

Current status of 5 α -reductase inhibitors in the management of lower urinary tract symptoms and BPH

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Abstract

Purpose Benign prostatic hyperplasia (BPH) is a progressive disease that is commonly associated with bothersome lower urinary tract symptoms (LUTS) and might result in complications, such as acute urinary retention and BPH-related surgery. Therefore, the goals of therapy for BPH are not only to improve LUTS in terms of symptoms and urinary flow, but also to identify those patients at a risk of unfavorable disease progression and to optimize their management. This article reviews the current status of therapy with 5 α -reductase inhibitors (5ARIs), namely finasteride and dutasteride, for men with LUTS and BPH.

Method Data from key randomized controlled trials (Oxford level 1b) on the use of 5ARIs are analyzed.

Results The efficacy of 5ARIs either as monotherapy or in combination with α_1 -adrenoceptor antagonists in the management of LUTS and the impact of monotherapy and combined therapy on BPH progression are discussed. Further promises, including the withdrawal of the α -blocker from the combined medical treatment and the potential clinical implications from the use of 5ARIs for prostate cancer chemoprevention in patients receiving 5ARIs for symptomatic BPH are highlighted.

Conclusions Current evidence shows that 5ARIs are effective in treating LUTS and preventing disease progression and represent a recommended option in treatment guidelines for men who have moderate to severe LUTS and enlarged prostates.

Keywords Benign prostatic hyperplasia · Lower urinary tract symptoms · 5 α -Reductase inhibitors · Dutasteride · Finasteride · Combination treatment · Disease progression · Chemoprevention

Introduction

Lower urinary tract symptoms (LUTS) are very common in aging men and women. There is an increasing understanding that male LUTS result from several pathophysiological conditions, but benign prostatic hyperplasia (BPH) has been recognized as a major contributing factor for LUTS in aging men. It is also known that LUTS affect quality of life in the majority of those who reach average life expectancy [1]. In addition, longitudinal population-based studies which best analyse natural history of the disease have shown that BPH is a progressive disease. Progression includes increase of symptoms, acute urinary retention (AUR), and the need for BPH-related surgery [1, 2]. Therefore, it becomes evident that BPH-LUTS has significant economical implications, since an increasing number of elderly men will eventually seek help for this condition. In daily practice, therapeutic approach is usually initiated with medical treatment and, if drugs fail, minimally invasive interventions or other surgical procedures will follow.

First-line pharmacologic treatment options for men with moderate to severe LUTS include the α_1 -adrenoceptor antagonist alfuzosin, doxazosin, tamsulosin, or terazosin and the 5 α -reductase inhibitor (5ARI) finasteride or

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dutasteride. This article focuses on the role of 5ARIs in the management of LUTS and disease progression.

Mechanism of action

Normal and abnormal growth of the prostate is dependent on the presence of hormones and growth factors. The androgen dihydrotestosterone (DHT) which is converted in the cell from its precursor testosterone by the enzyme 5α -reductase, a nuclear-bound steroid enzyme localized primarily in prostatic stromal cells, is crucial in the initial development and normal growth of the prostate [3]. Two isoforms of 5ARIs have been identified: type 1 with minor expression and activity in the prostate, but predominant activity in extraprostatic tissues, such as skin or liver, and type 2 with predominant expression and activity in the prostate [4]. Both 5ARI isoenzymes are expressed in normal prostatic tissue, but over-expressed in BPH where they are responsible for the hyperplasia of stromal and epithelial cells in the transition zone and periurethral glands of the prostate that is associated with prostate gland enlargement, while in prostate cancer (PCa) cells 5AR1 expression is increased and 5AR2 expression is decreased compared with BPH tissue [5, 6]. Furthermore, both 5aR1 and 5aR2 are more prevalent in high-grade when compared with low-grade PCa [7]. 5ARIs act by apoptosis of prostatic epithelial cells, thereby reducing prostate size by an average of 15–25% over time [5, 8, 9].

Although dutasteride and finasteride are both 5ARIs, their pharmacologic and clinical profiles are different. Table 1 displays the main characteristics of 5ARIs. Clark et al. directly compared the two 5ARIs and found that dutasteride achieved a greater reduction in serum DHT concentration (94.7%) compared with finasteride (70.8%) [10]. There is no direct comparative study with regard to intraprostatic DHT concentration, but the reported suppression appears to be slightly better for dutasteride than finasteride (94–97 vs. 85–91%) [11].

