Benign Prostatic Hyperplasia

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM-August 2023

To the CHI Original Benign Prostatic Hyperplasia Clinical Guidance-Issued March 2020

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

5-ARI	5-Alpha Reductase Inhibitor
AC/AP	Anticoagulant (AC) Or Antiplatelet (AP) Therapy
AEEP	Anatomic Endoscopic Enucleation of The Prostate
AUA	American Urological Association
AUR	Acute Urinary Retention
BOO	Bladder Outflow Obstruction
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
CHI	Council of Health Insurance
CPG	Clinical Practice Guidelines
DRE	Digital Rectal Exam
EAU	European Association of Urology
ED	Erectile Dysfunction
EMA	European Medicines Agency
FDA	Food and Drug Administration
HESr	hexane extracted Serenoa repens
IDF	CHI Drug Formulary
IPSS	International Prostate Symptoms Score
JUA	Japanese Urological Association
LOE	Level of Evidence
LOR	Level of Recommendation
LSP	Laparoscopic simple prostatectomy
LUTS	Lower Urinary Tract Symptoms
MLUTS	Male Lower Urinary Tract Symptoms
NICE	National Institute for Health and Care Excellence
OAB	Overactive Bladder
OSP	Open Simple Prostatectomy
PDE5	Phosphodiesterase Type 5
PSA	Prostate Specific Antigen
PVR	Post-Void Residual
RASP	Robotic-Assisted Simple Prostatectomy
SFDA	Saudi Food and Drug Authority
TUIP	Transurethral Incision of The Prostate
TURP	Transurethral Resection of the Prostate
TWOC	Trial Without Catheter

Executive Summary

Benign prostatic hyperplasia (BPH) is the noncancerous growth of prostate tissue, which commonly leads to lower urinary tract symptoms (LUTS) in men. LUTS can be further categorized into storage, voiding or mixed symptoms, replacing the older term "prostatism". Storage symptoms occur when the bladder should otherwise be storing urine, therefore symptoms include urgency, frequency, nocturia, and urge incontinence. On the other hand, voiding symptoms usually occur due to bladder outlet obstruction making it more difficult to pass urine. Voiding symptoms include hesitancy, intermittency, straining, terminal dribbling and incomplete emptying and mixed LUTS include a mix of any of the voiding and storage symptoms[1].

The development of BPH involves the proliferation of stromal and epithelial cells in the transition zone of the prostate surrounding the urethra. This leads to compression of the urethra and the development of bladder outflow obstruction (BOO), which can cause the symptoms detailed above, as well as urinary retention, and infections due to incomplete bladder emptying. If left untreated, long-term BPH can result in chronic high-pressure retention, as well as lasting changes to the bladder detrusor muscle, leading to both overactivity and reduced contractility which can results in recurrent urinary tract infection, recurrent hematuria, urinary retention, formation of bladder stones, or obstructive uropathy[1].

BPH is a condition dependent on testosterone and di-hydrotestosterone production. It has multiple predisposing risk factors: some are modifiable such as obesity, physical inactivity, diabetes mellitus, hypertension, dyslipidemia, and alcohol, while others are nonmodifiable and include age and family history[2,3].

Among men aged 65 to 70 years, there is a notably higher prevalence of BPH in the eastern region of Saudi Arabia compared to other regions. The age-standardized incidence rate of BPH in the eastern region is 10.1 per 100,000 men. In Riyadh, the rate is 7.1, while in Makkah Province, it is 5.2. The incidence is relatively lower in Jizan at 1.4 and in the Najran region at 2.0[2].

In the United States, the total cost of treating men with LUTS and BPH was estimated to be at least $1.9 billion in 2013. The expenses incurred per individual increased as they advanced in age. Within specific age groups, the average cost per person was $269 under a commercial data model and $248 under Medicare for that year[4].

Treatment options for BPH range from watchful waiting to medical and surgical treatments[1].

CHI issued Benign Prostatic Hyperplasia clinical guidance after thorough review of renowned international and national clinical guidelines in March 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI BPH clinical guidance and seeks to offer guidance for the effective management of BPH. It provides an **update on the BPH Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

The main triggers for the update are **the issuance of updated versions of previously reviewed guidelines,** namely the Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I Initial Work-up and Medical Management (**2021**), the EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction (BPO) (**2023)**, and UPDATE – Canadian Urological Association guideline: Male lower urinary tract symptoms/benign prostatic hyperplasia (**2022)**. Moreover, **new guidelines are added to the report** such as the Korean clinical practice guideline for benign prostatic hyperplasia (**2016),** Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia (**2017)**, and EAU Guidelines on Urinary Incontinence in Adults (**2020)**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to remove **Terazosin** from the CHI formulary, as it is no longer registered on the SFDA Drug List of June 2023. There have been no additional approved drugs nor changes and updates made to any of the previously listed drugs in terms of drug information and prescribing edits since March 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the BPH therapeutic management.

Below is a table summarizing the major changes based on the different BPH guidelines used to issue this report:

Table 1. General Recommendations for the Management of Benign Prostatic Hyperplasia

