

## Review

# Optimising the Medical Management of Benign Prostatic Hyperplasia

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Accepted 17 October 2003

Published online 26 November 2003

**Keywords:** BPH; Management

## 1. Introduction

As demographics change, with the elderly constituting an increasing proportion of the population, the prevalence of benign prostatic hyperplasia (BPH) is increasing, with a resultant impact on medical practice [1,2]. The last decade has seen considerable advances in our understanding of the demographics and natural history of BPH. Management has also changed significantly, with the use of surgical intervention diminishing, and medical therapy taking a more prominent role [3,4]. It is becoming clear that the different classes of medical intervention for BPH have different patterns of benefits. This review examines our understanding of the epidemiology and natural history of BPH, the implications of these for therapeutic intervention, and ways in which men with BPH can be identified to ensure optimum response to medical therapy.

## 2. Epidemiology and natural history of BPH

It is commonly understood that BPH is a frequent problem in older men [5], with the prevalence increasing with age [6]. Indeed, more than 50% of men aged over 60 years old have histological evidence of BPH [7,8], with this figure rising to 80–90% in men aged over 80 years [9]. A workable case definition of clinical BPH, which is now often applied, combines at least two

of the following: moderate-to-severe lower urinary tract symptoms (LUTS) (International Prostate Symptom Score [IPSS]  $\geq 8$ ), an enlarged prostate (volume  $>30$  ml), and a decreased peak urinary flow rate  $Q_{\max}$  ( $<15$  ml/s) [10,11]. It is now clear that a significant proportion of the symptoms of BPH are due to a mass-related increase in urethral resistance causing obstruction as well as age-induced detrusor dysfunction.

A series of longitudinal studies and the placebo arms of several clinical trials have confirmed the chronicity of BPH and the progressive nature of the disease in many men [12]. Progression has been varyingly defined in these studies, with some examining single endpoints such as increases in prostate volume, deterioration in  $Q_{\max}$  or symptoms, or episodes of acute urinary retention (AUR) or surgery, whilst others have used composite endpoints.

One of the largest and longest running longitudinal studies, the Olmsted County study [7], has provided strong evidence for the progressive nature of BPH. Ninety-two-month data demonstrated a worsening of symptom severity over the time course of the study, with a mean annual increase in IPSS of 0.34 points [13]. Indeed, 31% of men reported at least a 3-point increase in American Urological Association Symptom Index (AUA-SI) over this 92-month period.

Another potential marker of BPH progression is the need for surgical intervention in men undergoing watchful waiting. Surgical intervention is typically triggered by deterioration in symptoms, flow or quality of life, and may be precipitated more acutely by an episode of AUR. The longitudinal ‘Veterans Affairs

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Study' conducted in the US has demonstrated that 36% of BPH patients who were randomised to watchful waiting switched to invasive therapy within five years of enrolment, demonstrating significant progression in over one-third of men in this time period [14].

More objective measures of BPH progression can be obtained from evaluation of prostate volume and urinary flow, and the incidence of AUR. Data from three large-scale clinical studies with the dual selective 5 $\alpha$ -reductase inhibitor dutasteride have shown an increase in transitional zone volume (TZV) over the 2-year duration of the study amongst men treated with placebo [15], while the four-year Medical Therapy of Prostatic Symptoms (MTOPS) study identified an 18% increase in total prostate volume in placebo-treated men from baseline to endpoint [16].

With regard to AUR, the Olmsted County study has shown an increase in the risk of AUR associated with increasing age [17]; a finding confirmed by a longitudinal study of health workers [18]. Placebo arms of clinical studies have also demonstrated the risk of AUR: 7% over four years in the Proscar Long-term Efficacy and Safety Study (PLESS), and 4.2% over the two-year duration of the dutasteride Phase III studies [15,19]. Indeed, the overall risk of AUR has been estimated as 23% for an average 60-year-old man if he survives a further 20 years [17].