Table 1 Key pharmacokinetic and pharmacodynamic characteristics of 5α -reductase inhibitors

Parameters	Dutasteride	Finasteride
5α -Reductase inhibition target	Type 1 and 2	Type 2
Metabolized in	Liver	Liver
Recommended daily dosage (mg)	1 × 0.5	1 × 5.0
Oral bioavailability (%)	60	80
T_{max} (h)	1–3	2
$T_{1/2}$	5 Weeks	6–8 h
Bound to plasma proteins (%)	99.5	90
Serum DHT suppression (%)	94.7	70.8

T_{max} time of peak serum concentration, $T_{1/2}$ elimination half time, DHT dihydrotestosterone

Efficacy in terms of International Prostate Symptom Score (IPSS) and peak urinary flow rate (Q_{max})

Monotherapy

Finasteride is the most extensively studied 5ARI. Boyle et al. performed a meta-analysis of six randomized, placebo-controlled clinical trials [12]. The most significant finding was a positive correlation between mean baseline prostate volume and mean change in symptom score or Q_{max} . Symptoms decreased by 1.8 points on the Quasi-International Prostate Symptom Score (IPSS) Scale and Q_{max} increased by 0.9 ml/s in men with prostate volumes < 20 ml compared with 2.8 points and 1.8 ml/s for men with prostate volumes > 60 ml [12]. The difference between finasteride and placebo becomes significant for men, with a baseline prostate volume of > 40 ml. Following this meta-analysis, the outcomes of the 4-year Proscar Long-term Efficacy and Safety Study (PLESS) were released [13]. Finasteride reduced prostate volume by 18% compared with an increase of 14% with placebo, improved symptom scores (3.3 points vs. 1.3 for placebo) and increased Q_{max} (1.9 vs. 0.2 ml/s for placebo) [13].

The combined analysis of the AUA-BPH Guidelines Panel found that finasteride leads to an IPSS improvement of 3.4 points at 12 months in both randomized placebo-controlled and open-label extension studies [14]. Symptom improvement is durable for up to 6 years in patients who maintained treatment. In addition, finasteride achieves a sustained Q_{max} improvement of approximately 2 ml/s. In most trials, 5ARIs are slightly less effective than α -blockers.

More recently, data from the monotherapy arm of the Medical Therapy of Prostatic Symptoms (MTOPS) study showed that prostate volume decreased by a median of 19% in patients receiving finasteride when compared with 24% increase in those receiving placebo [15]. Significant improvements over time in the IPSS and Q_{max} occurred in all monotherapy groups compared with the placebo group.

The clinical efficacy of dutasteride was evaluated in the three pivotal, 2-year, randomized, double-blind, placebo-controlled phase III trials [16]. Pooled analysis of these studies included 4,325 men and showed that dutasteride achieved a 4.5-point IPSS reduction resulting in a net difference of 2.2 points compared with placebo. Q_{max} improved significantly in the dutasteride group from 1 month, with an increase of 2.2 ml/s reported at 24 months (compared with 0.6 in the placebo group). A 26% reduction in prostate volume relative to placebo was found, with significant reductions from 1 month after treatment initiation and continuation until study end-point at 2 years. Following the completion of the blinded phase, 2,340 men entered the open-label, 24-months extension trial [17]. Dutasteride

further reduced IPSS significantly; at the end of the 48-month trial, IPSS was reduced by 6.5 points in men who received dutasteride during the entire study period and by 5.6 points in men who were initially treated with placebo and later with dutasteride. In contrast to previous findings with finasteride, there was no difference in the efficacy between prostate volumes 30–39 and ≥ 40 ml.

In a 12-month, randomized, comparative study, the Enlarged Prostate International Comparator Study (EPICS), 1,630 patients older than 50 years were randomized to dutasteride ($n = 813$) or finasteride ($n = 817$) [18]. After 1 year of treatment, prostate volume reduction from baseline was similar in both groups at 27.4%. Improvements in IPSS (6.2 vs. 5.8) and Q_{\max} (2.1 vs. 1.8 ml/s) were greater for dutasteride than finasteride, but not statistically significant.