Management of Benign Prostatic Hyperplasia		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
When prescribing an alpha blocker for the treatment of LUTS/BPH, the choice of alpha blocker should be based on patient age and comorbidities, and different adverse event profiles (eg, ejaculatory dysfunction, changes in blood pressure).	Moderate Recommendation; Evidence Level: Grade A	AUA PART 1 guidelines 2021[5]
Clinicians may consider 5α-reductase inhibitors (5-ARIs) as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH.	Expert Opinion	AUA PART 1 guidelines 2021[5]
Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone.	Moderate Recommendation; Evidence Level: Grade C	AUA PART 1 guidelines 2021[5]
When initiating alpha blocker therapy, patients with planned cataract surgery should be informed of the associated risks and be advised to discuss these risks with their ophthalmologists.	Expert Opinion	AUA PART 1 guidelines 2021[5]
5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery.	Strong Recommendation; Evidence Level: Grade A	AUA PART 1 guidelines 2021[5]
Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side	Moderate	AUA PART 1 guidelines 2021[5]

effects, certain uncommon physical side effects, and the low risk of prostate cancer.	Recommendation; Evidence Level: Grade C	
Patients newly treated for acute urinary retention (AUR) with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC).	Expert Opinion	AUA PART 1 guidelines 2021[5]
Watchful waiting is usually a safe alternative for men who are less bothered by urinary difficulty or who wish to delay treatment. The treatment failure rate over a period of five years was 21%; 79% of patients were clinically stable.	Level of Evidence: 1b	EAU guidelines 2023[6]
Do not offer phosphodiesterase type 5 (PDE5) inhibitors for the treatment of nocturia.	Strength rating: Weak	EAU guidelines 2023[6]
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy.	Strength rating: Weak	EAU guidelines 2023[6]
Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS.	Strength rating: Strong	EAU guidelines 2023[6]
Offer Aquablation to patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate.	Strength rating: Weak	EAU guidelines 2023[6]
Inform patients about the risk of bleeding and the lack of long-term follow-up data.	Strength rating: Strong	EAU guidelines 2023[6]
Offer prostatic artery embolization (PAE) to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with transurethral resection of the prostate.	Strength rating: Weak	EAU guidelines 2023[6]

Perform PAE only in units where the work up and follow-up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients.	Strength rating: Strong	EAU guidelines 2023[6]
Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe.	Strength rating: Strong	EAU guidelines 2023[6]
Consider offering desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication.	Strength rating: Strong	EAU 2020[7]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Benign Prostatic Hyperplasia clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI BPH report, and the second includes **newly added guidelines** that have helped generate this report.

1.1. Revised Guidelines

*This section contains the **updated versions** of the guidelines mentioned in the March 2020 CHI BPH Report and the corresponding recommendations:*

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1. **American Urological Association Guideline**: Management of Benign Prostatic Hyperplasia (BPH) **[Published 2010; Reviewed and Validity Confirmed 2014]**	Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: **AUA GUIDELINE PART I** Initial Work-up and Medical Management (**2021**)
1.1.2. **European Association of Urology 2018**: Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) with Effusion (Update) & [2004] GUIDELINES ON BENIGN PROSTATIC HYPERPLASIA	**EAU Guidelines** on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) **2023**
1.1.3. **Canadian Urological Association guideline** on male lower urinary tract symptoms/benign prostatic hyperplasia (MLUTS/BPH): **2018 update**	UPDATE – **Canadian Urological Association guideline**: Male lower urinary tract symptoms/benign prostatic hyperplasia **2022**
1.1.4. **NICE guidelines** of Lower urinary tract symptoms in men: management [**published 2010 and updated 2015 then 2019**]	N/A*

*****: *No updated versions available*

1.1.1 Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I Initial Work-up and Medical Management (2021)

*Please refer to **Section 1.2** of CHI BPH original clinical guidance*

The 2021 revised edition (Part I) of the American Urological Association (AUA)'s 2014 Guidelines for Management of Benign Prostatic Hyperplasia (BPH) introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 3. AUA's Part I 2021 BPH Grading Scheme for Recommendations

	Evidence Strength A (High Certainty)	**Evidence Strength B (Moderate Certainty)**	**Evidence Strength C (Low Certainty)**
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate

	circumstances and future research is unlikely to change confidence	circumstances but better evidence could change confidence	Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		

The recommendations listed below are assigned the grades defined in the preceding table[5]:

- In the initial evaluation of patients presenting with bothersome LUTS possibly attributed to BPH, clinicians should obtain a medical history, conduct a physical examination, utilize the International Prostate Symptom Score (IPSS), and perform a urinalysis. (Clinical Principle)
- Patients should be counselled on options for intervention, which can include behavioral/lifestyle modifications, medical therapy and/or referral for discussion of procedural options. (Expert Opinion)
- Patients should be evaluated by their providers 4-12 weeks after initiating treatment (provided adverse events do not require earlier consultation) to assess response to therapy. Revaluation should include the International Prostate Symptom Score (IPSS). Further evaluation may include a post-void residual (PVR) and uroflowmetry. (Clinical Principle)

- Patients with bothersome LUTS/BPH who elect initial medical management and do not have symptom improvement and/or experience intolerable side effects should undergo further evaluation and consideration of change in medical management or surgical intervention. (Expert Opinion)
- Clinicians should offer one of the following alpha blockers as a treatment option for patients with bothersome, moderate to severe LUTS/BPH: alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin. (Moderate Recommendation; Evidence Level: Grade A)
- When prescribing an alpha blocker for the treatment of LUTS/BPH, the choice of alpha blocker should be based on patient age and comorbidities, and different adverse event profiles (eg, ejaculatory dysfunction, changes in blood pressure). (Moderate Recommendation; Evidence Level: Grade A)
- When initiating alpha blocker therapy, patients with planned cataract surgery should be informed of the associated risks and be advised to discuss these risks with their ophthalmologists. (Expert Opinion)
- For symptom improvement, 5-ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of >30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE). (Moderate Recommendation; Evidence Level: Grade B)
- 5-ARIs alone or in combination with alpha blockers are recommended as a treatment option to prevent progression of LUTS/BPH and/or reduce the risks of urinary retention and need for future prostate-related surgery. (Strong Recommendation; Evidence Level: Grade A)
- Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risk of prostate cancer. (Moderate Recommendation; Evidence Level: Grade C)
- Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. (Expert Opinion)
- For patients with LUTS/BPH irrespective of comorbid erectile dysfunction (ED), 5mg daily tadalafil should be discussed as a treatment option. (Moderate Recommendation; Evidence Level: Grade B)

- 5-ARI in combination with an alpha blocker should be offered as a treatment option only to patients with LUTS associated with demonstrable prostatic enlargement as judged by a prostate volume of >30cc on imaging, a PSA >1.5ng/dL, or palpable prostate enlargement on DRE. (Strong Recommendation; Evidence Level: Grade A)
- Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
- Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C)
- Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)
- Physicians should prescribe an oral alpha blocker prior to a voiding trial to treat patients with acute urinary retention (AUR) related to BPH. (Moderate Recommendation; Evidence Level: Grade B).
- Patients newly treated for AUR with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). (Expert Opinion)
- Clinicians should inform patients who pass a successful TWOC for AUR from BPH that they remain at increased risk for recurrent urinary retention. (Moderate Recommendation; Evidence Level: Grade C).

