

# Korean clinical practice guideline for benign prostatic hyperplasia

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In 2014, the Korean Urological Association organized the Benign Prostatic Hyperplasia Guideline Developing Committee composed of experts in the field of benign prostatic hyperplasia (BPH) with the participation of the Korean Academy of Family Medicine and the Korean Continence Society to develop a Korean clinical practice guideline for BPH. The purpose of this clinical practice guideline is to provide current and comprehensive recommendations for the evaluation and treatment of BPH. The committee developed the guideline mainly by adapting existing guidelines and partially by using the *de novo* method. A comprehensive literature review was carried out primarily from 2009 to 2013 by using medical search engines including data from Korea. Based on the published evidence, recommendations were synthesized, and the level of evidence of the recommendations was determined by using methods adapted from the 2011 Oxford Centre for Evidence-Based Medicine. Meta-analysis was done for one key question and four recommendations. A draft guideline was reviewed by expert peer reviewers and discussed at an expert consensus meeting until final agreement was achieved. This evidence-based guideline for BPH provides recommendations to primary practitioners and urologists for the diagnosis and treatment of BPH in men older than 40 years.

**Keywords:** Guideline; Lower urinary tract symptoms; Prostate; Prostatic hyperplasia

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## INTRODUCTION

We aimed to provide guidelines for the evidence-based diagnosis and treatment of benign prostatic hyperplasia (BPH) and basic information about diagnostic testing, drug therapy, and surgical treatment. The target population in which to apply the guideline is men over 40 years of age who complain of lower urinary tract symptoms (LUTS). The intended users of this guideline are all physicians who care for men with BPH. This comprehensive guideline covers the

diagnosis and treatment of BPH with key questions that can be applied in clinical practice.

## METHODS USED TO FORMULATE THE GUIDELINE

The Korean Urological Association (KUA) launched a committee to develop a clinical practice guideline for BPH with the participation of the Korean Academy of Family Medicine (KAFM) and the Korean Continence Society

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(KCS). The committee comprised 17 members appointed by the KUA, KCS, and KAFM. Guideline development was based on “The manual for guideline adaptation version 20” and “The guideline for development of clinical practice guidelines version 10” published by the National Evidence-Based Healthcare Collaborating Agency in 2011. The clinical practice guideline development committee consulted with experts for the data search and meta-analysis. The committee determined 13 key questions that were required for the diagnosis and treatment of BPH under the principle of PICO (population, intervention, comparison, and outcome). For the development of this guideline, preexisting guidelines of other countries were searched from 2009 to 2013 by using the keywords “benign prostate hyperplasia” OR “lower urinary tract symptoms disease” and “guideline” OR “guideline prostate hyperplasia” OR “guideline adherence” OR “practice guideline” OR “practice guidelines as topic” OR “clinical guideline” OR “consensus” OR “recommendation” using PubMed, Cochrane Library, National Guideline Clearing House, CMA, Infobase, SIGN, and NICE for English and KoreaMed, KmBase, and RISS for Korean guidelines. The most recent version was selected when the guideline had been updated. A guideline was excluded if it was not supported by objective evidence. Six guidelines were finally selected for adaptation [1-6].

Twelve committee members evaluated the quality of the selected guidelines for adaptation by use of the Korean Appraisal of Guidelines for Research & Evaluation II (K-AGREE II). K-AGREE II was developed as a Korean version of the AGREE instrument by the Clinical Practice Guideline Executive Committee of the Korean Academy of Medical Science (KAMS). Three guidelines [2,4,5] that had over 50% standardized scores were finally selected in domain 3 (Rigor of Development).

The literature search was done in PubMed and Embase and the searching parameters were restricted to studies performed on humans between 2000 and 2013 and published in English. The reference articles are based on research conducted in men over 40 years of age with BPH. If a more recent systematic review or a meta-analysis study was found, studies with a lower level of evidence were excluded.

The Delphi method was used to arrive at consensus for the recommendations. The committee for the Delphi consensus process comprised 15 panels who were appointed by the KUA and KCS. The development committee made a first draft of the Korean BPH guideline with adaptation. The committee then prepared a questionnaire based on this first draft. The final recommendations were established with the outcomes through three rounds of the Delphi

consensus process. Recommendations that needed more scientific evidence but for which the experts agreed through the Delphi technique were clinically important questions were included. Recommendations that did not have enough scientific evidence or that did not take up a large part of debate were excluded. The agreement for each recommendation was graded with a response scale as follows: 1–3 points as without agreement, 4–6 points as uncertain, and 7–9 points as reaching agreement. If over 75% of the panels replied with a specific response scale grade, the recommendation was regarded as the consensus of the panels. The survey for the Delphi consensus consisted of the level of recommendation of each category, level of evidence based on the searched literatures, the response scale (9-point scale), and the other comment section. The recommendations were not modified if consensus was not reached in the previous round. Of a total of 30 questions, 12 questions reached consensus in the first round, 15 questions in the second, and the 3 remaining questions in the third round. The panel's response rate was 88.2%, 76.5%, and 100% at each round, respectively. The selected recommendations were incorporated into the final draft of the guideline.

The levels of evidence consisted of 3 grades based on the levels of evidence for therapy, prognosis, and diagnosis published by the Oxford Centre for Evidence-Based Medicine in 2011 ([www.cebm.net/ocebml-levels-of-evidence](http://www.cebm.net/ocebml-levels-of-evidence)). The levels of recommendation were defined with two ratings according to the median value of the Delphi consensus: (1) Strong: most or all individuals will be best served by the recommended course of action. (2) Weak: not all individuals will be best served by the recommended course of action. There is a need to consider more carefully than usual individual patient's circumstances, preferences, and values.

With the help of statistics experts, systematic reviews and meta-analysis were conducted for key question number 8 by use of RevMan ver. 7.0 (Cochrane Collaboration, Oxford, UK).

A peer review of the recommendations selected by consensus was done by a review committee consisting of 7 panels made up of 5 panels of urologists working in hospitals, 1 panel of internal medicine practitioners, and 1 panel of urology practitioners with an independent process. We held outside public hearings twice to collect opinions about the guideline. The guideline was certified by the KUA, KAFM, and KCS and obtained the certification mark of excellence from the Clinical Practice Guideline Evaluation System of the KAMS. This guideline should be updated every 4 to 5 years. The recommendations of the Korean BPH guideline are summarized in Table 1.