Combination therapy

It is reasonable to assume that the combination of a 5ARI and α -blocker, which have different and complementary modes of action, would potentially maximize treatment response. However, the first randomized, placebo-controlled trials with a follow-up ≤ 12 months did not report superiority of combination treatment. Both the PROspective European Doxazosin and Combination Therapy (PRE-DICT) trial (using doxazosin and/or finasteride) and the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study (using terazosin and/or finasteride) showed that combination therapy was superior to 5ARI monotherapy, but failed to demonstrate a significant benefit over α -blocker monotherapy [19, 20]. The MTOPS Study with a follow-up of > 4 years was conducted to address the question of long-term benefit [15]. Although it was designed as a progression trial, MTOPS demonstrated that long-term combination therapy is superior to either α -blocker or 5ARI monotherapy in improving LUTS and Q_{\max} . The 4-year mean reduction in IPSS was 4.9, 6.6, 5.6, and 7.4 in the placebo, doxazosin, finasteride, and combination therapy groups, respectively. Similarly, the mean improvement in Q_{\max} was 2.8, 4.0, 3.2, and 5.1 ml/s, respectively. IPSS decrease and Q_{\max} increase in either active treatment was significantly better than placebo, doxazosin was significantly better than finasteride, and combination treatment was significantly better than either monotherapy.

The Combination of Avodart and Tamsulosin (CombAT) trial compared the efficacy of dutasteride and tamsulosin alone with the efficacy of combination therapy in men with larger prostates (> 30 ml) and higher serum PSA concentrations (1.5–10 $\mu\text{g/l}$) [21]. However, the trial did not have a placebo arm. In the pre-planned 2-year analysis, the combination treatment provided a significantly greater improvement in symptoms than either monotherapy alone [21]. At 2 years, the mean decrease from baseline IPSS was

6.2 with combination therapy, 4.9 with dutasteride, and 4.3 with tamsulosin. A statistically significant difference was achieved for combination therapy over dutasteride alone from month 3 and over tamsulosin alone from month 9. A combination therapy was also significantly more effective than either monotherapy in improving Q_{\max} at month 6 throughout month 24. The adjusted mean Q_{\max} increase in the combination group was 2.4 ml/s and significantly greater than for dutasteride and tamsulosin (1.9 and 0.9 ml/s, respectively). The adjusted mean decrease from baseline prostate volume was 26.9% in the combination therapy group and 28.0% in the dutasteride group but unchanged for tamsulosin-treated patients.

Post hoc analyses of 2-year data from the CombAT study provided useful insights into the impact of several baseline parameters on changes of IPSS and Q_{\max} [22]. It was found that combination therapy was more effective than tamsulosin or dutasteride monotherapy alone in improving IPSS and Q_{\max} after 2 years regardless of baseline parameters [22]. When compared with tamsulosin, dutasteride showed greater IPSS improvement in certain subgroups, most notably in those men with values higher than the median: IPSS > 16 , prostate volume > 49 ml, PSA > 3.5 $\mu\text{g/l}$, and IPSS-QoL score ≥ 4 . In addition, dutasteride alone or in combination was associated with significantly greater improvements in Q_{\max} compared with tamsulosin.

The 4-year data of the CombAT study has been published recently [23]. For patients who completed the study period, mean change in IPSS from baseline to year 4 was significantly higher for the combination therapy compared with tamsulosin or dutasteride alone (-7.3 , -4.9 , -6.4 , respectively). Decrease in IPSS-QoL score was significantly greater for the combination treatment (-1.5) compared with tamsulosin (-1.1) or dutasteride (-1.3). Q_{\max} improvement was significantly higher for combination treatment (2.4 ml/s) compared with tamsulosin (0.7 ml/s) or dutasteride (2 ml/s). There was a tendency towards a continuous decrease in IPSS and continuous increase in Q_{\max} for dutasteride monotherapy and combination treatment over time, whereas both parameters worsened again during tamsulosin treatment after 15–18 months. Interestingly, postvoid residual urine significantly decreased in the treatment arms containing dutasteride, but not with tamsulosin alone. Table 2 displays the key RCTs with 5ARIs.