1.1.2 EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) 2023

*Please refer to **Section 1.3** of CHI BPH original clinical guidance*

The 2023 revised edition of the European Association of Urology (EAU)'s 2018 Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction (BPO) with Effusion, introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 4. EAU'S 2023 BPH Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Strong Recommendation	For using an intervention
Weak Recommendation	For using an intervention
Weak Recommendation	Against using an intervention
Strong Recommendation	Against using an intervention

Please note that the recommendations for principles of treatment were developed using the GRADE approach[9].

The recommendations are assigned the class of recommendations defined in the preceding figure[6]:

- Offer men with mild/moderate symptoms, minimally bothered by their symptoms watchful waiting. (Strength rating: Strong)
- Offer men with LUTS lifestyle advice and self-care information prior to, or concurrent with, treatment. (Strength rating: Strong)
- Offer α1-blockers to men with moderate-to-severe LUTS. (Strength rating: Strong)
- Use 5α-reductase inhibitors (5-ARIs) in men who have moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume > 40 mL). (Strength rating: Strong)
- Counsel patients about the slow onset of action of 5-ARIs. (Strength rating: Strong)
- Use muscarinic receptor antagonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. (Strength rating: Strong)
- Do not use antimuscarinic overactive bladder medications in men with a post-void residual volume > 150 mL. (Strength rating: Weak)
- Use beta-3 agonists in men with moderate-to-severe LUTS who mainly have bladder storage symptoms. (Strength rating: Weak)
- Use phosphodiesterase type 5 inhibitors in men with moderate-to-severe LUTS with or without erectile dysfunction. (Strength rating: Strong)
- Offer hexane extracted Serenoa repens (HESr) to men with LUTS who want to avoid any potential adverse events especially related to sexual function. (Strength rating: Weak)

- Inform the patient that the magnitude of efficacy of HESr may be modest. (Strength rating: Strong)
- Offer combination treatment with an α1-blocker and a 5α-reductase inhibitor to men with moderate-to-severe LUTS and an increased risk of disease progression (e.g. prostate volume > 40 mL). (Strength rating: Strong)
- Use combination treatment of a α1-blocker with a muscarinic receptor antagonist in patients with moderate-to-severe LUTS if relief of storage symptoms has been insufficient with monotherapy with either drug. (Strength rating: Strong)
- Do not prescribe combination treatment in men with a post-void residual volume > 150 mL. (Strength rating: Weak)
- Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy. (Strength rating: Weak)
- Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS. (Strength rating: Strong)
- Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria. (Strength rating: weak)
- Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia. (Strength rating: Strong)
- Discuss with the patient the potential clinical benefit relative to the associated risks from the use of desmopressin, especially in men > 65 years of age. (Strength rating: Strong)
- Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS. (Strength rating: Weak)
- Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder. (Strength rating: Weak)
- Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL). (Strength rating: Weak)
- Do not offer PDE5 inhibitors for the treatment of nocturia. (Strength rating: Weak)

- Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment. (Strength rating: Strong)
- Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy. (Strength rating: Weak)
- With the botulinum toxin A, warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterization (ensure that they are willing and able to do so). (Strength rating: Strong)
- Offer bipolar- or monopolar-transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size of 30-80 mL. (Strength rating: Strong)
- Offer laser resection of the prostate using Tm:YAG laser (ThuVARP) as an alternative to transurethral resection of the prostate. (Strength rating: Weak)
- Offer transurethral incision of the prostate to surgically treat moderate-to-severe LUTS in men with prostate size < 30 mL, without a middle lobe. (Strength rating: Strong)
- Offer open prostatectomy in the absence of bipolar transurethral enucleation of the prostate and holmium laser enucleation of the prostate to treat moderate-to-severe LUTS in men with prostate size > 80 mL. (Strength rating: Strong)
- Offer bipolar transurethral (plasmakinetic) enucleation of the prostate to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate. (Strength rating: Weak)
- Offer laser enucleation of the prostate using Ho:YAG laser (HoLEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate or open prostatectomy. (Strength rating: Strong)
- Offer enucleation of the prostate using the Tm:YAG laser (ThuLEP, ThuVEP) to men with moderate-to-severe LUTS as an alternative to transurethral resection of the prostate, holmium laser enucleation or bipolar transurethral (plasmakinetic) enucleation. (Strength rating: Weak)
- Offer Tm:YAG laser enucleation of the prostate to patients receiving anticoagulant or antiplatelet therapy. (Strength rating: Weak)
- Offer 120-W 980 nm, 1,318 nm or 1,470 nm diode laser enucleation of the prostate to men with moderate-to-severe LUTS as a comparable

alternative to bipolar transurethral (plasmakinetic) enucleation or bipolar transurethral resection of the prostate. (Strength rating: Weak)