**Table 1.** The summary of the recommendations of the Korean clinical practice guideline on benign prostatic hyperplasia

Recommendation	Level of recommendation	Level of evidence
<b>1. Is the IPSS questionnaire more helpful than a simple medical history for diagnosis during initial assessment in BPH patients?</b>		
1-1. The IPSS is recommended for an objective assessment of symptoms at initial contact, for follow-up of symptom evolution for those on watchful waiting, and for evaluation of response to treatment.	Strong	B
<b>2. Is a voiding diary more helpful than a simple medical history to diagnose BPH patients?</b>		
2-1. A voiding diary is helpful for clarifying the information obtained from history taking and for accurate diagnosis.	Strong	B
<b>3. Do uroflowmetry and measurement of PVR volume have advantages in the establishment of treatment strategy in BPH patients?</b>		
3-1. Uroflowmetry can be conducted selectively in patients with lower urinary tract symptoms.	Strong	C
3-2. Measurement of PVR volume can be conducted selectively in patients with lower urinary tract symptoms.	Strong	C
3-3. Uroflowmetry and measurement of PVR volume can be conducted in patients with lower urinary tract symptoms and in those who need the specific evaluation of urologists.	Strong	B
<b>4. Does TRUS have a better role than DRE for the measurement of prostatic anatomy in BPH patients?</b>		
4-1. For precise evaluation of prostatic anatomy, besides DRE, TRUS is warranted.	Strong	B
<b>5. Should PSA be measured in BPH patients?</b>		
5-1. PSA should be measured in patients aged 40 years or older with LUTS.	Strong	A
<b>6. Does lifestyle modification have an advantage to improve symptoms in BPH patients?</b>		
6-1. Watchful waiting is preferred for men with mild LUTS symptoms.	Strong	B
6-2. Men with LUTS should be advised about lifestyle modification before and during treatment.	Strong	B
<b>7. Should medical treatment be considered first as the primary treatment ahead of surgical treatment in BPH patients?</b>		
7-1. Medication therapy is recommended as a primary treatment in patients with moderate or severe symptoms. But surgical intervention is an appropriate treatment as an alternative for patients with moderate to severe LUTS and for patients who develop AUR or other BPH-related complications (bladder stone, bladder diverticulum, renal failure, hematuria).	Strong	B
7-2. 5-Alpha-reductase inhibitors should be offered to men with moderate to severe lower urinary tract symptoms and enlarged prostate volume by DRE/prostate ultrasound or elevated serum PSA as BPH progression.	Strong	A
7-3. Cholinergic receptor antagonists might be considered in men with moderate to severe lower urinary tract symptoms with predominant storage symptoms. However, caution is warranted for their use in men with bladder outlet obstruction.	Strong	A
7-4. Alpha 1-blockers should be offered to men with moderate to severe lower urinary tract symptoms.	Strong	A
<b>8. Can combination therapy increase the treatment effect of alpha-blocker monotherapy in BPH patients?</b>		
8-1. The combination therapy of 5 $\alpha$ -reductase inhibitor and alpha-blocker is more effective treatment for improving lower urinary tract symptoms than alpha-blocker monotherapy in BPH patients.	Strong	A
8-2. The combination therapy of anticholinergics and alpha-blocker is performed when the effect of alpha-blocker monotherapy is insufficient in patients with moderate to severe lower urinary tract symptoms.	Strong	A
8-3. The combination therapy of anticholinergics and alpha blocker is carefully performed for men suspected of having bladder outlet obstruction and large postvoid urine volume.	Strong	A
8-4. The combination therapy of phosphodiesterase type 5 inhibitors and alpha-blocker is more effective than alpha-blocker monotherapy in reducing moderate to severe lower urinary tract symptoms.	Weak	A
<b>9. Should TWOC be considered first before surgical treatment in BPH patients with AUR?</b>		
9-1. TWOC should be considered first before surgical treatment in BPH patients with AUR.	Strong	A
9-2. Alpha-blockers are helpful for treatment of AUR before/after indwelling urethral catheter.	Strong	B
9-3. The optimal duration of urethral catheter indwelling is between 2 and 7 days after AUR.	Strong	B
<b>10. Is TURP considered the primary surgical treatment option in BPH patients rather than open prostatectomy?</b>		
10-1. TURP is considered the primary surgical treatment option in BPH patients.	Strong	C
10-2. Not only open prostatectomy but also endoscopic surgery is considered the primary treatment option, especially for prostate volume of 70 g or higher.	Strong	A

Table 1. Continued

Recommendation	Level of recommendation	Level of evidence
<b>11. What kinds of treatment can we recommend in patients inappropriate for surgical treatments for various reasons such as high-risk comorbidities?</b>		
11-1. We can recommend intermittent or indwelling catheterization for patients inappropriate for surgical treatments.	Strong	B
11-2. We can recommend the transurethral microwave thermotherapy or transurethral needle ablation as minimally invasive surgical therapies for patients inappropriate for to surgical treatments. However, patients should be aware of significant retreatment rates and less improvement in symptoms and quality of life in the aspect of long-term effects compared with transurethral resection of prostate.	Strong	A
11-3. In some patients inappropriate for surgical treatments, intraprostatic injection of botulinum toxin or emergent materials are being tried and positive results are being reported but should be performed only in clinical trials.	Strong	A
<b>12. What diagnostic tests are necessary for follow-up and how should we set the period of follow-up in BPH patients?</b>		
12-1. Follow-up for watchful waiting, medical, or surgical treatment is based on physicians' empirical data or preference.	Strong	C
12-2. IPSS, DRE, PSA, uroflowmetry, PVR volume, and TRUS are recommended at follow-up visits for monitoring of disease progression.	Strong	C
<b>13. When should you refer BPH patients to urologists?</b>		
13-1. If patients with lower urinary tract symptoms do not improve with primary medication, the patients should be referred to a urologist.	Strong	B
13-2. If patients with lower urinary tract symptoms worsen with objective findings such as urinary tract infection, hematuria, and repetitive urinary retention, the patients should be referred to a urologist.	Strong	A
13-3. If patients with lower urinary tract symptoms have abnormal results on a serum PSA test or DRE, the patients should be referred to a urologist for differential diagnosis of prostate cancer.	Strong	A

IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; PSA, prostate-specific antigen; LUTS, lower urinary tract symptoms; AUR, acute urinary retention; TWOC, trial without catheter; TURP, transurethral resection of the prostate; DRE, digital rectal examination; PVR, postvoid residual; TRUS, transrectal ultrasonography.

## RECOMMENDATIONS

### 1. Diagnostic evaluation of BPH

**KQ 1. Is the International Prostate Symptom Score (IPSS) questionnaire more helpful than a simple medical history for diagnosis during initial assessment in BPH patients?**

1-1. The IPSS is recommended for an objective assessment of symptoms at initial contact, for follow-up of symptom evolution for those on watchful waiting, and for evaluation of response to treatment. (level of evidence, B; level of recommendation, strong)

The International Prostate Symptom Score (IPSS) was adopted as a basic questionnaire standard at the International Council of BPH organized by the World Health Organization in 1993, and various studies on epidemiology and therapeutic efficacy have been done using the IPSS [7]. The IPSS is used to assess the severity of storage symptoms and voiding symptoms with one additional quality of life question. The IPSS can also be performed

multiple times to compare the progression of symptoms and their severity over months and years. However, because the IPSS and other diagnostic tests are not entirely consistent, symptom scores alone will not absolutely determine the patient's problem [8-10].

**KQ 2. Is a voiding diary more helpful than a simple medical history to diagnose BPH patients?**

2-1. A voiding diary is helpful for clarifying the information obtained from history taking and for accurate diagnosis. (level of evidence, B; level of recommendation, strong)

A frequency volume chart (time and volume of voids including any episodes of incontinence) or a bladder diary (a 24-hour record of liquid intake and urine output) is recommended for men with daytime or nocturnal frequency. A voiding diary provides objective clinical information about the patient [11,12]. Patients must be instructed to continue their normal activities during the course of the assessment, so as to obtain an accurate representation of their normal lower urinary tract function [13,14]. Nocturnal polyuria (>33%

of the 24-hour urine excretion overnight) can be diagnosed only by a bladder diary [13]. Voiding diaries are simple, noninvasive, and cost-effective and are frequently part of the initial evaluation of patients complaining of LUTS, particularly those who have storage symptoms such as increased urinary frequency and incontinence.