The MTOPS study has examined the risk of progression, defined as one of the following events: AUR, renal insufficiency due to BPH ( $\geq 50\%$  rise in baseline serum creatinine and  $\geq 1.5$  mg/dl), recurrent urinary tract infection or urosepsis, urinary incontinence, or a  $\geq 4$ -point rise in baseline AUA-SI confirmed within 2–4 weeks. In men receiving placebo, 17.4% experienced progression of their disease over the 4-year duration of the study. The majority of events, 78%, were deteriorations in symptoms, with 12% being AUR events [16]. From these multiple studies, it can be concluded that BPH is a progressive disease in many men—a finding that shifts the focus of management from short-term symptomatic relief to the need to encompass reductions in the risk of progression.

### 3. Identifying men with progressive BPH

Clearly, identifying men with progressive disease could have clinical utility in directing therapy to those most likely to benefit from a preventative approach. The two most extensively investigated, and routinely assessable risk factors for BPH progression, are prostate volume and serum PSA [20–26]. Although the relationship between prostate size and the magnitude

of symptoms is not always linear, a number of large-scale studies, such as the Olmsted County and PLESS studies, have found a significant correlation between prostate volume and the risk of BPH progression. Men with a prostate volume  $\geq 30$  ml are more likely to have moderate-to-severe symptoms (3.5 times), decreased flow rates (2.5 times), and AUR (3–4 times), compared with men with prostate volumes  $< 30$  ml [27]. The population of men with a prostate volume  $> 30$  ml has been found to be 7.5%, 37.5%, 57.5%, and 65.0% in the 40–49, 50–59, 60–69, and 70–79 year-old age ranges, respectively [28]. An enlarged prostate is also predictive of the need for BPH-related surgery [17,29,30]. However, despite the value of prostate volume as a predictor of BPH progression, data from an analysis of four epidemiological studies determined that DRE systematically underestimates prostate size compared with transrectal ultrasound by up to 55% [31,32].

An increasing serum PSA level is also a strong predictor of prostate volume increase and BPH progression [20–26]. In the placebo-treated arm of PLESS, the annual prostate growth rate of 0.7 ml in patients with PSA levels  $< 1.4$  ng/ml was found to be similar to that of community-dwelling men [21]. The annual growth was as high as 3.3 ml in patients with PSA levels  $\geq 1.4$  ng/ml, which has been associated with an increased risk of AUR, greater symptom severity and decreases in  $Q_{\max}$  and quality of life [20–22].

A number of analyses have sought to examine whether unimodal or multimodal approaches to predicting progression are more advantageous. Using a global definition of progression incorporating worsening symptoms and/or the occurrence of AUR or BPH-related surgery, Djavan et al. demonstrated that an artificial neural network incorporating age, PSA, IPSS, obstructive symptom score, irritative symptom score, quality of life score, flow rate, prostate volume and TZV provided 82% accuracy in predicting disease progression [33]. However, using data from recently completed large-scale dutasteride studies, Boyle et al. have determined that PSA, PV and  $Q_{\max}$  are independently associated with the occurrence of AUR, a single marker of progression [34]. Furthermore, a recent analysis aiming to identify risks for progression by comparing approaches using a single risk factor (serum PSA), combined risk factors (serum PSA, symptom problem index,  $Q_{\max}$ , frequency of urination  $\leq 2$  hours and hesitancy) and an algorithm for predicting progression, demonstrated that PSA alone was comparable with multimodal and algorithmic approaches for predicting the occurrence of AUR [23].

Evidence of a relationship between serum PSA and prostate volume provides a simple test for routine

practice that can be used to evaluate the risk of progression in patients. Although transrectal ultrasound (TRUS) and magnetic resonance imaging (MRI) are currently the most accurate methods for estimating prostate volume, the use of these techniques is limited by their relatively high costs, invasiveness and lack of availability [27]. Therefore, serum PSA measurement can provide a relatively inexpensive and straightforward surrogate marker of prostate size [25,35], helping to identify those patients most at risk of BPH progression. DRE can be used as a clinical adjunct to this, and as part of the screening process for prostate malignancy.