- Offer bipolar transurethral vaporization of the prostate as an alternative to transurethral resection of the prostate to surgically treat moderate-to-severe LUTS in men with a prostate volume of 30-80 mL. (Strength rating: Weak)
- Offer 80-W 532-nm Potassium-Titanyl-Phosphate (KTP) laser vaporization of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate (TURP). (Strength rating: Strong)
- Offer 120-W 532-nm Lithium Borat (LBO) laser vaporization of the prostate to men with moderate-to-severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP. (Strength rating: Strong)
- Offer 180-W 532-nm LBO laser vaporization of the prostate to men with moderate-to- severe LUTS with a prostate volume of 30-80 mL as an alternative to TURP. (Strength rating: Strong)
- Offer laser vaporization of the prostate using 80-W KTP, 120- or 180-W LBO lasers for the treatment of patients receiving antiplatelet or anticoagulant therapy with a prostate volume < 80 mL. (Strength rating: Weak)
- Offer Aquablation (remains under investigation) to patients with moderate-to-severe LUTS and a prostate volume of 30-80 mL as an alternative to transurethral resection of the prostate. (Strength rating: Weak)
- Inform patients about the risk of bleeding and the lack of long-term follow-up data. (Strength rating: Strong)
- Offer prostatic artery embolization (PAE) (remains under investigation) to men with moderate-to-severe LUTS who wish to consider minimally invasive treatment options and accept less optimal outcomes compared with transurethral resection of the prostate. (Strength rating: Weak)
- Perform PAE only in units where the work up and follow-up is performed by urologists working collaboratively with trained interventional radiologists for the identification of PAE suitable patients. (Strength rating: Strong)
- Offer Prostatic urethral lift (Urolift®) to men with LUTS interested in preserving ejaculatory function, with prostates < 70 mL and no middle lobe. (Strength rating: Strong)

1.1.3 UPDATE – Canadian Urological Association guideline: Male lower urinary tract symptoms/benign prostatic hyperplasia 2022

*Please refer to **Section 1.4** of CHI BPH original clinical guidance*

Please note that the recommendations for principles of treatment were developed using the GRADE approach[9].

The guidelines recommend the following recommendations[10]:

- Alpha-blockers as an excellent first-line therapeutic option for men with symptomatic bother due to BPH who desire treatment (strong recommendation, evidence level A).
- 5-ARIs (dutasteride and finasteride) as appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement (strong recommendation, evidence level A).
- It is suggested that a combination of an alpha-adrenergic receptor blocker and a 5-ARI as an appropriate and effective treatment strategy for patients with symptomatic LUTS associated with prostatic enlargement (>30 cc) (strong recommendation, evidence level B).
- Antimuscarinics or beta-3 agonists may be useful in predominately storage symptoms and BPH and should be used with caution in those with significant BOO and/or an elevated PVR (conditional recommendation, evidence level C).
- An alpha-blocker combined with an antimuscarinic or beta-3 agonist may be useful to treat LUTS/BPH in men with both voiding and storage symptoms and failure of alpha-blocker monotherapy (conditional recommendation, evidence level B).
- Long-acting PDE5Is as monotherapy for men with LUTS/BPH, particularly in men with both LUTS and erectile dysfunction (strong recommendation, evidence level B).
- Desmopressin as a therapeutic option in men with LUTS/BPH with nocturia as result of NP (conditional recommendation, evidence level B).
- M-TURP as a standard first-line surgical therapy for men with moderate-to-severe LUTS/BPH with prostate volume of 30–80 cc (strong recommendation, evidence level A).
- Open simple prostatectomy (OSP) is recommended as a first-line surgical therapy when anatomic endoscopic enucleation of the prostate (AEEP) is

unavailable for men with moderate-to-severe LUTS/BPS and enlarged prostate volume >80 cc (strong recommendation, evidence level A).

- Laparoscopic simple prostatectomy (LSP) or Robotic-assisted simple prostatectomy (RASP) as alternative surgical therapies for men with moderate-to-severe LUTS/BPS and enlarged prostate volume >80 cc are recommended in centers where there are surgeons with high-level expertise in robotics or laparoscopy (conditional recommendation, evidence level B).
- AEEP as an alternative to TURP or OSP is recommended in men with moderate-to-severe LUTS and any size prostate >30 cc if performed by an AEEP-trained surgeon. AEEP can be safely performed in patients on AC/AP therapy (strong recommendation, evidence level A).
- TUIP to treat moderate-to-severe LUTS in men with prostate volume <30 cc without a middle lobe. Patients should be made aware of the high retreatment rate (strong recommendation, evidence level B).
- TUMT therapy as a consideration for treatment of carefully selected, well-informed men (conditional recommendation, evidence level C).
- Prostatic stents only as an alternative to catheterization in men unfit for surgery with a functional detrusor (conditional recommendation, evidence level C).
- Photoselective vaporization of the prostate (PVP) is recommended as an alternative to M-TURP or B-TURP in men with moderate-to-severe LUTS (strong recommendation based on high-quality evidence). PVP therapy is also recommended as an alternate surgical approach in men on anticoagulation or with a high cardiovascular risk (conditional recommendation, evidence level B).
- Prostatic urethral lift (UroLift) may be considered as an alternative treatment for men with LUTS interested in preserving ejaculatory function with prostates <80 cc. Prostatic urethral lift can also be be offered to patients with a small-to-moderate median lobe and bothersome LUTS. Patients (with or without a median lobe) should be made aware of the higher retreatment rate at five years (conditional recommendation, evidence level C).Rezum system of convective water vapor energy ablation may be considered an alternative treatment for men with LUTS interested in preserving ejaculatory function with prostates <80 cc, including those with a median lobe (conditional recommendation, evidence level C).