**KQ 3. Do uroflowmetry and measurement of postvoid residual volume (PVR) have advantages in the establishment of treatment strategy in BPH patients?**

- 3-1. Uroflowmetry can be conducted selectively in patients with LUTS. (level of evidence, C; level of recommendation, strong)
- 3-2. Measurement of PVR can be conducted selectively in patients with LUTS. (level of evidence, C; level of recommendation, strong)
- 3-3. Uroflowmetry and measurement of PVR can be conducted in patients with LUTS and in those who need the specific evaluation of urologists. (level of evidence, B; level of recommendation, strong)

Uroflowmetry is one of the broadly used evaluation tools that can provide essential information about voiding function, and it is noninvasive and swift. If maximal flow rate is low in uroflowmetry, pathologic findings including bladder outlet obstruction (BOO) or decreased detrusor muscle contraction are suspected. However, the big pitfall of uroflowmetry and measurement of PVR is that it lacks reproducibility.

For evaluation of PVR, two representative methods including sonography and catheterization can be introduced. Sonography has been validated for use as a substitute for direct catheterization for evaluation of PVR and could be useful in patients with large PVR [15,16].

**KQ 4. Does transrectal ultrasonography have a better role than digital rectal examination (DRE) for the measurement of prostatic anatomy in BPH patients?**

- 4-1. For precise evaluation of prostatic anatomy, besides DRE, transrectal ultrasonography is warranted. (level of evidence, B; level of recommendation, strong)

The DRE is one of the essential tests in the initial evaluation of BPH patients. In cases of palpable nodules by DRE, prostate biopsy is warranted. In the treatment of BPH, the precise measurement of prostate size is a quite

important issue, because prostate size itself can affect the whole course of BPH treatment [17,18]. Using prostate ultrasonography, physicians can estimate the degree of intravesical prostate protrusion (IPP), which is categorized as mild (less than 5 mm), moderate (from 5 mm to less than 10 mm), and severe (more than 10 mm). This degree of IPP is known to be related to the degree of BOO [19-21]. The accuracy of prostate ultrasonography in the measurement of prostate size has been validated for its superiority over DRE. In a large population cohort study of men who underwent radical prostatectomy for prostate cancer, the accuracy of DRE compared with a real prostate specimen was inferior to that of prostate ultrasonography, and the discrepancy was larger in cases of small prostate [22]. In cases of a large prostate size of more than 40 mL, measurement of prostate size using DRE could underestimate the real prostate size [23].

**KQ 5. Should prostate-specific antigen (PSA) be measured in BPH patients?**

- 5-1. PSA should be measured in patients aged 40 years or older with LUTS. (level of evidence, A; level of recommendation, strong)

The PSA test should only be performed if life expectancy is greater than 10 years and if a diagnosis of prostate cancer would modify the management approach [24]. Among patients without prostate cancer, serum PSA may also be a useful surrogate marker of prostate size and may also predict risk of BPH progression [25].

In Korea, a large-scale multicenter study showed that the prostate volume and serum PSA level had an age-dependent log-linear relationship, and PSA had good predictive value for various prostate volume thresholds (30, 40, and 50 mL) [26]. Many studies have reported that baseline PSA levels are positively related to overall BPH progression and the incidence rate of invasive therapy (e.g., surgery) [27-30]. Laguna et al. [31] reported that the change in quality of life was negatively related to pretreatment PSA levels. When multiple logistic regression equations were used to obtain the odds ratio (OR) of moderate plus severe symptomatic (>7) versus mild IPSS ( $\leq 7$ , reference category), the OR (and 95% confidence interval [CI]) of moderate plus severe IPSS (>7) increased as PSA levels increased (PSA $\leq 2$ : 1.0, PSA>2-4: 1.62 [1.2-2.2], PSA>4-10: 2.64 [1.5-4.7], PSA>10: 4.28 [1.8-10.3]) [32].



## 2. The treatment and follow-up of BPH

### **KQ 6. Does lifestyle modification have an advantage to improve symptoms in BPH patients?**

- 6-1. Watchful waiting is preferred for men with mild LUTS symptoms. (level of evidence, B; level of recommendation, strong)
- 6-2. Men with LUTS should be advised about lifestyle modification before and during treatment. (level of evidence, B; level of recommendation, strong)

LUTS may be stable without deterioration or may be reduced with watchful waiting (WW) [33]. A study comparing WW and transurethral resection of the prostate (TURP) in men with moderate LUTS showed that 36% of patients with WW were treated with surgical treatment within 5 years, leaving 64% being stable with WW. Response to surgery was better in men with moderate to severe LUTS than in those with mild LUTS [34]. Another study showed that 85% of men were stable with WW at 1 year; however, this percentage deteriorated progressively to 65% in 5 years [35,36].

Treatment failure rates with WW were lower in men in the lifestyle modification group, being 10% (vs. 42%), 27% (vs. 57%), and 32% (vs. 64%) at 3, 6, and 12 months, respectively [37]. Patients with WW should be monitored and reevaluated periodically in order to check for deterioration of LUTS or disease progression.

### **KQ 7. Should medical treatment be considered first as the primary treatment ahead of surgical treatment in BPH patients?**

- 7-1. Medication therapy is recommended as a primary treatment in patients with moderate or severe symptoms. But surgical intervention is an appropriate treatment as an alternative for patients with moderate to severe LUTS and for patients who develop acute urinary retention (AUR) or other BPH-related complications (bladder stone, bladder diverticulum, renal failure, hematuria). (level of evidence, B; level of recommendation, strong)
- 7-2. 5-Alpha-reductase inhibitors should be offered to men with moderate to severe LUTS and enlarged prostate volume by DRE/prostate ultrasound or elevated serum PSA as BPH progression. (level of evidence, A; level of recommendation, strong)

7-3. Cholinergic receptor antagonists might be considered in men with moderate to severe LUTS with predominant storage symptoms. However, caution is warranted for their use in men with BOO. (level of evidence, A; level of recommendation, strong)

7-4. Alpha1-blockers should be offered to men with moderate to severe LUTS. (level of evidence, A; level of recommendation, strong)

Currently, alpha1-blockers (terazosin, doxazosin, alfuzosin, tamsulosin, silodosin, and naftopidil) are appropriate and effective treatment regimens for patients with mild, moderate, or severe LUTS due to BPH [38]. Although there are slight differences in the adverse event profiles of these agents, there is no difference in clinical effectiveness among alpha-blockers. Randomized controlled studies have shown that alpha1-blockers can reduce the IPSS by approximately 35% to 40% and increase the maximum urinary flow rate (Q<sub>max</sub>) by approximately 20% to 25% [39-42]. In open-label studies (without a run-in period), the degree of improvement in the IPSS was shown to be up to 50% and that of Q<sub>max</sub> up to 40% [38]. Alpha1-blockers do not reduce prostate size and do not prevent AUR in long-term studies [39].

The most frequent side-effects of alpha-blockers are asthenia, dizziness, and orthostatic hypotension. Although a reduction in blood pressure may benefit hypertensive patients, at least some of the observed asthenia and dizziness can be attributed to a decrease in blood pressure [43]. Patients with cardiovascular comorbidity or vasoactive comedication may be susceptible to alpha-blocker-induced vasodilation [44]. A systematic review concluded that alpha1-blockers do not adversely affect libido and have a small beneficial effect on erectile function but sometimes cause abnormal ejaculation [45]. The apparently greater risk for abnormal ejaculation with tamsulosin is intriguing, because even more alpha1A-selective drugs, such as silodosin, carry a greater risk. However, all alpha1-blockers are dosed to block alpha1A-adrenoceptors effectively [45,46].