#### 4. Principles of the medical management of BPH

Traditionally, the medical management of BPH has tended to focus on the short-term goals of alleviating symptoms and improving urinary flow. However, the progressive nature of BPH is associated with worsening bother, increasing severity of symptoms, and a greater degree of prostatic enlargement [36–39]. A feeling of negative well-being is also significantly more common in men with symptomatic BPH compared with the general male population [40]. This difference is due to significant worry over urinary symptoms and the risk of prostate cancer, and also increased embarrassment over urinary symptoms [41]. Many patients are also significantly concerned over the need for future BPH-related surgery, as well as their increased risk of developing AUR [42]. ‘Treatment success’, typically defined in terms of improvements in symptoms and urinary flow, should therefore be widened to encompass long-term outcomes.

Overall, medical therapy is indicated for patients with uncomplicated BPH, those with mild-to-moderate symptoms (IPSS  $\geq 8$ ), awaiting surgery, or unwilling

or unsuitable to undertake surgery [43,44]. Patients with BPH who have complications such as AUR, recurrent urinary tract infections, haematuria, bladder stones, or renal insufficiency/failure secondary to BPH, should be treated surgically [43]. A ‘watchful waiting’ approach is frequently adopted for patients with mild symptoms (IPSS  $< 8$ ).

The main classes of medical therapies licensed to date for the treatment of BPH are the  $\alpha_1$ -blockers and the 5 $\alpha$ -reductase inhibitors (5-ARIs): two classes of drugs that have very different modes of action, and which are associated with different outcomes. Current American Urological Association (AUA) guidelines on the short-term management of BPH recommend  $\alpha_1$ -blockers for men with symptoms secondary to BPH, and 5ARIs or combination therapy for men with symptoms and demonstrable prostatic enlargement [45]. Phytotherapy is also a treatment option which is used to varying degrees in different countries. However, this will not be reviewed further here.

#### 5. Efficacy of $\alpha_1$ -blockers

Short- and long-acting  $\alpha_1$ -selective antagonists treat the dynamic component of BPH through relaxation of smooth muscle in the prostate, by blockade of  $\alpha_1$ -receptor-mediated sympathetic stimulation. A number of double-blind, placebo-controlled studies evaluating the efficacy of  $\alpha_1$ -blockers have been conducted in patients with symptomatic BPH [46–54].  $\alpha_1$ -blocker studies have recently undergone meta-analysis by the AUA, and the findings of their analysis are presented in Table 1 [45]. These studies were designed to evaluate the effect of these drugs on symptom severity and urinary flow rate, but not on disease progression. The  $\alpha_1$ -blockers alfuzosin, doxazosin, tamsulosin and terazosin demonstrate statistically significant

**Table 1**

Outcome parameters with  $\alpha_1$ -blockers: estimates of changes in symptom score and peak urinary flow rate [45]

	AUA/IPSS			Peak flow rate ( $Q_{max}$ )			QoL question score		BPH impact index	
	3–9 months	10–16 months	>16 months	3–9 months	10–16 months	>16 months	3–9 months	10–16 months	3–9 months	10–16 months
$\alpha_1$ -blockers										
Alfuzosin	–4.44			2.05			–1.10			
Doxazosin	–5.10	–5.63		3.11	2.98	1.90*	–1.25	–1.47	–2.00	–2.47
Tamsulosin	–4.63	–7.53*		1.85	1.86*		–1.43			
Terazosin	–6.22	–5.99		2.51	1.94	2.61*	–1.70*	–1.37	–1.45*	–2.09

Reproduced from American Urological Association: AUA Guideline on the Management of Benign Prostatic Hyperplasia (BPH) (2003).

\*These numbers are based on single-arm analyses—no RCT data available.

Numbers without asterisks are based on RCT results with placebo controls.

improvements, compared with placebo, in symptom scores. Typically, they provide a 2–4 point decrease in AUA-SI versus placebo. They are also associated with improvements in  $Q_{\max}$ , quality of life and BPH Impact Index (BII). Data for the slow-release form of alfuzosin, unavailable at the time of this analysis, have shown a similar degree of efficacy [54]. In common with a meta-analysis of  $\alpha_1$ -blocker studies conducted in 1999, the AUA guidelines conclude that the four  $\alpha_1$ -blockers examined provided equivalent benefits in improving symptoms and flow [45,55].