- Aquablation may be offered to men with LUTS interested in preserving ejaculatory function with prostates <150 cc, with or without a middle lobe (conditional recommendation, evidence level C).
- iTind may be offered to men with LUTS interested in preserving ejaculatory function, with prostates 30-80 cc. Patients should be made aware of the higher retreatment rate at 3 years (conditional recommendation, evidence level C).
- At centers with urological and radiological collaboration and technical expertise, highly selected, well-informed patients may be offered PAE if they wish to consider an alternative treatment option. Patients should be informed of lack of long-term durability (conditional recommendation, evidence level C).
- We have no evidence-based specific recommendation for management of detrusor underactivity (not graded).

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI BPH report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
Korean clinical practice guideline for benign prostatic hyperplasia **2016**
Clinical guidelines for **male lower urinary tract symptoms** and **benign prostatic hyperplasia 2017**
EAU Guidelines on Urinary Incontinence in Adults **2020**

1.2.1 Korean Clinical Practice Guideline for Benign Prostatic Hyperplasia (2016)

Please note that the recommendations provided have been derived from published evidence. The level of evidence supporting these recommendations was determined by using methodologies adapted from the 2011 Oxford Centre for Evidence-Based Medicine.

The Korean 2016 recommendations are listed below[8]:

- PSA should be measured in patients aged 40 years or older with LUTS. (Level of evidence, A; level of recommendation, strong)
- TWOC should be considered first before surgical treatment in BPH patients with AUR. (Level of evidence, A; level of recommendation, strong)
- Alpha-blockers are helpful for treatment of AUR before/after indwelling urethral catheter. (Level of evidence, B; level of recommendation, strong)
- The optimal duration of urethral catheter indwelling is between 2 and 7 days after AUR. (Level of evidence, B; level of recommendation, strong)
- 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)

1.2.2 Clinical Guidelines for Male Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia (2017)

The Japanese Urological Association (JUA) 2017 Grade of Recommendation and Levels of Evidence are outlined below:

Table 6. JUA'S 2017 Grading Scheme of Recommendations

Grading Scheme for Recommendations		
Evidence Level	A	Highly recommended
	B	Recommended
	C	No clear recommendation possible
	C1	Can be considered
	C2	Not recommended
	D	Recommended not to do
	Reserved	No recommendation made
	1	Evidence obtained from multiple RCTs

Recommendation Grade	2	Evidence obtained from a single RCT or low quality RCTs
	3	Evidence obtained from non-randomized controlled studies
	4	Evidence obtained from observational studies or case series
	5	Evidence obtained from case studies or expert opinions

The main recommendations issued by the JUA 2017 clinical guidelines are summarized below[11]:

- The efficacies of a1-blockers (as far as tamsulosin is concerned) and PDE5i for BPH are almost equivalent (level 2; grade B). PDE5i has efficacy for erectile dysfunction (ED); however, it is indicated differently in terms of dose and usage.

- Most cases can switch to monotherapy of 5a-reductase inhibitors without symptom aggravation after combined therapy of a1-blockers and 5a-reductase inhibitors for 6 months to 1 year (level 2; grade C1). Switching to monotherapy of a1-blockers might result in prostate regrowth and/or symptomatic worsening (level 4; grade C1). The outcomes of switching to monotherapy after combined therapy for longer than 1 year are unknown.

- PDE5i are recommended to avoid ED. Surgical therapies other than holmium laser enucleation of the prostate and photoselective vaporization of the prostate might result in ED. Surgeries, a1-blockers, 5a-reductase inhibitors and anti-androgens should be avoided to prevent ejaculatory dysfunction. To retain libido, 5a-reductase inhibitors and especially anti-androgens should be avoided (level 1–2; grade A).

- Chlormadinone and allylestrenol suppress prostate growth by inhibiting pituitary secretion of gonadotropin, and testosterone action in the prostate. The efficacy is not supported by a high level of evidence (level 2). Various adverse effects including severe sexual dysfunction can occur.

- There is some evidence for flavoxate and antidepressants improving LUTS (level 2), although they are not approved for BPH or OAB. Drowsiness is an adverse event of antidepressants.

- Cholinergics are approved for voiding difficulty as a result of detrusor underactivity; however, the efficacy is negated (level 1). Adverse events, such as diarrhea, angina, and especially cholinergic crises, are serious concerns. Cholinergics are contraindicated for BOO. They can be used by urologists with special care.

1.2.3 EAU Guidelines on Urinary Incontinence in Adults 2020

The EAU 2020 Grading Scheme for Recommendations is outlined in table 4.

Table 4. EAU'S 2020 Guidelines on Urinary Incontinence Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Strong Recommendation	For using an intervention
Weak Recommendation	For using an intervention
Weak Recommendation	Against using an intervention
Strong Recommendation	Against using an intervention

Please note that the recommendations for principles of treatment were developed using the GRADE approach[9].

The guideline recommends the following[7]:

- Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction. (Strong)

- Consider offering desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication. (Strong)

- Monitor plasma sodium levels in patients on desmopressin. (Strong)

- Offer duloxetine only to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events and that its use is off label for this indication in most European countries. (Weak).

Section 2.0 Drug Therapy in Benign Prostatic Hyperplasia

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

2.1 Additions

No new drugs have been approved by the FDA or EMA for the treatment Benign Prostatic Hyperplasia since March 2020.