Two 5-alpha-reductase inhibitors are available for clinical use: dutasteride and finasteride. These drugs induce apoptosis of prostate epithelial cells and improve LUTS [47]. Clinical effects compared with placebo have been meaningful only after a minimum treatment duration of at least 6 to 12 months. After 2 to 4 years of treatment, 5-alpha-reductase inhibitors reduce LUTS (IPSS) by approximately 15% to 30%, decrease prostate volume by approximately 18% to 28%, and increase Q<sub>max</sub> of free uroflowmetry by approximately 1.5 to 2.0 mL/s in patients with LUTS due to prostate enlargement and delay acute urinary tract

retention (more than 1 year) [48-50]. Symptom reduction by finasteride depends on initial prostate size and may not be more efficacious than placebo in patients with prostates smaller than 40 mL [51,52]. However, dutasteride seems to reduce IPSS, prostate volume, and the risk of AUR. It also increases Q<sub>max</sub> even in patients with prostate volumes between 30 and 40 mL at baseline [53,54].

Anticholinergics (tolterodine, trospium, solifenacin, fesoterodine, propiverine, oxybutynin, and imidafenacin) are appropriate and effective regimens. In open-label trials with tolterodine, daytime frequency, nocturia, urgency incontinence, and IPSS were all significantly improved after medication at 12 to 25 weeks [55,56]. Randomized, placebo-controlled trials demonstrated that tolterodine can significantly reduce urgency incontinence and daytime or 24-hour frequency compared to placebo. Although nocturia, urgency, or IPSS have shown improvement in the majority of patients, these parameters have not made a consistent deduction without statistical significance in most clinical trials [57-59]. In men with BOO, antimuscarinic drugs are not recommended for the theoretical reason that these drugs could diminish detrusor function, resulting in an increase of PVR urine or urinary retention [60].

**KQ 8. Can combination therapy increase the treatment effect of alpha-blocker monotherapy in BPH patients?**

- 8-1. The combination therapy of 5-alpha-reductase inhibitor and alpha-blocker is a more effective treatment for improving LUTS than alpha-blocker monotherapy in BPH patients. (level of evidence, A; level of recommendation, strong)
- 8-2. The combination therapy of anticholinergics and alpha-blocker is performed when the effect of alpha-blocker monotherapy is insufficient in patients with moderate to severe LUTS. (level of evidence, A; level of recommendation, strong)
- 8-3. The combination therapy of anticholinergics and alpha-blocker is carefully performed for men suspected of having BOO and large postvoid urine volume. (level of evidence, A; level of recommendation, strong)
- 8-4. The combination therapy of phosphodiesterase type 5 (PDE5) inhibitors and alpha-blocker is more effective than alpha-blocker monotherapy in reducing moderate to severe LUTS. (level of evidence, A; level of recommendation, weak)

The SMART-1 study was performed to investigate

whether treatment effects following 24 weeks of combination treatment with dutasteride and tamsulosin could be maintained following tamsulosin discontinuation. Subjective symptoms worsened by 9% at 30 weeks for patients receiving combination therapy, and 23% for single therapy, and another 4% and 7%, respectively, by 36 weeks, thereby demonstrating prolonged benefit even after discontinuing alpha-blockers following long-term use [61].

Meta-analysis of alpha-blocker single therapy and combination therapy of alpha-blockers and 5-alpha-reductase inhibitors showed a mean improvement in IPSS of -0.49 (95% CI, -1.01 to 0.02) with combination therapy over single therapy, but without statistical significance, and a statistically significant benefit on Q<sub>max</sub> of 0.88 mL/s (95% CI, 0.40 to 1.35) for combination therapy over single therapy [27,48,49].

In 50% to 75% of cases of BOO due to BPH, storage symptoms coexist. After treatment of the BOO, those storage symptoms persist in about 38% of cases [62]. Combination treatment with alpha-blockers and anticholinergics have shown better efficacy for treating urgency or episodes of urge incontinence, which favorably enhances quality of life, compared with solitary alpha-blocker treatment or placebo treatment [63]. Combination treatment has shown superior efficacy to placebo, but additional treatment with tolterodine showed efficacy only in those patients with a PSA level less than 1.3 ng/mL [64]. Persistent or refractory LUTS have been related to bladder overactivity; hence, additional treatment with anticholinergics is effective for clinical outcomes [55,65,66].

A total of 573 records in the literature from January 1, 1990, to July 1, 2014, were searched by using search engines including MEDLINE, Embase, Cochrane, and KoreaMed. After duplicated literature was excluded, the full text of a total of 430 articles was reviewed. The final literature sample included 13 articles. The mean difference in IPSS in the combination treatment group was -1.24 (95% CI, -2.16 to -0.32), which was a significant improvement compared with the monotherapy group. The mean difference in the maximal urinary flow rate in the combination treatment group was -0.26 (95% CI, -0.60 to 0.09), which was insignificant compared with the monotherapy group. The heterogeneity of the included studies was not large, but the subgroup analysis on the types of anticholinergics was not implemented owing to the small number of included studies. This combination treatment has shown better positive clinical outcomes in improvement of LUTS, but has failed to show significant improvement of maximal urinary flow rate by systematic review and meta-analyses. In conclusion,

this combination treatment has shown efficacy and safety for those patients with moderate to severe LUTS. However, caution is warranted for the use of anticholinergics in those patients with BOO, in whom urinary retention may result [67].

As shown in a recent study on daily low-dose PDE5 inhibitors, the concomitant use of alpha-blockers and PDE5 inhibitors indicates a positive effect on voiding symptoms as well as improvement of sexual function [68]. Currently, five PDE5 inhibitors are available: sildenafil, tadalafil, vardenafil, udenafil, and mirodenafil. However, low-dose (5 mg) tadalafil is the only allowed dosage regimen for daily medication. Sildenafil is the first developed PDE5 inhibitor shown to decrease LUTS as measured by the IPSS questionnaire and improves the quality of life related to voiding [69,70]. Studies conducted to prove the efficacy of the various PDE5 inhibitors have reported positive changes in symptoms (IPSS), maximum urine flow rate (Q<sub>max</sub>), and residual volume after urination in most of the clinical trials [71-73]. Meta-analysis of the combination medication showed more effectiveness than with alpha-blocker in improving symptoms; the mean difference in IPSS was -1.93 (95% CI, -2.54 to -1.32). Furthermore, Q<sub>max</sub> was increased more in combination medication patients than in the alpha-adrenergic blocker monotherapy group; the mean difference was 0.71 (95% CI, 0.08 to 1.33). In addition, improvements in erectile function as shown by International Index of Erectile Function score were greater in the combination therapy group than in the alpha-adrenergic blocker monotherapy group; the mean difference was 3.99 (95% CI, 2.42 to 5.56). Residual urine was reduced more in combination medication patients than in alpha-blocker monotherapy patients with mean difference of -7.09 (95% CI, -13.15 to -1.04). PDE5 inhibitors show a positive effect on LUTS, as well as improved sexual function.