## 6. Safety and tolerability of $\alpha_1$ -blockers

Discontinuation due to adverse events ranges between 4 and 10% for alfuzosin and tamsulosin—rates that are comparable with placebo. However, for terazosin and doxazosin, an additional 4–10% of patients withdraw due to adverse events [55]. The most common adverse events observed with  $\alpha_1$ -blockers at a significantly higher frequency than placebo are dizziness and postural hypotension, although again there may be differences between individual agents within the class [55]. Both the PREDICT (Prospective European Doxazosin and Combination Therapy) and MTOPS studies have examined the efficacy and tolerability of 5ARI monotherapy,  $\alpha_1$ -blocker monotherapy, combination therapy and placebo in men with BPH [16,56]. In both studies, the incidence of postural hypotension and dizziness was significantly greater in the doxazosin groups versus both the placebo and finasteride groups. The incidence of postural hypotension was 4.4% in MTOPS and 5.8% in PREDICT, with rates of dizziness of 4.8% and 15.6% respectively.

Although in general the  $\alpha_1$ -blockers are associated with a similar incidence of sexual adverse events compared with placebo, tamsulosin appears to be an exception. Placebo-controlled trials [57–59], and an open-label extension study [60], have demonstrated an incidence of retrograde or delayed ejaculation of 4.5–10% versus 0–1% for placebo.

## 7. Efficacy of 5 $\alpha$ -reductase inhibitors

5ARIs inhibit the conversion of testosterone to dihydrotestosterone (DHT), the primary androgen involved in both normal and abnormal prostate development and the prostatic transitional zone hyperplasia found in BPH. By reducing the production of DHT, 5ARIs significantly reduce prostate volume in men with BPH. Two 5ARIs are currently available for the treatment of BPH: finasteride and dutasteride, which differ in their profile of 5AR binding and inhibition of the type 1 and type 2 isoenzymes of 5AR. Finasteride is a mono-inhibitor of 5AR type 2, whilst dutasteride, the first agent in its class, is a selective dual inhibitor of both 5AR type 1 and 2 [61,62]. Dutasteride treatment results in an increased and more consistent level of serum DHT suppression, namely  $\geq 90\%$  DHT suppression in  $>85\%$  of subjects receiving dutasteride, compared with  $\geq 90\%$  in 2.2% of subjects receiving finasteride [63,64].

The effects of finasteride 5.0 mg on the symptoms and progression of BPH have been evaluated in PLESS, a large-scale, long-term, double-blind, placebo-controlled trial conducted in 3040 men with moderate-to-severe urinary symptoms, a  $Q_{\max}$  of  $<15$  ml/s and an enlarged prostate on DRE [19]. Finasteride reduced prostate volume by 18% compared with an increase of 14% in the placebo group (mean difference 32%,  $p < 0.001$ ), improved symptom scores (2.6 points versus 1.0,  $p < 0.001$ ), increased  $Q_{\max}$  (1.9 versus 0.2 ml/s,  $p < 0.001$ ) and reduced the risk of AUR by 57% and surgery by 55% ( $p < 0.001$  for both versus placebo, Table 2). Although the 7-year Prostate Cancer Prevention Trial (PCPT) recruited men with a normal digital rectal examination, a PSA  $\leq 3.0$  ng/ml and an AUA-SI  $<20$ , and was designed to examine the effect of finasteride versus placebo on the risk of prostate cancer, it also confirmed that finasteride treatment was associated with a lower risk of AUR (4.2% versus 6.3%), need for TURP (1.0% versus 1.9%) and number of diagnoses of BPH (5.2% versus 8.7%), compared with placebo treatment [65].

