003) Improvements in benign prostatic hyperplasia-specific quality of life with dutasteride, the novel dual 5alpha-reductase inhibitor. *BJU Int* 92: 262–266.

Ou, R., You, M., Tang, P., Chen, H., Deng, X. and Xie, K. (2010) A randomized trial of transvesical prostatectomy versus transurethral resection of the prostate for prostate greater than 80 mL. *Urology* 76: 958–961.

Patankar, S., Jamkar, A., Dobhada, S. and Gorde, B. (2006) PlasmaKinetic Superpulse transurethral resection versus conventional transurethral resection of prostate. *J Endourol* 20: 215–219.

Prieto, L., Romero, J., Lopez, C., Ortiz, M. and Pacheco, J. (2008) Efficacy of doxazosin in the treatment of acute urinary retention due to benign prostatic hyperplasia. *Urol Int* 81: 66–71.

Riehmann, M., Knes, J., Heisey, D., Masden, P. and Bruskewitz, R. (1995) Transurethral resection versus incision of the prostate: a randomized, prospective study. *Urology* 45: 768–775.

Roehrborn, C. (2008) BPH progression: concept and key learning from MTOPS, ALTESS, CombAT and ALF-ONE. *BJU Int* 101(Suppl. 3): 17–21.

Roehrborn, C. (2009) Efficacy of alpha-adrenergic receptor blockers in the treatment of male lower urinary tract symptoms. *Rev Urol* 11(Suppl. 1): S1–S8.

Roehrborn, C., Barkin, J., Siami, P., Tubaro, A., Wilson, T., Morrill, B. *et al.* (2011) Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. *BJU Int* 107: 946–954.

Roehrborn, C., Boyle, P., Bergner, D., Gray, T., Gittelman, M., Shown, T. *et al.* (1999) 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. *Urology* 54: 662–669.

Roehrborn, C., Boyle, P., Nickel, J., Hoefner, K. and Andriole, G. for the ARIA3001, ARIA3002l, ARIA3003 Study Investigators (2002) Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 60: 434–441.

Roehrborn, C., McVary, K., Elion-Mboussa, A. and Viktrup, L. (2008a) Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J Urol* 180: 1228–1234.

Roehrborn, C., Siami, P., Barkin, J., Damião, R., Major-Walker, K., Morrill, B. *et al.* for the CombAT Study Group (2008b) 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* 179: 616–621.

Roehrborn, C., Siami, P., Barkin, J., Damião, R., Major-Walker, K., Nandy, I. *et al.* for the CombAT Study Group (2010) 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* 57: 123–131.

Saporta, L., Aridogan, I., Erlich, N. and Yachia, D. (1996) Objective and subjective comparison of transurethral resection, transurethral incision and balloon dilatation of the prostate. A prospective study. *Eur Urol* 29: 439–445.

Scheife, R. and Takeda, M. (2005) Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. *Clin Ther* 27: 144–153.

Schünemann, H., Jaeschke, R., Cook, D., Bria, W., El-Solh, A., Ernst, A. *et al.* (2006) An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 174: 605–614.

Seckiner, I., Yesilli, C., Akduman, B., Alan, K. and Mungan, N. (2006) A prospective randomized study for comparing bipolar plasmakinetic resection of the prostate with standard TURP. *Urol Int* 76: 139–143.

Shiffman, R., Shekelle, P., Overhage, J., Slutsky, J., Grimshaw, J. and Deshpande, A. (2003) Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. *Ann Intern Med* 139: 493–498.

Singh, H., Desai, M., Shrivastav, P. and Vani, K. (2005) Bipolar versus monopolar transurethral resection of prostate: randomized controlled study. *J Endourol* 19: 333–338.

Singhania, P., Nandini, D., Sarita, F., Hemant, P. and Hemalata, I. (2010) Transurethral resection of prostate: a comparison of standard monopolar versus bipolar saline resection. *Int Braz J Urol* 36: 183–189.

Skolarikos, A., Papachristou, C., Athanasiadis, G., Chalikooulos, D., Deliveliotis, C. and Alivizatos, G. (2008) 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* 22: 2333–2340.

Spatafora, S., Conti, G., Perachino, M., Casarico, A., Mazzi, G. and Pappagallo, G. for the AURO.it BPH Guidelines Committee (2007) Evidence-based guidelines for the management of lower urinary tract symptoms related to uncomplicated benign prostatic hyperplasia in Italy: updated summary. *Curr Med Res Opin* 23: 1715–1732.

Stief, C., Porst, H., Neuser, D., Beneke, M. and Ulbrich, E. (2008) A randomised, placebo-controlled study to assess the efficacy of twice-daily vardenafil in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Eur Urol* 53: 1236–1244.

Suer, E., Gokce, I., Yaman, O., Anafarta, K. and Göğüş, O. (2008) Open prostatectomy is still a valid option for large prostates: a high-volume, single-center experience. *Urology* 72: 90–94.

Tammela, T. and Konturri, M. (1995) 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* 154: 1466–1469.

Tkocz, M. and Prajsner, A. (2002) Comparison of long-term results of transurethral incision of the prostate with transurethral resection of the prostate, in patient with benign prostatic hypertrophy. *Neurourol Urodyn* 21: 112–116.

Tugcu, V., Tasci, A., Sahin, S. and Zorluoglu, F. (2008) Comparison of photoselective vaporization of the prostate and transurethral resection of the prostate: a prospective nonrandomized bicenter trial with 2-year follow-up. *J Endourol* 22: 1519–1525.

van Exel, N., Koopmanschap, M., McDonnell, J., Chapple, C., Berges, R. and Rutten, F. for the TRIUMPH Pan-European Expert Panel (2006) Medical consumption and costs during a one-year follow-up of patients with LUTS suggestive of BPH in six European countries: report of the TRIUMPH study. *Eur Urol* 49: 92–102.

Wessels, H., Roy, J., Bannow, J., Grayhack, J., Matsumoto, A., Tenover, L. *et al.* for the PLESS Study Group (2003) Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. *Urology* 61: 579–584.

Wilson, L., Gilling, P., Williams, A., Kennet, K., Frampton, C., Westenberg, A. *et al.* (2006) A randomized trial comparing holmium laser enucleation versus transurethral resection in the treatment of prostates larger than 40 grams: results at 2 years. *Eur Urol* 50: 569–573.

Wilt, T., Ishani, A., MacDonald, R., Rutks, I. and Stark, G. (2002) Pygeum africanum for benign prostatic hyperplasia. *Cochrane Database Syst Rev* (1): CD001044.

Xia, S., Zhuo, J., Sun, S., Han, B., Shao, Y. and Zhang, Y. (2008) Thulium laser versus standard transurethral resection of the prostate: a randomized prospective trial. *Eur Urol* 53: 382–389.

Yang, S., Lin, W., Chang, H., Hsu, J., Lin, W., Chow, Y. *et al.* (2004) Gyrus plasmasect: is it better than monopolar transurethral resection of prostate? *Urol Int* 73: 258–261.

Yoon, C., Kim, J., Moon, K., Jung, H. and Park, T. (2006) Transurethral resection of the prostate with a bipolar tissue management system compared to conventional monopolar resectoscope: one-year outcome. *Yonsei Med J* 47: 715–720.