**KQ 9. Should trial without catheter (TWOC) be considered first before surgical treatment in BPH patients with AUR?**

- 9-1. TWOC should be considered first before surgical treatment in BPH patients with AUR. (level of evidence, A; level of recommendation, strong)
- 9-2. Alpha-blockers are helpful for treatment of AUR before/after indwelling urethral catheter. (level of evidence, B; level of recommendation, strong)
- 9-3. The optimal duration of urethral catheter indwelling is between 2 and 7 days after AUR. (level of evidence, B; level of recommendation, strong)

Recently, the use of alpha-blockers after or before urethral catheter indwelling is recommended in cases of AUR. After the removal of the urethral catheter (between 2 and 7 days after AUR) with continuation of the alpha-blocker, voiding is tried in BPH patients [74,75]. Murray et al. [76] reported that TURP is not needed in 23% of patients with a history of AUR in urodynamic study. Pickard et al. [77] showed that 9.2% patients who underwent TURP failed self-voiding, repeatedly received an indwelling urethral catheter, or did clean intermittent catheterization. Furthermore, 0.9% of patients who failed self-voiding required a permanent catheter. TWOC with concomitant use of an alpha-blocker is a simple treatment method and has an economical benefit. Manikandan et al. [78] surveyed 264 UK urologists about the first treatment method of BPH patients with AUR. A total of 98% of UK urologists reported that they used transient indwelling of a urethral catheter for these patients and 70.5% reported that they used both transient indwelling of a urethral catheter and an alpha-blocker.

**KQ 10. Is TURP considered the primary surgical treatment option in BPH patients rather than open prostatectomy?**

- 10-1. TURP is considered the primary surgical treatment option in BPH patients. (level of evidence, C; level of recommendation, strong)
- 10-2. Not only open prostatectomy but also endoscopic surgery is considered the primary treatment option, especially for prostate volume of 70 g or higher. (level of evidence, A; level of recommendation, strong)

Open prostatectomy has the advantage of complete removal of prostatic adenoma and no risk of diluted hyponatremia compared with TURP [79]. However, longer hospital stay and larger bleeding volume are observed in open prostatectomy compared with TURP due to the open surgery. Recently, Giulianelli et al. [80] reported that bipolar TURP showed a comparable surgical outcome with open prostatectomy in patients with a prostate volume of 100 g or more. In addition, holmium laser enucleation of the prostate also showed an effective surgical outcome in patients with a prostate volume of 70 g or more [81]. Even though there is controversy about the advantage of TURP over open prostatectomy in a large prostate, TURP should be considered as a primary surgical treatment option in BPH [82].



**KQ 11. What kinds of treatment can we recommend in patients inappropriate for surgical treatments for various reasons such as high-risk comorbidities?**

- 11-1. We can recommend intermittent or indwelling catheterization for patients inappropriate for surgical treatments. (level of evidence, B; level of recommendation, strong)
- 11-2. We can recommend transurethral microwave thermotherapy (TUMT) or transurethral needle ablation (TUNA) as minimally invasive surgical therapies for patients inappropriate for surgical treatments. However, patients should be aware of significant retreatment rates and less improvement in symptoms and quality of life in the aspect of long-term effects compared with transurethral resection of prostate. (level of evidence, A; level of recommendation, strong)
- 11-3. In some patients inappropriate for surgical treatments, intraprostatic injection of botulinum toxin or emergent materials are being tried and positive results are being reported but should be performed only in clinical trials. (level of evidence, A; level of recommendation, strong)

Although the complication rate associated with surgical treatment is relatively low, some patients cannot receive or accept surgical treatments because they have severe comorbidities and cannot quit medications such as anti-platelet agents or anti-coagulant agents; they do not want to experience adverse events such as retrograde ejaculation, urethral stricture, hemorrhage, electrolyte disturbances; or they are of extremely old age. Until now, several therapeutic modalities have been introduced in these patients, such as catheterization, TUMT, TUNA, prostatic stent, intraprostatic injection of botulinum toxin or emergent materials, and others. When patients choose catheterization, intermittent catheterization has significant advantages compared with indwelling catheterization in the aspects of the quality of life or satisfaction and adverse events such as symptomatic urinary tract infections [83,84]. When we consider minimally invasive surgical treatments such as TUMT or TUNA, these procedures have advantages in terms of fewer complications, possible procedures under local anesthesia, and similar short-term effects compared with TURP. However, we have to consider that these treatments have insufficient long-term effects [85-87].

Intraprostatic injection with emergent materials and embolization of prostatic arteries as minimally invasive surgical treatment is being introduced or studied, but require further evaluation for application to practice [88-90].

**KQ 12. What diagnostic tests are necessary for follow-up and how should we set the period of follow-up in BPH patients?**

- 12-1. Follow-up for watchful waiting, medical, or surgical treatment is based on physicians' empirical data or preference. (level of evidence, C; level of recommendation, strong)
- 12-2. IPSS, DRE, PSA, uroflowmetry, PVR volume, and transrectal ultrasonography are recommended at follow-up visits for monitoring of disease progression. (level of evidence, C; level of recommendation, strong)

Owing to a lack of evidence about follow-up strategies, follow-up periods and follow-up assessments are dependent on the empirical data of physicians or preference according to the treatment modalities. Patients on WW or behavioral modification should be reviewed after 6 months and then have periodic follow-up visits annually to evaluate symptom progression or the need for medical or surgical treatment. Patients with alpha-blockers should be reviewed after 2 to 6 weeks to evaluate the adverse effects of alpha-blockers and treatment response. Patients should then be monitored every 6 to 12 months [91,92]. Patients with anticholinergics should be reviewed every 4 to 6 weeks to evaluate adverse effects and to determine the treatment response. Patients with surgical treatments should be reviewed at 4 to 6 weeks after catheter removal to evaluate the treatment response, adverse events, and pathologic results.

**KQ 13. When should you refer BPH patients to urologists?**

- 13-1. If patients with LUTS do not improve with primary medication, the patients should be referred to a urologist. (level of evidence, B; level of recommendation, strong)
- 13-2. If patients with LUTS worsen with objective findings such as urinary tract infection, hematuria, and repetitive urinary retention, the patients should be referred to a urologist. (level of evidence, A; level of recommendation, strong)
- 13-3. If patients with LUTS have abnormal results on a serum PSA test or DRE, the patients should be referred to a urologist for differential diagnosis of prostate cancer. (level of evidence, A; level of recommendation, strong)

If the LUTS are not sufficiently improved after medical treatment or drug dose escalation is needed or if complications have developed that require surgical

intervention, urologist consultation or referral should be considered [93]. Drug dose escalation, adding another medication, and urologic evaluations such as uroflowmetry, PVR, and transrectal ultrasonography of the prostate are needed by a urologic specialist [94]. Also, further urological evaluations and treatments should be considered in cases of recurrent AUR after medical treatment, development of urinary incontinence, and suspicion of concomitant bladder dysfunction [28,95]. Urologist consultation is needed in case of abnormal serum PSA values [96] and abnormal DRE findings.