**Table 2**

Outcome parameters with 5 $\alpha$ -reductase inhibitors: changes in symptom score, peak urinary flow rate and risk of AUR and BPH-related surgery

Study	Patients (n)	Agent	Change in AUA-SI score	Change in peak flow (ml/s)	Change in prostate volume (%)	Reduction in risk of AUR (%)	Reduction in risk of BPH-related surgical intervention (%)
McConnell et al., 1998 [19]	3040	Finasteride	3.3	+1.9	-18	57	55
		Placebo	1.3	+0.2	+14		
Roehrborn et al., 2002 [15]	4325	Dutasteride	4.5	+2.2	-25.7	57	48
		Placebo	2.3	+0.6	+1.7		

The efficacy of dutasteride has been examined in three identical, 2-year, double-blind, placebo-controlled Phase III studies (Table 2) [15]. A total of 4325 men with a prostate volume  $\geq 30$  ml and a serum PSA  $\geq 1.5$  ng/ml were randomised to dutasteride 0.5 mg or placebo. Compared with placebo, dutasteride provided statistically significant improvements in voiding symptoms from six months in the majority, and from 3 months in some subjects. After 2 years, symptom scores were reduced by 4.5 points in the dutasteride group compared with 2.3 points in the placebo group ( $p < 0.001$ ). An improvement in  $Q_{\max}$  was also demonstrated from one month, with a mean improvement after 2 years of 2.2 ml/s in the dutasteride group compared with 0.6 ml/s in the placebo group ( $p < 0.001$ ). The amelioration in symptoms and flow translated into sustained improvements in quality of life (as measured by the BII) with an onset at six months. Dutasteride was also associated with a reduction in the risk of AUR of 57%, and a reduction of 48% in the risk of surgical intervention compared with placebo after 2 years (both  $p < 0.001$  versus placebo). These changes in clinical parameters were underscored by a significant reduction in total and transitional zone prostate volumes from 1 month continuing to endpoint at 2 years.

### 8. Safety and tolerability of 5 $\alpha$ -reductase inhibitors

Data from PLESS demonstrate that finasteride is generally well tolerated. Withdrawals due to adverse events were similar in the finasteride- and placebo-treated groups (11.5% versus 10.9%). Adverse events occurring in  $\geq 1\%$  of men and significantly more frequently in the finasteride than placebo groups were decreased libido, impotence, decreased ejaculate volume, ejaculation disorders, breast enlargement, breast tenderness and rash [19]. These findings are consistent with those of the PCPT, which also determined that sexual adverse events and gynaecomastia were more common with finasteride than placebo treatment [65]. Three large-scale, randomised, placebo-controlled studies of dutasteride have shown that it is generally well tolerated, with an incidence of drug-related adverse events of 19% compared with 14% in the placebo group [15]. The same proportion of men treated with dutasteride and placebo withdrew from treatment due to adverse events (8.9% in each group). The rate of new sexual function adverse events was low and decreased with time. With the exception of two sexual adverse events, impotence and decreased libido,

no other drug-related adverse event was reported in excess of 2% of patients.

### 9. Predictors of treatment outcome with $\alpha_1$ -blockers and 5 $\alpha$ -reductase inhibitors

The most significant baseline factor indicating the likelihood of treatment success with 5ARIs is the presence of prostatic enlargement. For finasteride, analyses have demonstrated that it is significantly more effective amongst men with a prostate volume  $>40$  ml or a serum PSA  $\geq 1.4$  ng/ml [66], leading to the recommendation that it should be reserved for men meeting these criteria [29]. A similar analysis has been conducted with the results of the three large-scale studies of dutasteride, which included men with a prostate volume  $\geq 30$  ml and/or a PSA  $\geq 1.5$  ng/ml [67]. Dutasteride significantly reduced prostate volume compared with placebo from month one to endpoint for patients with a prostate volume 30–40 ml and  $\geq 40$  ml ( $p < 0.001$ ), and was significantly more effective than placebo at reducing the risk of AUR and BPH-related surgery, and improving  $Q_{\max}$ , symptom scores and BII scores versus placebo regardless of baseline prostate volume. These data show that dutasteride reduces the risk of serious complications of BPH and improves objective disease measures in men with prostates  $\geq 30$  ml and/or a PSA  $\geq 1.5$  ng/ml.