2.2 Modifications

Below are the modifications made to the list of Benign Prostatic Hyperplasia drugs since the CHI report in March 2020, reflecting the changes and updates:

Table 7. Prescribing Edits Modifications of Certain Drugs Used for the Management of BPH

Drugs	PE modifications
Alpha-blockers	Alpha-blockers: Alfuzosin, Doxazosin, and Tamsulosin An "**ST, CU**" prescribing edit was added: **ST**: alpha blockers are recommended as first line therapy for BPH. **CU**: can also be used in combination with 5-alpha-reductase (in case of unresponsiveness to monotherapy) or antimuscarinic agents (in case of OAB) or b3 agonists agents (in case of OAB) in case of unresponsiveness to monotherapy.
5-alpha reductase	5-alpha reductase: Dutasteride, Finasteride **ST, CU: ST**: 5-alpha-reductase are recommended for BPH as second line therapy after alpha blockers or PDE5 inhibitors trial. **CU**: it can be used in combination with alpha blockers (in case of unresponsiveness to monotherapy) or antimuscarinic agents (in case of OAB) or b3 agonists agents (in case of OAB).
PDE5 Inhibitors	PDE5 inhibitors: Tadalafil, **Sildenafil, Avanafil, Vardenafil** added as well. **ST, CU**: **ST**: PDE5 inhibitors are recommended as first line therapy for BPH in case of Erectile Dysfunction (ED). **CU**: can also be used

	in combination with 5-alpha-reductase (in case of unresponsiveness to monotherapy) or antimuscarinic agents (in case of OAB) or b3 agonists agents (in case of OAB) in case of unresponsiveness to monotherapy.
Dutasteride + Tamsulosin hydrochloride combination	**ST, CU**: **ST**: 5-alpha-reductase are recommended for BPH as second line therapy after alpha blockers trial. **CU**: this combination can be used with antimuscarinic agents (in case of OAB) or b3 agonists agents (in case of OAB).
PDE5 inhibitors	**PDE5 inhibitors:** - Tadalafil: Maximum Daily Dose: 10 mg/day[12] instead of 5 mg/day - Vardenafil, Sildenafil, Avanafil are added All of which have as prescribing edits the following: **ST**: alpha blockers are recommended as first line therapy for BPH. **CU**: can also be used in combination with 5-alpha-reductase (in case of unresponsiveness to monotherapy) or antimuscarinic agents (in case of OAB) or b3 agonists agents (in case of OAB) in case of unresponsiveness to monotherapy.

2.3 Delisting

The medications below are no longer SFDA registered (SFDA Drug List, June 2023), therefore, it is advisable to delist the following drugs from CHI formulary.

*Please refer to **Drugs in the disease - section 2** of CHI BPH original clinical guidance*

- Terazosin active ingredient

Section 3.0 Key Recommendations Synthesis

- Patients should be evaluated by their providers 4-12 weeks after initiating treatment (provided adverse events do not require earlier consultation) to assess response to therapy. Revaluation should include the IPSS. Further evaluation may include a post-void residual (PVR) and uroflowmetry. (Clinical Principle)[5]
- Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. (Expert Opinion)[5]
- Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C)[5]
- Patients newly treated for AUR with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). (Expert Opinion)[5]
- Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia. (Strength rating: Weak)[6]
- Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy. (Strength rating: Weak)[6]
- Most cases can switch to monotherapy of 5a-reductase inhibitors without symptom aggravation after combined therapy of a1-blockers and 5a-reductase inhibitors for 6 months to 1 year (level 2; grade C1)[11]
- Surgeries, a1-blockers, 5a-reductase inhibitors, and anti-androgens should be avoided to prevent ejaculatory dysfunction. To retain libido, 5a-reductase inhibitors and especially anti-androgens should be avoided (level 1–2; grade A)[11]
- 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)[8]
- Consider offering desmopressin to patients requiring occasional short-term relief from daytime urinary incontinence and inform them that this drug is not licensed for this indication. (Strength rating: Strong)[7]

- Offer duloxetine only to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events and that its use is off label for this indication in most European countries. (Strength rating: weak)[7]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Benign Prostatic Hyperplasia report** and aims to provide recommendations to aid in the management of BPH. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with BPH. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. BPH Scope

Benign Prostatic Hyperplasia Scope

Section	Rationale/Updates
Section 1.1.1 **American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH) [Published 2010; Reviewed and Validity Confirmed 2014]**	**Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I Initial Work-up and Medical Management (2021)** [5] <u>Additional Recommendations:</u> • Patients should be evaluated by their providers 4-12 weeks after initiating treatment (provided adverse events do not require earlier consultation) to assess response to therapy. Revaluation should include the IPSS. Further evaluation may include a post-void residual (PVR) and uroflowmetry. (Clinical Principle) • For the purpose of symptom improvement, 5- ARI monotherapy should be used as a treatment option in patients with LUTS/BPH with prostatic enlargement as judged by a prostate volume of >30cc on imaging, a prostate specific antigen (PSA) > 1.5ng/dL, or palpable prostate enlargement on digital rectal exam (DRE). (Moderate Recommendation; Evidence Level: Grade B) • Before starting a 5-ARI, clinicians should inform patients of the risks of sexual side effects, certain uncommon physical side effects, and the low risk of prostate cancer. (Moderate Recommendation; Evidence Level: Grade C) • Clinicians may consider 5-ARIs as a treatment option to reduce intraoperative bleeding and peri- or postoperative need for blood transfusion after transurethral resection of the prostate (TURP) or other surgical intervention for BPH. (Expert Opinion) • Anticholinergic agents, alone or in combination with an alpha blocker, may be offered as a treatment option to patients with moderate to severe predominant storage LUTS. (Conditional Recommendation; Evidence Level: Grade C) • Beta-3-agonists in combination with an alpha blocker may be offered as a treatment option to patients with moderate to severe predominate storage LUTS. (Conditional Recommendation; Evidence Level: Grade C) • Clinicians should not offer the combination of low-dose daily 5mg tadalafil with alpha blockers for the treatment of LUTS/BPH as it offers no advantages in symptom improvement over either agent alone. (Moderate Recommendation; Evidence Level: Grade C) • Physicians should prescribe an oral alpha blocker prior to a voiding trial to treat patients with AUR related to BPH. (Moderate Recommendation; Evidence Level: Grade B). • Patients newly treated for AUR with alpha blockers should complete at least three days of medical therapy prior to attempting trial without a catheter (TWOC). (Expert Opinion) • Clinicians should inform patients who pass a successful TWOC for AUR from BPH that they remain at increased risk for recurrent urinary