## CONCLUSIONS

This first clinical practical guideline following the evidence-based guideline development manual provides evidence-based advice for the diagnosis and treatment of patients with BPH in Korea. But, these guidelines cannot provide all information about every clinical case and should not restrain the clinical judgment or responsibility of individual practitioners.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## REFERENCES

1. The Korean Prostate Society. The clinical practice guidelines for benign prostatic hyperplasia. Seoul: Medrang; 2010.
2. The Management of lower urinary tract symptoms in men [Internet]. London: National Clinical Guideline Centre at the Royal College of Physicians; c2010 [cited 2014 Jun 16]. Available from: [http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0033879/pdf/PubMedHealth\\_PMH0033879.pdf](http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0033879/pdf/PubMedHealth_PMH0033879.pdf).
3. Jones C, Hill J, Chapple C; Guideline Development Group. Management of lower urinary tract symptoms in men: summary of NICE guidance. *BMJ* 2010;340:c2354.
4. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2013;64:118-40.
5. McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskewitz RC, Donnell RF, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011;185:1793-803.
6. Nickel JC, Mendez-Probst CE, Whelan TF, Paterson RF, Razvi H. 2010 Update: guidelines for the management of benign prostatic hyperplasia. *Can Urol Assoc J* 2010;4:310-6.
7. Kim JH, Doo SW, Yang WJ, Song YS. Homogeneity among the Korean international prostate symptom score questionnaires used in real practice. *Korean J Urol* 2013;54:249-51.
8. Weissfeld JL, Fagerstrom RM, O'Brien B; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Project Team. Quality control of cancer screening examination procedures in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000;21(6 Suppl):390S-399S.
9. Roehrborn CG. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. *Urology* 1998;51(4A Suppl):19-22.
10. Roehrborn CG, Sech S, Montoya J, Rhodes T, Girman CJ. Interexaminer reliability and validity of a three-dimensional model to assess prostate volume by digital rectal examination. *Urology* 2001;57:1087-92.

11. Abrams P, Klevmark B. Frequency volume charts: an indispensable part of lower urinary tract assessment. *Scand J Urol Nephrol Suppl* 1996;179:47-53.
12. Reynard JM, Yang Q, Donovan JL, Peters TJ, Schafer W, de la Rosette JJ, et al. The ICS-'BPH' Study: uroflowmetry, lower urinary tract symptoms and bladder outlet obstruction. *Br J Urol* 1998;82:619-23.
13. Weiss JB, van Kerrebroeck PE, Klein BM, Norgaard JP. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. *J Urol* 2011;186:1358-63.
14. Groutz A, Blaivas JG, Chaikin DC, Resnick NM, Engleman K, Anzalone D, et al. Noninvasive outcome measures of urinary incontinence and lower urinary tract symptoms: a multicenter study of micturition diary and pad tests. *J Urol* 2000;164(3 Pt 1):698-701.
15. D'Silva KA, Dahm P, Wong CL. Does this man with lower urinary tract symptoms have bladder outlet obstruction?: The Rational Clinical Examination: a systematic review. *JAMA* 2014;312:535-42.
16. Marks LS, Dorey FJ, Macairan ML, Park C, deKernion JB. Three-dimensional ultrasound device for rapid determination of bladder volume. *Urology* 1997;50:341-8.
17. Marks LS, Roehrborn CG, Wolford E, Wilson TH. The effect of dutasteride on the peripheral and transition zones of the prostate and the value of the transition zone index in predicting treatment response. *J Urol* 2007;177:1408-13.
18. Peeling WB. Diagnostic assessment of benign prostatic hyperplasia. *Prostate Suppl* 1989;2:51-68.
19. Foo KT. Decision making in the management of benign prostatic enlargement and the role of transabdominal ultrasound. *Int J Urol* 2010;17:974-9.
20. Chia SJ, Heng CT, Chan SP, Foo KT. Correlation of intravesical prostatic protrusion with bladder outlet obstruction. *BJU Int* 2003;91:371-4.
21. Nose H, Foo KT, Lim KB, Yokoyama T, Ozawa H, Kumon H. Accuracy of two noninvasive methods of diagnosing bladder outlet obstruction using ultrasonography: intravesical prostatic protrusion and velocity-flow video urodynamics. *Urology* 2005;65:493-7.
22. Loeb S, Han M, Roehl KA, Antenor JA, Catalona WJ. Accuracy of prostate weight estimation by digital rectal examination versus transrectal ultrasonography. *J Urol* 2005;173:63-5.
23. Roehrborn CG, Girman CJ, Rhodes T, Hanson KA, Collins GN, Sech SM, et al. Correlation between prostate size estimated by digital rectal examination and measured by transrectal ultrasound. *Urology* 1997;49:548-57.
24. Homma Y, Araki I, Igawa Y, Ozono S, Gotoh M, Yamanishi T, et al. Clinical guideline for male lower urinary tract symptoms. *Int J Urol* 2009;16:775-90.
25. Roehrborn CG, McConnell J, Bonilla J, Rosenblatt S, Hudson PB, Malek GH, et al. Serum prostate specific antigen is a strong predictor of future prostate growth in men with benign prostatic hyperplasia. PROSCAR long-term efficacy and safety study. *J Urol* 2000;163:13-20.
26. Chung BH, Hong SJ, Cho JS, Seong DH. Relationship between serum prostate-specific antigen and prostate volume in Korean men with benign prostatic hyperplasia: a multicentre study. *BJU Int* 2006;97:742-6.
27. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003;349:2387-98.
28. McConnell JD, Barry MJ, Bruskewitz RC. Benign prostatic hyperplasia: diagnosis and treatment. Agency for Health Care Policy and Research. *Clin Pract Guidel Quick Ref Guide Clin* 1994;(8):1-17.
29. Bautista OM, Kusek JW, Nyberg LM, McConnell JD, Bain RP, Miller G, et al. Study design of the Medical Therapy of Prostatic Symptoms (MTOPS) trial. *Control Clin Trials* 2003;24:224-43.
30. Roehrborn CG, Boyle P, Bergner D, Gray T, Gittelman M, Shown T, et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology* 1999;54:662-9.
31. Laguna MP, Kiemeny LA, Debruyne FM, de la Rosette JJ. Baseline prostatic specific antigen does not predict the outcome of high energy transurethral microwave thermotherapy. *J Urol* 2002;167:1727-30.
32. Tubaro A, La Vecchia C; Uroscreeing Study Group. The relation of lower urinary tract symptoms with life-style factors and objective measures of benign prostatic enlargement and obstruction: an Italian survey. *Eur Urol* 2004;45:767-72.
33. Isaacs JT. Importance of the natural history of benign prostatic hyperplasia in the evaluation of pharmacologic intervention. *Prostate Suppl* 1990;3:1-7.
34. Flanigan RC, Reda DJ, Wasson JH, Anderson RJ, Abdellatif M, Bruskewitz RC. 5-year outcome of surgical resection and watchful waiting for men with moderately symptomatic benign prostatic hyperplasia: a Department of Veterans Affairs cooperative study. *J Urol* 1998;160:12-6.
35. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* 1995;332:75-9.