A retrospective evaluation of 150 men with LUTS suggestive of BPH and receiving  $\alpha_1$ -blocker therapy has been conducted to determine baseline risk factors for treatment success [68]. Subjects with treatment failure (defined as an ultimate requirement or request for surgical intervention for the treatment of symptoms) had significantly higher baseline prostate mass and serum PSA values versus those with treatment success (48.8 g versus 33.0 g [ $p < 0.0001$ ] and 2.47 ng/ml versus 1.87 ng/ml [ $p = 0.01$ ], respectively). The findings of this study have been confirmed in a review of the outcomes of 326 men receiving  $\alpha_1$ -blocker therapy followed for 3–5 years [44]. Re-treatment rates varied from 27% with tamsulosin to 49% with terazosin. Men with severe symptoms had a re-treatment rate of 70% versus 33% and 27% for moderate and mild symptoms, respectively. Concordant with the study of Jaffe et al. [68], subjects with a prostate volume  $<40$  ml had a re-treatment rate of 48%, while those with enlarged prostates ( $>40$  ml) had a higher rate of 72%. The investigators concluded that re-treatment rates with  $\alpha_1$ -blockers were high, and that baseline parameters may be of use in selecting patients likely to respond to therapy. Overall therefore, men with smaller prostates appear to benefit

from  $\alpha_1$ -blocker therapy, while those with prostate volumes  $\geq 30$ –40 ml benefit from 5ARI therapy.

## 10. The relative benefits of $\alpha_1$ -blockers and 5 $\alpha$ -reductase inhibitors

It is possible to conclude from placebo-controlled studies of  $\alpha_1$ -blockers and 5ARIs that the two classes of agents have different efficacy profiles. However, until recently, a long-term, large-scale, randomised, placebo-controlled comparative study of 5ARIs and  $\alpha_1$ -blockers has not been available. One previous study, the Veterans Affairs Study, examined the efficacy of finasteride, terazosin, or a combination of finasteride and terazosin versus placebo over a 1-year period in 1229 men. This study failed to show a significant benefit for finasteride over placebo in improving symptoms or  $Q_{\max}$ , with men in the terazosin and combination arms experiencing similar, and significant benefits in these parameters [69,70]. However, this study is severely limited by inclusion of men regardless of baseline prostate volume. The mean prostate volume in the finasteride group, 36.2 cc, is below the value of 40 cc considered to be the minimum for therapeutic response for finasteride [29]. This, coupled with the short duration of the study, meant that, in contrast with earlier studies, a significant response to finasteride therapy was unlikely to occur and that comparisons with  $\alpha_1$ -blocker and combination arms were therefore flawed. Similar findings were observed in the PREDICT trial comparing the efficacy and tolerability of doxazosin and finasteride, alone or in combination. Again, this study was limited by low patient numbers, a mean prostate volume below 40 cc and a short study duration [71].

The reporting of the landmark, 4-year MTOPS study, which randomised 3047 men with BPH to treatment with finasteride, doxazosin, a combination of both, or placebo [16], has provided new insight into the relative benefits of the two classes of agent. While all active treatment arms were associated with a significant improvement in symptoms, only treatment arms containing 5ARI therapy were associated with significant reductions in the risk of AUR and invasive therapy for BPH. Doxazosin monotherapy delayed the time to progression to AUR and need for invasive therapy, but did not reduce the long-term risk of either event. The MTOPS study confirms that 5ARI therapy is unique in affording longer-term reductions in the risks of AUR or invasive therapy combined with improvements in symptoms and flow.

Observational studies are a useful adjunct to clinical study data in assessing the relative benefits of different

agents. One population-based observational study has examined a cohort of 5671 men using data from the PHARMO Record Linkage System in the Netherlands that records prescription events from 950,000 community-dwelling men [72]. The risk of progressing to BPH-related prostatic surgery was assessed between patients receiving  $\alpha_1$ -blockers and 5ARIs. The study found that patients receiving  $\alpha_1$ -blockers were at a significantly higher risk of undergoing BPH-related surgery than those receiving 5ARIs. These findings are echoed in an analysis of the UK General Practice Research Database (GPRD), which examined data from 4500 men treated for BPH. Significantly fewer men receiving 5ARI therapy required surgery for BPH, had an episode of AUR or were catheterised compared with those receiving  $\alpha_1$ -blockers [73].