	retention. (Moderate Recommendation; Evidence Level: Grade C).
Section 1..1.2 **European Association of Urology 2018: Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) with Effusion (Update) & [2004] GUIDELINES ON BENIGN PROSTATIC HYPERPLASIA**	EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) 2023 [6] <u>Additional Recommendations:</u> • Offer hexane extracted Serenoa repens to men with LUTS who want to avoid any potential adverse events especially related to sexual function. (Strength rating: Weak) • Inform the patient that the magnitude of efficacy of HESr may be modest. (Strength rating: Strong) • Use combination treatment of a α1-blocker with mirabegron in patients with persistent storage LUTS after treatment with α1-blocker monotherapy. (Strength rating: Weak) • Do not offer intraprostatic Botulinum toxin-A injection treatment to patients with male LUTS. (Strength rating: Strong) • Offer low dose desmopressin for men > 65 years of age with nocturia at least twice per night due to nocturnal polyuria. (Strength rating: weak) • Screen for hyponatremia at baseline, day three and day seven, one month after initiating therapy and periodically during treatment. Measure serum sodium more frequently in patients > 65 years of age and in patients at increased risk of hyponatremia. (Strength rating: Strong) • Offer α1-adrenergic antagonists for treating nocturia in men who have nocturia associated with LUTS. (Strength rating: Weak) • Offer antimuscarinic drugs for treating nocturia in men who have nocturia associated with overactive bladder. (Strength rating: Weak) • Offer 5α-reductase inhibitors for treating nocturia in men who have nocturia associated with LUTS and an enlarged prostate (> 40 mL). (Strength rating: Weak) • Do not offer phosphodiesterase type 5 inhibitors for the treatment of nocturia. (Strength rating: Weak) • Offer antimuscarinic drugs or mirabegron to adults with urge urinary incontinence who failed conservative treatment. (Strength rating: Strong) • Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to medical therapy. (Strength rating: Weak) • With the botulinum toxin A, warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterisation (ensure that they are willing and able to do so). (Strength rating: Strong)
Section 1..1.3 **Canadian Urological Association guideline on male lower urinary tract symptoms/benign**	**UPDATE – Canadian Urological Association guideline: Male lower urinary tract symptoms/benign prostatic hyperplasia 2022** [10] <u>Additional Recommendations:</u> • We suggest that antimuscarinics or beta-3 agonists may be useful in predominately storage symptoms and BPH, and used with caution in

prostatic hyperplasia (MLUTS/BPH): 2018 update	those with significant BOO and/or an elevated PVR (conditional recommendation, evidence level C). • We suggest that an alpha-blocker combined with an antimuscarinic or beta-3 agonist may be useful to treat LUTS/BPH in men with both voiding and storage symptoms and failure of alpha-blocker monotherapy (conditional recommendation, evidence level B). • We recommend OSP as a first-line surgical therapy when anatomic endoscopic enucleation of the prostate (AEEP) (see below) is unavailable for men with moderate-to-severe LUTS/BPS and enlarged prostate volume >80 cc (strong recommendation, evidence level A). • We recommend LSP or RASP as alternative surgical therapies for men with moderate-to-severe LUTS/BPS and enlarged prostate volume >80 cc in centers where there are surgeons with high-level expertise in robotics or laparoscopy (conditional recommendation, evidence level B). • We recommend AEEP as an alternative to TURP or OSP in men with moderate-to-severe LUTS and any size prostate >30 cc if performed by an AEEP-trained surgeon. AEEP can be safely performed in patients on AC/AP therapy (strong recommendation, evidence level A). • We recommend PVP as an alternative to M- TURP or B-TURP in men with moderate-to-severe LUTS (strong recommendation based on high-quality evidence). We also suggest GreenLight PVP therapy as an alternate surgical approach in men on anticoagulation or with a high cardiovascular risk (conditional recommendation, evidence level B). • We suggest that prostatic urethral lift (UroLift) may be considered as an alternative treatment for men with LUTS interested in preserving ejaculatory function with prostates <80 cc. Prostatic urethral lift can also be be offered to patients with a small-to-moderate median lobe and bothersome LUTS. Patients (with or without a median lobe) should be made aware of the higher retreatment rate at five years (conditional recommendation, evidence level C). • We suggest that Aquablation be offered to men with LUTS interested in preserving ejaculatory function with prostates <150 cc, with or without a middle lobe (conditional recommendation, evidence level C). • We recommend that iTind may be offered to men with LUTS interested in preserving ejaculatory function, with prostates 30-80 cc. Patients should be made aware of the higher retreatment rate at 3 years (conditional recommendation, evidence level C). • We have no evidence-based specific recommendation for management of detrusor underactivity.
Section 1.1.4 **Korean clinical practice guideline for benign prostatic hyperplasia 2016** [8]	• PSA should be measured in patients aged 40 years or older with LUTS. LOR Strong, LOE A • TWOC should be considered first before surgical treatment in BPH patients with AUR. (level of evidence, A; level of recommendation, strong) • Alpha-blockers are helpful for treatment of AUR before/after indwelling urethral catheter. (level of evidence, B; level of recommendation, strong) • The optimal duration of urethral catheter indwelling is between 2 and 7