36. Netto NR Jr, de Lima ML, Netto MR, D'Ancona CA. Evaluation of patients with bladder outlet obstruction and mild international prostate symptom score followed up by watchful waiting. *Urology* 1999;53:314-6.
37. Brown CT, Yap T, Cromwell DA, Rixon L, Steed L, Mulligan K, et al. Self management for men with lower urinary tract symptoms: randomised controlled trial. *BMJ* 2007;334:25.
38. Djavan B, Chapple C, Milani S, Marberger M. State of the art on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Urology* 2004;64:1081-8.
39. Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P. Alfuzosin for treatment of benign prostatic hypertrophy. The BPH-ALF Group. *Lancet* 1991;337:1457-61.
40. Buzelin JM, Roth S, Geffriaud-Ricouard C, Delauche-Cavallier MC. Efficacy and safety of sustained-release alfuzosin 5 mg in patients with benign prostatic hyperplasia. ALGEBI Study Group. *Eur Urol* 1997;31:190-8.
41. van Kerrebroeck P, Jardin A, Laval KU, van Cangh P. Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. ALFORTI Study Group. *Eur Urol* 2000;37:306-13.
42. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 2005;66:780-8.
43. Nickel JC, Sander S, Moon TD. A meta-analysis of the vascular-related safety profile and efficacy of alpha-adrenergic blockers for symptoms related to benign prostatic hyperplasia. *Int J Clin Pract* 2008;62:1547-59.
44. Barendrecht MM, Koopmans RP, de la Rosette JJ, Michel MC. Treatment of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. *BJU Int* 2005;95 Suppl 4:19-28.
45. van Dijk MM, de la Rosette JJ, Michel MC. Effects of alpha(1)-adrenoceptor antagonists on male sexual function. *Drugs* 2006;66:287-301.
46. Kawabe K, Yoshida M, Homma Y; Silodosin Clinical Study Group. 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* 2006;98:1019-24.
47. Rittmaster RS, Norman RW, Thomas LN, Rowden G. Evidence for atrophy and apoptosis in the prostates of men given finasteride. *J Clin Endocrinol Metab* 1996;81:814-9.
48. Roehrborn CG, Siami P, Barkin J, Damiao R, Major-Walker K, Morrill B, et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J Urol* 2008;179:616-21.
49. Roehrborn CG, Siami P, Barkin J, Damiao R, Major-Walker K, Nandy I, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010;57:123-31.
50. Roehrborn CG, Siami P, Barkin J, Damiao R, Becher E, Minana B, et al. The influence of baseline parameters on changes in international prostate symptom score with dutasteride, tamsulosin, and combination therapy among men with symptomatic benign prostatic hyperplasia and an enlarged prostate: 2-year data from the CombAT study. *Eur Urol* 2009;55:461-71.
51. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 1996;48:398-405.
52. Kaplan SA, Roehrborn CG, McConnell JD, Meehan AG, Suryanawanshi S, Lee JY, et al. Long-term treatment with finasteride results in a clinically significant reduction in total prostate volume compared to placebo over the full range of baseline prostate sizes in men enrolled in the MTOPS trial. *J Urol* 2008;180:1030-2.
53. Roehrborn CG, Lukkarinen O, Mark S, Siami P, Ramsdell J, Zinner N. Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5alpha-reductase inhibitor dutasteride: results of 4-year studies. *BJU Int* 2005;96:572-7.
54. Gittelman M, Ramsdell J, Young J, McNicholas T. Dutasteride improves objective and subjective disease measures in men with benign prostatic hyperplasia and modest or severe prostate enlargement. *J Urol* 2006;176:1045-50.
55. Kaplan SA, Walmsley K, Te AE. Tolterodine extended release attenuates lower urinary tract symptoms in men with benign prostatic hyperplasia. *J Urol* 2005;174:2273-5.
56. Höfner K, Burkart M, Jacob G, Jonas U. Safety and efficacy of tolterodine extended release in men with overactive bladder symptoms and presumed non-obstructive benign prostatic hyperplasia. *World J Urol* 2007;25:627-33.
57. Kaplan SA, Roehrborn CG, Chancellor M, Carlsson M, Barendam T, Guan Z. Extended-release tolterodine with or without tamsulosin in men with lower urinary tract symptoms and overactive bladder: effects on urinary symptoms assessed by the International Prostate Symptom Score. *BJU Int* 2008;102:1133-9.
58. Kaplan SA, Roehrborn CG, Dmochowski R, Rovner ES, Wang JT, Guan Z. Tolterodine extended release improves overactive bladder symptoms in men with overactive bladder and nocturia. *Urology* 2006;68:328-32.



59. Dmochowski R, Abrams P, Marschall-Kehrel D, Wang JT, Guan Z. Efficacy and tolerability of tolterodine extended release in male and female patients with overactive bladder. *Eur Urol* 2007;51:1054-64.
60. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 2006;175(3 Pt 1):999-1004.
61. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, van Vierssen Trip OB. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. *Eur Urol* 2003;44:461-6.
62. Douchamps J, Derenne F, Stockis A, Gangji D, Juvent M, Hershchuelz A. The pharmacokinetics of oxybutynin in man. *Eur J Clin Pharmacol* 1988;35:515-20.
63. Rovner ES, Kreder K, Sussman DO, Kaplan SA, Carlsson M, Bavendam T, et al. Effect of tolterodine extended release with or without tamsulosin on measures of urgency and patient reported outcomes in men with lower urinary tract symptoms. *J Urol* 2008;180:1034-41.
64. Roehrborn CG, Kaplan SA, Kraus SR, Wang JT, Bavendam T, Guan Z. Effects of serum PSA on efficacy of tolterodine extended release with or without tamsulosin in men with LUTS, including OAB. *Urology* 2008;72:1061-7.
65. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Fisis J, Perimenis P, Barbalias G. Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. *J Urol* 2003;169:2253-6.
66. Yang Y, Zhao XF, Li HZ, Wang W, Zhang Y, Xiao H, et al. Efficacy and safety of combined therapy with terazosin and tolteradine for patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: a prospective study. *Chin Med J (Engl)* 2007;120:370-4.
67. Hao N, Tian Y, Liu W, Wazir R, Wang J, Liu L, et al. Antimuscarinics and  $\alpha$ -blockers or  $\alpha$ -blockers monotherapy on lower urinary tract symptoms: a meta-analysis. *Urology* 2014;83:556-62.
68. Uckert S, Oelke M, Stief CG, Andersson KE, Jonas U, Hedlund P. Immunohistochemical distribution of cAMP- and cGMP-phosphodiesterase (PDE) isoenzymes in the human prostate. *Eur Urol* 2006;49:740-5.
69. Sairam K, Kulinskaya E, McNicholas TA, Boustead GB, Hanbury DC. Sildenafil influences lower urinary tract symptoms. *BJU Int* 2002;90:836-9.
70. Mulhall JP, Guhring P, Parker M, Hopps C. Assessment of the impact of sildenafil citrate on lower urinary tract symptoms in men with erectile dysfunction. *J Sex Med* 2006;3:662-7.
71. McVary KT, Roehrborn CG, Kaminsky JC, Auerbach SM, Wachs B, Young JM, et al. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2007;177:1401-7.
72. Porst H, McVary KT, Montorsi F, Sutherland P, Elion-Mboussa A, Wolka AM, et al. Effects of once-daily tadalafil on erectile function in men with erectile dysfunction and signs and symptoms of benign prostatic hyperplasia. *Eur Urol* 2009;56:727-35.
73. Stief CG, Porst H, Neuser D, Beneke M, Ulbrich E. 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* 2008;53:1236-44.
74. Lucas MG, Stephenson TP, Nargund V. Tamsulosin in the management of patients in acute urinary retention from benign prostatic hyperplasia. *BJU Int* 2005;95:354-7.
75. McNeill SA, Hargreave TB, Roehrborn CG; Alfaur study group. Alfuzosin 10 mg once daily in the management of acute urinary retention: results of a double-blind placebo-controlled study. *Urology* 2005;65:83-9.
76. Murray K, Massey A, Feneley RC. Acute urinary retention: a urodynamic assessment. *Br J Urol* 1984;56:468-73.
77. Pickard R, Emberton M, Neal DE. The management of men with acute urinary retention. National Prostatectomy Audit Steering Group. *Br J Urol* 1998;81:712-20.
78. Manikandan R, Srirangam SJ, O'Reilly PH, Collins GN. Management of acute urinary retention secondary to benign prostatic hyperplasia in the UK: a national survey. *BJU Int* 2004;93:84-8.
79. Tubaro A, Carter S, Hind A, Vicentini C, Miano L. A prospective study of the safety and efficacy of suprapubic transvesical prostatectomy in patients with benign prostatic hyperplasia. *J Urol* 2001;166:172-6.
80. Giulianelli R, Brunori S, Gentile BC, Vincenti G, Nardoni S, Pisanti F, et al. Comparative randomized study on the effectiveness of treatment of BOO due to BPH in patients with prostate up to 100 gr by endoscopic gyrus prostate resection versus open prostatectomy. Preliminary data. *Arch Ital Urol Androl* 2011;83:88-94.
81. Chen H, Tang P, Ou R, Deng X, Xie K. Holmium laser enucleation versus open prostatectomy for large volume benign prostatic hyperplasia: a meta-analysis of the therapeutic effect and safety. *Nan Fang Yi Ke Da Xue Xue Bao* 2012;32:882-5.
82. Lee SW, Choi JB, Lee KS, Kim TH, Son H, Jung TY, et al. Transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement: a quality and meta-analysis. *Int Neurourol J* 2013;17:59-66.
83. Logan K, Shaw C, Webber I, Samuel S, Broome L. Patients' experiences of learning clean intermittent self-catheterization: a