Efficacy in terms of disease progression

Monotherapy

The goal of BPH therapy is not only to improve LUTS, but also prevent disease progression. Analysis of the placebo

Table 2 Key randomized trials with 5 α -reductase inhibitors in men with benign prostatic enlargement and LUTS

Trial	Duration (month)	Treatment arms	Patients (n)	Symptom change (IPSS)	Q_{max} change (ml/s)	Change PV (%)	BPH-surgery RR (%)	AUR RR (%)	Oxford level of evidence (1a–5)
Andersen et al. [24] ^a	24	Placebo	2,109						1b
		Finasteride	2,113	NA	NA	NA	–34 ^c	–57 ^c	
McConnell et al. [13]	48	Placebo	1,503	–1.3	+0.2	+14.0			1b
		Finasteride	1,513	–3.3 ^c	+1.9 ^c	–18.0 ^c	–55 ^c	–57 ^c	
McConnell et al. [15] ^b	54	Placebo	737	–4.0	1.4	+24.0			1b
		Doxazosin	756	–6.0 ^c	2.5 ^c	+24.0	–3	–35	
		Finasteride	768	–5.0 ^c	2.2 ^c	–19.0 ^{c,d}	–64 ^{c,d}	–68 ^{c,d}	
		Combination	786	–7.0 ^{c,d,e}	3.7 ^{c,d,e}	–19.0 ^{c,d}	–67 ^{c,d}	–81 ^{c,d}	
Roehrborn et al. [16] ^a	24	Placebo	2,158	–2.3	0.6	+1.5			1b
		Dutasteride	2,167	–4.5 ^c	2.2 ^c	–25.7 ^c	–48 ^c	–57 ^c	
Roehrborn et al. [21]	24	Tamsulosin	1,611	–4.3	0.9	0.0			1b
		Dutasteride	1,623	–4.9	1.9	–28.0	NA	NA	
		Combination	1,610	–6.2 ^{d,e}	2.4 ^{d,e}	–26.9 ^d	NA	NA	
Roehrborn et al. [23]	48	Tamsulosin	1,611	–3.8	0.7	+4.6			1b
		Dutasteride	1,623	–5.3	2.0	–28.0 ^d	–31.1 ^d	–18.3 ^d	
		Combination	1,610	–6.3 ^{d,e}	2.4 ^{d,e}	–27.3 ^d	–70.6 ^d	–67.6 ^d	

Q_{max} maximum urinary flow rate, PV prostate volume, AUR acute urinary retention, RR risk reduction vs. placebo, NA not assessed

^a Pooled data

^b Median values

^c Significant compared with placebo

^d Significant compared with α -blocker

^e Significant compared with 5 α -reductase inhibitor

arm (737 men) of the MTOPS study showed that the rate of overall clinical progression of BPH events in the placebo group was 4.5 per 100 person-years, for a cumulative incidence of 17% among men who had follow-up data of at least 4 years [15]. Several risks factors at baseline were identified for disease progression, such as prostate volume ≥ 31 ml, PSA concentration ≥ 1.6 μ g/l, $Q_{max} \leq 10.6$ ml/s, postvoid residual volume ≥ 39 ml, and age ≥ 62 years. Risk reduction is mediated through decrease in prostate volume and possibly through decrease in bladder outlet resistance. In the PLESS study after 4 years, finasteride treatment reduced the relative risk of AUR by 57% (AUR occurred in 7% of men receiving placebo and 3% receiving finasteride) and surgery by 55% (10% of men receiving placebo and 5% receiving finasteride) [13]. In the MTOPS study, a significant reduction in the risk of overall clinical progression (defined as IPSS increase ≥ 4 points, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infections) by 34% in the finasteride arm compared with placebo (to 2.9 per 100 person-years) was shown [15]. An earlier pooled analysis of randomized trials with 2-year follow-up data clearly indicated that the treatment with finasteride significantly decreased the occurrence

of AUR by 57% and surgical intervention by 34% with an overall 35% reduction in the two BPH-related endpoints relative to placebo in patients with moderately symptomatic BPH [24].

Dutasteride has also demonstrated efficacy in reducing the risks for AUR and BPH-related surgery. Pooled phase III studies have shown a reduced relative risk of AUR (57%) and a surgical intervention (48%) compared with placebo at 2 years [16]. In addition, this reduction was maintained to 4 years during the open-label phase of the study [23, 25].