	days after AUR. (level of evidence, B; level of recommendation, strong) • 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)
Section 1.1.5 **Clinical guidelines for male lower urinary tract symptoms and benign prostatic hyperplasia 2017** [11]	• The efficacy of a1-blockers (as far as tamsulosin is concerned) and PDE5i for BPH is almost equivalent (level 2; grade B). PDE5i has efficacy for erectile dysfunction (ED); however, it is indicated differently in terms of dose and usage. • Most cases can switch to monotherapy of 5a-reductase inhibitors without symptom aggravation after combined therapy of a1-blockers and 5a-reductase inhibitors for 6 months to 1 year (level 2; grade C1). Switching to monotherapy of a1-blockers might result in prostate regrowth and/or symptomatic worsening (level 4; grade C1). The outcomes of switching to monotherapy after combined therapy for longer than 1 year are unknown. • PDE5i are recommended to avoid ED. Surgical therapies other than holmium laser enucleation of the prostate and photoselective vaporization of the prostate might result in ED. Surgeries, a1-blockers, 5a-reductase inhibitors and anti-androgens should be avoided to prevent ejaculatory dysfunction. To retain libido, 5a-reductase inhibitors and especially anti-androgens should be avoided (level 1–2; grade A). • Chlormadinone and allylestrenol suppress prostate growth by inhibiting pituitary secretion of gonadotropin, and testosterone action in the prostate. The efficacy is not supported by a high level of evidence (level 2). Various adverse effects including severe sexual dysfunction can occur. • There is some evidence for flavoxate and antidepressants improving LUTS (level 2), although they are not approved for BPH or OAB. Drowsiness is an adverse event of antidepressants. • Cholinergics are approved for voiding difficulty as a result of detrusor underactivity; however, the efficacy is negated (level 1). Adverse events, such as diarrhea, angina and especially cholinergic crises, are serious concerns. Cholinergics are contraindicated for BOO. They can be used by urologists with special care.
Section 1.1.6 **EAU Guidelines on Urinary Incontinence in Adults 2020** [7]	• Long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction. Strong • Consider offering desmopressin to patients requiring occasional short-term relief from daytime UI and inform them that this drug is not licensed for this indication. Strong • Monitor plasma sodium levels in patients on desmopressin. Strong • Offer duloxetine only to hasten recovery of continence after prostate surgery but inform the patient about the possible adverse events and that its use is off label for this indication in most European countries weak
HTA Pharmacoeconomics Analysis	Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Benign Prostatic Hyperplasia:

Query	Search Details	Results
((((((((((((((((((Prostatic Hyperplasia[MeSH Terms]) OR (Hyperplasia, Prostatic[Title/Abstract])) OR (Adenoma, Prostatic[Title/Abstract])) OR (Adenomas, Prostatic[Title/Abstract])) OR (Prostatic Adenomas[Title/Abstract])) OR (Prostatic Adenoma[Title/Abstract])) OR (Benign Prostatic Hyperplasia[Title/Abstract])) OR (Benign Prostatic Hyperplasias[Title/Abstract])) OR (Hyperplasia, Benign Prostatic[Title/Abstract])) OR (Hyperplasias, Benign Prostatic[Title/Abstract])) OR (Prostatic Hyperplasias, Benign[Title/Abstract])) OR (Prostatic Hypertrophy, Benign[Title/Abstract])) OR (Benign Prostatic Hypertrophy[Title/Abstract])) OR (Hypertrophy, Benign Prostatic[Title/Abstract])) OR (Prostatic Hyperplasia, Benign[Title/Abstract])) OR (Prostatic Hypertrophy[Title/Abstract])) OR (Hypertrophies, Prostatic[Title/Abstract])) OR (Hypertrophy, Prostatic[Title/Abstract])) OR	"prostatic hyperplasia"[MeSH Terms] OR "hyperplasia prostatic"[Title/Abstract] OR "adenoma prostatic"[Title/Abstract] OR (("Adenoma"[MeSH Terms] OR "Adenoma"[All Fields] OR "Adenomas"[All Fields] OR "adenoma s"[All Fields]) AND "Prostatic"[Title/Abstract]) OR "prostatic adenomas"[Title/Abstract] OR "prostatic adenoma"[Title/Abstract] OR "benign prostatic hyperplasia"[Title/Abstract] OR "benign prostatic hyperplasias"[Title/Abstract] OR "hyperplasia benign prostatic"[Title/Abstract] OR (("Hyperplasia"[MeSH Terms] OR "Hyperplasia"[All Fields] OR "Hyperplasias"[All Fields]) AND "benign prostatic"[Title/Abstract]) OR (("prostat"[All Fields] OR "prostate"[MeSH Terms] OR "prostate"[All Fields] OR "prostates"[All Fields] OR "Prostatic"[All Fields] OR "prostatism"[MeSH Terms] OR "prostatism"[All Fields] OR "prostatitis"[MeSH Terms] OR "prostatitis"[All Fields]) AND "hyperplasias benign"[Title/Abstract]) OR (("prostat"[All Fields] OR "prostate"[MeSH Terms] OR "prostate"[All Fields] OR "prostates"[All Fields] OR "Prostatic"[All Fields] OR "prostatism"[MeSH Terms] OR "prostatism"[All Fields] OR "prostatitis"[MeSH Terms] OR "prostatitis"[All Fields]) AND "hypertrophy benign"[Title/Abstract]) OR "benign prostatic hypertrophy"[Title/Abstract] OR (("Hypertrophy"[MeSH Terms] OR "Hypertrophy"[All Fields] OR "hypertrophied"[All Fields] OR "Hypertrophies"[All Fields] OR "hypertrophying"[All Fields]) AND "benign prostatic"[Title/Abstract]) OR "prostatic hyperplasia benign"[Title/Abstract] OR "prostatic hypertrophy"[Title/Abstract] OR (("Hypertrophy"[MeSH Terms] OR "Hypertrophy"[All Fields] OR "hypertrophied"[All Fields] OR "Hypertrophies"[All Fields] OR "hypertrophying"[All Fields]) AND "Prostatic"[Title/Abstract]) OR "hypertrophy prostatic"[Title/Abstract] OR "prostatic hypertrophies"[Title/Abstract]	30,507

(Prostatic Hypertrophies[Title/Abstract])		

Appendix D. Treatment Algorithm