- qualitative study. *J Adv Nurs* 2008;62:32-40.
84. Shaw C, Logan K, Webber I, Broome L, Samuel S. Effect of clean intermittent self-catheterization on quality of life: a qualitative study. *J Adv Nurs* 2008;61:641-50.
  85. de la Rosette JJ, Laguna MP, Gravas S, de Wildt MJ. Transurethral microwave thermotherapy: the gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? *J Endourol* 2003;17:245-51.
  86. Hill B, Belville W, Bruskwewitz R, Issa M, Perez-Marrero R, Roehrborn C, et al. 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* 2004;171(6 Pt 1):2336-40.
  87. Mattiasson A, Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, et al. Five-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology* 2007;69:91-6.
  88. Li Y, Zhao Q, Dong L. Efficacy and safety of ultrasound-guided transrectal ethanol injection for the treatment of benign prostatic hyperplasia in patients with high-risk comorbidities: a long-term study at a single tertiary care institution. *Urology* 2014;83:586-91.
  89. Kuo HC. Prostate botulinum A toxin injection: an alternative treatment for benign prostatic obstruction in poor surgical candidates. *Urology* 2005;65:670-4.
  90. Silva J, Silva C, Saraiva L, Silva A, Pinto R, Dinis P, et al. Intraprostatic botulinum toxin type a injection in patients unfit for surgery presenting with refractory urinary retention and benign prostatic enlargement. Effect on prostate volume and micturition resumption. *Eur Urol* 2008;53:153-9.
  91. Chung BH. Medical management for benign prostatic hyperplasia. *Korean J Urol* 2007;48:233-43.
  92. Joung JY, Park JK, Park CH, Lee JG, Chung BH, Hong SJ, et al. The role of alpha 1 (a) adrenoceptor antagonist tamsulosin for the treatment of patients with benign prostatic hyperplasia: the effect on lower urinary tract symptoms and nocturia. *Korean J Urol* 2006;47:1-6.
  93. Abrams P, Chapple C, Khoury S, Roehrborn C, de la Rosette J; International Scientific Committee. Evaluation and treatment of lower urinary tract symptoms in older men. *J Urol* 2009;181:1779-87.
  94. Kaplan SA. Update on the american urological association guidelines for the treatment of benign prostatic hyperplasia. *Rev Urol* 2006;8 Suppl 4:S10-7.
  95. Mebust WK, Holtgrewe HL, Cockett AT, Peters PC. Transurethral prostatectomy: immediate and postoperative complications: a cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol* 1989;141:243-7.
  96. Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJ. EAU 2004 guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). *Eur Urol* 2004;46:547-54.

## EDITORIAL COMMENT

Traditionally, clinical guidelines have been based on the development of consensus among experts. However, recent guidelines should be based on the systematic identification and synthesis of the best available scientific evidence even if methodological quality does not necessarily ensure high quality content. The comprehensive and practical recommendations in this article are the first evidence-based guidelines for the diagnosis and treatment of benign prostatic hyperplasia in Korea[1] based upon the adaptation process and quality evaluation of the literature according to Appraisal of Guidelines for Research & Evaluation II [2].

Developing high-quality guidelines requires substantial time and resources. In order to reduce duplication of effort and enhance efficiency, adaptation methodology has been applied worldwide to develop high-quality clinical practice guidelines (CPG) [3]. Organization of expert panel is of paramount importance because expert panel critically review the articles and make the final recommendations and recommendation statement. Multidisciplinary academic members did participate in the developing and reviewing committee of this guideline.

Quality of evidence does not always mean the strength of recommendation. However, higher quality of evidence is more likely to receive a strong recommendation. Among 29 key questions, 28 key questions all received strong grade of recommendation even though their level of evidence was low (C in 3-1, 3-2, 10-1, 12-1, 12-2 key questions) or moderate (B in 1-1, 1-2, 3-3, 4-1, 6-1, 6-2, 7-1, 9-2, 9-3, 11-1, 13-1 key questions). However 8-4 key question 'The combination therapy of phosphodiesterase type 5 inhibitors and alpha-blocker is more effective than alpha-blocker mono-therapy in reducing moderate to severe lower urinary tract symptoms' received a weak recommendation in spite of high quality of evidence. This discrepant ranking of recommendation may be related to selection bias of review committee or inharmonious process of Delphi consensus [4]. Improving transparency from evidence to recommendations and arranging balanced participation are prerequisite to developing a better CPG. Medical guidelines are tools to assist clinicians and health policy makers in the decision making process. Therefore, strength of recommendation is usually graded by three or

four levels [5]. However, only two levels of recommendation are arbitrarily applied in this article. Hopefully, these limitations can be revised in the next updated version.

The methodology associated with developing guidelines by either de novo or adaptation process is a complex and labor-intensive process. And expertise is required at every step, from key question creation to data collection, analysis and interpretation. To make a best CPG, comprehensive strategies from urological academic society for training experts in methodology of developing guidelines are mandatory.

## CONFLICTS OF INTEREST

The author has nothing to disclose.

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## REFERENCES

1. Yeo JK, Choi H, Bae JH, Kim JH, Yang SO, Oh CY, et al. Korean clinical practice guideline for benign prostatic hyperplasia. *Investig Clin Urol* 2016;57:30-44.
2. Appraisal of guidelines for research & evaluation II instrument. The AGREE Next Steps Consortium May 2009 [Internet]. The AGREE Research Trust; 2013 [updated 2013 Sep; [cited 2016 Jan 7]. Available from: [http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument\\_2009\\_UPDATE\\_2013.pdf](http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf).
3. Fervers B, Burgers JS, Voellinger R, Brouwers M, Browman GP, Graham ID, et al. Guideline adaptation: an approach to enhance efficiency in guideline development and improve utilisation. *BMJ Qual Saf* 2011;20:228-36.
4. Lee YK, Shin ES, Shim JY, Min KJ, Kim JM, Lee SH, et al. Developing a scoring guide for the Appraisal of Guidelines for Research and Evaluation II instrument in Korea: a modified Delphi consensus process. *J Korean Med Sci* 2013;28:190-4.
5. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009;301:831-41.