## 11. The role of combination therapy with $\alpha_1$ -blockers and 5 $\alpha$ -reductase inhibitors

Although a number of studies have examined the issue of combination therapy [68,69,71,74–80], this review will focus on the results of MTOPS, the largest and longest study to date comparing combination and monotherapy, and recent studies examining the issue of  $\alpha_1$ -blocker withdrawal following a period of combination therapy. Although final data analyses are awaited from MTOPS, it appears that, in selected patients, there are additive symptomatic benefits of receiving long-term combination treatment with a 5ARI and an  $\alpha_1$ -blocker, as symptom deterioration resulting from underlying BPH progression was observed to be less in patients receiving the combination than with those receiving either monotherapy.

The MTOPS study specifically examined the relative merits of long-term monotherapies versus combination treatment. Several recently completed studies have sought to examine the role of short-term combination therapy by studying whether withdrawal of an  $\alpha_1$ -blocker following an initial period of combination therapy is possible in routine practice [78,81]. In the first of these studies—of 129 men receiving combination therapy in whom  $\alpha_1$ -blocker treatment with doxazosin was withdrawn at 3, 6, 9 or 12 months—84% had stable or improved voiding following one year of subsequent 5ARI monotherapy [78]. The larger Symptom Management After Reducing Therapy (SMART-1) study was initiated to examine short-term dutasteride and tamsulosin combination therapy followed by dutasteride monotherapy in 327 men with BPH. SMART-1 demonstrated that 77% of patients with moderate-to-severe symptoms treated with a combination of dutasteride and

an  $\alpha_1$ -blocker who then had the  $\alpha_1$ -blocker withdrawn at six months, felt better or the same compared with their status before withdrawal [81]. In accordance with the MTOPS study, combination therapy was well tolerated. SMART-1 demonstrates that the combination of an  $\alpha_1$ -blocker and a 5ARI is effective in lowering and maintaining symptom scores for six months, but that these benefits can be maintained with dutasteride monotherapy in the majority of men with moderate-to-severe symptoms (77%) after this initial period. This defines a role for the addition of short-term (6 months)  $\alpha_1$ -blocker therapy, to cover the lag in onset of symptom relief seen with 5ARI monotherapy. Such short-term combination use would be optimal in providing symptomatic improvement among patients who require rapid symptom relief, while enabling the initiation of 5ARI therapy to reduce the risk of subsequent AUR or BPH-related surgery in men who are at greater risk of disease progression. A small proportion of patients with severe baseline symptoms (around one quarter of all patients) benefited from longer-term combination treatment, as demonstrated by the finding of a higher rate of worsening of symptoms when  $\alpha_1$ -blocker therapy was withdrawn compared with patients with moderate symptoms (42.5% versus 16%).

## 12. Conclusions

BPH is the most common disorder of ageing men, and its prevalence is set to rise in parallel with the

ageing population. Evidence from a wide range of studies demonstrate that BPH is a progressive disease in many men, and that men likely to progress are those with a prostate volume  $\geq 30$  ml and with a PSA level of  $\geq 1.5$  ng/ml. These men can be identified in everyday clinical practice through the use of serum PSA, which provides a practical approach for estimating prostate volume, and has advantages in accuracy over DRE, and where TRUS is not routinely available.

Preventing BPH progression, as well as the alleviation of symptoms, is an important aim of BPH therapy. Amongst available therapies, only the 5ARIs have been shown to reduce the risk of AUR and BPH-related surgery compared with placebo. This provides a mandate for their use in men with enlarged prostates ( $\geq 30$  ml). Although the 5ARIs provide symptomatic benefits, the onset of these are slower than those observed with the  $\alpha_1$ -blockers. Patients in need of rapid onset of symptom relief, and those without prostate enlargement, benefit from the use of  $\alpha_1$ -blockers. Short-term combination therapy has a role in men with enlarged prostates who require a rapid onset of symptom relief, whilst longer-term combination therapy may be appropriate in a small group of men with severe symptoms.

In conclusion, the rapid increase in our understanding of the natural history of BPH, and the benefits of available medical therapies, have provided insights that can be used to assess patients more accurately, and institute medical therapy that targets long-term, as well as short-term, outcomes of benefit for men with BPH.

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