Combination therapy

The impact of combination treatment on BPH progression has also been evaluated from the MTOPS trial that included 3,047 men treated for an average of 4.5 years. This landmark study showed that the risk of long-term clinical progression (primarily due to increasing IPSS) was reduced by 66% with combined therapy (vs. placebo) and to a greater extent than with either finasteride or doxazosin monotherapy (34 and 39%, respectively) [15]. When only the risks of AUR and need for BPH-related surgery over the 4-year

study were analyzed, finasteride, alone or in combination, but not doxazosin significantly reduced both risks. Rates of AUR were 0.2 events/100 person-years in the finasteride group, 0.1 events/100 person-years in the combination therapy group, 0.4 events/100 person-years in the doxazosin group, and 0.6 events/100 person-years in the placebo group. In terms of risk for invasive BPH therapy, the placebo group experienced 1.3 events/100 person-years compared to 0.5 events/100 person-years with finasteride, 0.4 events/100 person-years with combination therapy, and 1.3 events/100 person-years with doxazosin. Subsequent analysis of the MTOPS data concluded that men with prostate volumes of 25 ml or more have a greater benefit from combination therapy in terms of reducing risk of long-term clinical progression compared with either monotherapy [26].

In the CombAT trial, entry thresholds for prostate volume (≥ 30 ml) and PSA serum concentration (≥ 1.5 $\mu\text{g/l}$) have been used to select patients with higher risk of disease progression [21]. The predefined 4-year primary endpoints were reduction in the risks of AUR and BPH-related surgery [23]. BPH overall disease progression (defined as symptom deterioration ≥ 4 IPSS points, AUR, incontinence, recurrent urinary tract infections, or renal insufficiency) appeared after 4 years in 12.6% of patients with the combination of dutasteride and tamsulosin, but in 17.8% with dutasteride, and in 21.5% with tamsulosin. The reduction in the relative risk of overall disease progression was significantly greater for the combination treatment (-31.2% compared to dutasteride and -44.1% compared to tamsulosin). When compared with tamsulosin, combination therapy reduced the relative risks of AUR by 67.8%, BPH-related surgery by 70.6% and symptom deterioration by 41.3% after 4 years.

Discontinuation therapy

5ARIs need several months to develop clinical efficacy, whereas α -blockers act within hours or a couple of days; therefore, many clinicians initially use α -blockers for fast symptom relief until efficacy of 5ARIs is achieved. The randomized, double-blind, placebo-controlled Symptom Management After Reducing Therapy (SMART) trial evaluated the combination of tamsulosin with dutasteride and the impact of tamsulosin discontinuation after 6 months [27]. After discontinuation of the α -blocker, almost three quarters of patients reported no worsening of symptoms. However, patients with severe symptoms (IPSS ≥ 20) at baseline may benefit from longer combination therapy.

A recent prospective open-label multicentre trial evaluated the equivalence of the efficacy and safety of combination therapy (finasteride plus α -blocker) for 9 months, followed by monotherapy with finasteride alone for 3 or

9 months [28]. Equivalence was defined as mean difference of ≤ 2 IPSS points between the end of the combination period and the end of each monotherapy period. LUTS improvement after combination therapy was sustained for 3 months (IPSS difference 1.24) and 9 months (IPSS difference -0.44) with a similar safety profile. The main limitations of such studies include the short duration of the combination therapy and the short follow-up period.

In a retrospective study using a large managed care member database, the likelihood of α -blocker discontinuation was evaluated over a 12-month period in 1,674 patients aged ≥ 65 years receiving α -blockers in combination therapy with either dutasteride or finasteride [29]. Dutasteride patients discontinued α -blocker therapy 64% faster than finasteride patients at any time point. At 12 months, 62% of patients were treated with dutasteride alone compared to 43.7% of men treated with finasteride alone. Despite its limitations regarding the retrospective nature and the subjective decision of α -blocker cessation, this study has shown a difference in rate and timing in favor of dutasteride which may have clinical implications requiring further examination.

Safety-adverse events

5ARIs are well tolerated and have only minimal side effects. The most common adverse events (AE) are sexual dysfunction including, reduced libido, erectile dysfunction and, less frequently, ejaculation disorders which occur more frequently in recipients with 5ARIs than with placebo [5, 9]. Gynecomastia appears in approximately 1–2% of patients. The new onset of most drug-related AEs usually arises within the first year of treatment, and new-onset AE rates after the first year are often similar to those among patients receiving placebo. It seems that drug-related sexual dysfunction do not represent a clinically significant cause of treatment withdrawal [5, 9].

It has also been reported that dutasteride and finasteride have a similar safety profile. In a 1-year comparative trial in men who received either dutasteride ($n = 813$) or finasteride ($n = 817$), the incidence of impotence (7 vs. 8%), decreased libido (5 vs. 6%), ejaculation disorders (1% in both groups), gynecomastia (1% in both groups), headache (1% in both groups), and malaise/fatigue (1% in both groups) did not differ significantly [30]. In both COMBAT and MTOPS, drug-related AEs were more frequent during combination treatment than for either monotherapy [15, 21, 23].

5ARIs and PSA

Serum PSA concentration is used as a proxy parameter for prostate volume and marker for PCa. In most clinical

guidelines, PSA evaluation is recommended during initial evaluation of patients with LUTS [14, 31]. A higher PSA value is a good predictor for the risk of AUR and need for surgery in men with BPH-LUTS [15, 32].

Dihydrotestosterone, the predominant factor of exocrine secretion of prostatic epithelial cells, is the main source of intraprostatic and serum PSA. The use of 5ARIs results in serum PSA decrease of about 50% after 6–12 months [33, 34]. Therefore, PSA concentration has to be doubled for counseling and clinical decision making in men receiving 5ARIs. Marks et al. performed an extensive review of available studies and concluded that doubling of serum PSA concentration in men who have received 5ARIs for up to 6–9 months overestimated actual PSA, whereas correctly estimated actual PSA concentration during 1–3 years of treatment and underestimating it thereafter [34]. It was proposed that a PSA increase $\geq 0.3 \mu\text{g/l}$ from a nadir should be used as an additional biopsy trigger in men receiving a 5ARIs for BPH; these men should also be followed-up on a regular base.

5ARIs and chemoprevention

There is an increasing interest in the use of 5ARIs for PCa chemoprevention. The American Society of Clinical Oncology (ASCO) and American Urological Association Practice Guidelines Committee jointly convened a panel of experts to develop evidence-based recommendations [35]. Although this issue is beyond the scope of this article, some findings may have clinical implications in patients receiving 5ARIs for symptomatic BPH. Data from the Prostate Cancer Prevention Trial (PCPT), currently the only completed randomized PCa risk reduction trial, showed a 24.8% reduction in PCa prevalence during the 7-year period between the finasteride (18.4%) and the placebo group (24.4%) [36]. However, a higher incidence of high-grade cancers (Gleason scores 7–10) was found in the finasteride arm (37 vs. 22.2% for placebo). Several potential explanations have been proposed and the majority of the panel members judged that the higher incidence of high-grade tumors is likely due to confounding factors than to an actual increase in aggressive cancers [35]. However, men taking 5ARIs for the management of BPH-LUTS may also benefit from chemoprevention. In such cases, observed benefits must be weighed against theoretical harm in men who are being treated for symptomatic or bothersome conditions. New information are eagerly expected from the REDuction by DUtasteride of prostate Cancer Events (REDUCE) trial, an ongoing 4-year, multicentre, randomized, double-blind, placebo-controlled study aiming at the evaluation of the efficacy and safety of oral dutasteride 0.5 mg/day in PCa risk reduction [37].

Conclusions

Current evidence shows that monotherapy with 5ARIs is effective in men with BPH-LUTS and benign prostatic enlargement by altering the underlying disease process; in addition, 5ARIs provide the long-term benefit of risk reduction for disease progression. For this reason, both the European and the American Urological Association Guidelines recommend 5ARIs in the management of patients with LUTS associated with demonstrable prostatic enlargement [14, 31]. The MTOPS study demonstrated the long-term superiority of combination treatment to either monotherapy with regard to both symptom reduction and disease progression, while the analysis of the CombAT study, for the first time, has shown benefit in improving symptoms and Q_{max} for combination therapy over monotherapies during the first 12 months of treatment, thereby reinforcing the position of 5ARIs in the management of patients with BPH-LUTS.

Conflict of interest statement The authors declare that they have no conflict of interest.

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