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Fixed-dose combination therapy with dutasteride and tamsulosin in the management of benign prostatic hyperplasia

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***Abstract*:** Despite their multifactorial etiology, male lower urinary tract symptoms (LUTS) have been traditionally associated with benign prostatic enlargement (BPE) because of benign prostatic hyperplasia (BPH). Several pharmaceutical therapies have been used to manage LUTS, with α1-adrenergic receptor antagonists (α1-blockers) and inhibitors of 5α-reductase (5α-RIs) representing the most commonly prescribed agents currently in use for LUTS treatment. Due to their different modes of action, combined use of α1-blockers and 5α-RIs has been proven to offer more optimal control of symptoms and better associated quality of life, even though higher rates of adverse events have been shown. Following previous studies on the separate administration of dutasteride and tamsulosin, a fixed-dose combination capsule of tamsulosin 0.4 mg and dutasteride 0.5 mg has been approved and released for clinical use in men with BPH. The present review aims to discuss the rationale behind the combined use of tamsulosin and dutasteride for treating male LUTS, and to present the available data on the role of combination therapy in the management of BPH-related symptoms in terms of efficacy and safety. Special attention is given to the impact of combination treatment on the prevention of clinical progression of BPH. Cost-effectiveness of fixed-dose combination and patients' adherence to treatment are also discussed.

Keywords: benign prostatic hyperplasia, LUTS, dutasteride, tamsulosin, fixed dose combination

Introduction

Lower urinary tract symptoms (LUTS) are commonly reported by men aged over 45 years, with evidence showing up to two thirds of men reporting at least one LUTS complaint [Abrams *et al.* 2003; Irwin *et al.* 2006]. In men, LUTS have been historically attributed to bladder outlet obstruction (BOO) as a result of benign prostatic obstruction (BPO), which is often associated with benign prostatic enlargement (BPE) resulting from the histologic condition of benign prostatic hyperplasia (BPH) [Abrams *et al.* 2003; Chapple *et al.* 2008]. However, it has to be noted that BPE/BPH is not the only cause of LUTS, as several other urological and nonurological conditions have been proved to participate in LUTS pathogenetic pathways. Interestingly, LUTS of any type (voiding, storage or postmicturition) are characterized by a dynamic pattern of progression, with some patients complaining of gradually evolving symptoms, while others report improvement, or even complete remission of LUTS [Chapple and Abrams, 2013].

Analysis of the placebo arm of the Medical Therapy of Prostatic Symptoms (MTOPS) study showed that the rate of overall clinical progression of BPH events [defined as an International Prostate Symptom Score (IPSS) increase ⩾4 points, acute urinary retention (AUR), urinary incontinence, renal insufficiency, or recurrent urinary tract infections] 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 [McConnell *et al.* 2003]. Although AUR and surgery are less common than overall symptomatic worsening, they are important progression events because of the financial, emotional and health-related implications and represent the major concerns of BPH patients. Rate of AUR was 0.6 events/100 person-years in the placebo group of the MTOPS trial, whereas, in

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terms of risk for invasive BPH therapy, the placebo group experienced 1.3 events/100 person-years [McConnell *et al.* 2003].

A systematic review of the placebo arms of randomized trials of medical therapy for BPH tried to estimate rates of progression [Emberton *et al.* 2008]. Studies with a follow-up of 12–48 months reported rates of surgery that varied from 1% to 10% whereas the rates of AUR were 0.4–6.6%; these rates tended to be worse with a longer follow-up. This remarkable variety in results may be explained by the differences and heterogeneity observed among the studies.

Pharmacological management of LUTS includes several categories of drugs with different modes of action. Nevertheless, antagonists of α1-adrenergic receptors (α1-blockers) and inhibitors of 5α-reductase (5α-RIs) represent the main pharmaceutical agents used for control of LUTS due to BPE/BPH either as monotherapy or in combination. From 2010, a fixed-dose combination (FDC) capsule of an α1-blocker (tamsulosin hydrochloride 0.4 mg) with a 5α-RI (dutasteride 0.5 mg) is available (Duodart®, GlaxoSmithKline, Brentford, UK). The current study aims to review the literature about the role of FDC treatment with tamsulosin and dutasteride for controlling BPE/BPH-related LUTS.

A structured search was performed using articles in English language published in PubMed/Medline and Cochrane databases between 2000 and March 1, 2015, including the search terms 'lower urinary tract symptoms', 'LUTS', 'benign prostatic hyperplasia', 'BPH', 'dutasteride', 'tamsulosin', and 'fixed dose combination'. Articles were systematically retrieved, selected, assessed, and summarized for this review.

Introduction to tamsulosin and dutasteride use for BPH-related LUTS

Use of tamsulosin can offer fast response in terms of significant reduction in both storage and voiding LUTS within hours or days, compared with placebo treatment [Michel *et al.* 1998]. A systematic review of the available randomized controlled trials found that tamsulosin achieved an improvement in symptom scores that ranged from −20% to −48% and an increase in maximum flow rate (Q_{max}) that ranged from 1.2 to 4.0 ml/s (13–44% improvement) [Wilt *et al.* 2002]. The main adverse effects related to tamsulosin use comprise asthenia, dizziness, rhinitis, symptomatic postural hypotension, ocular disorders [intraoperative floppy iris syndrome (IFIS)] and disorders of ejaculation [Oelke *et al.* 2013]. Due to its high α1A selectivity, tamsulosin, and especially its oral-controlled absorption system (OCAS) formulation, offers a safe cardiovascular profile that is further strengthened by its significantly higher measured concentrations in the prostate than in plasma [Michel *et al.* 1998]. While tamsulosin was believed to cause loss of antegrade ejaculation due to bladder neck relaxation, resulting in retrograde ejaculation, newer studies have questioned that theory by proposing ejaculation side effects closer to anejaculation form [Van Dijk *et al.* 2006].

The advantage offered by 5α-RIs use is the induced apoptosis of prostatic cells as a result of DHT suppression that leads to reduction of prostate volume. Dutasteride has been proved to reduce serum DHT levels by 95%, leading to a reduction of approximately 94–97% of DHT levels in the prostate [Gravas and Oelke, 2010; Montorsi *et al.* 2009]. Thus, by mediating prostatic size, dutasteride can regulate the static component of BOO. After 6–12 months of 5α-RI treatment, prostate size is reduced by 18–28% approximately, circulating prostate-specific antigen (PSA) levels drop by 50% and Q_{max} is increased by 1.5–2.0 ml/s in patients with BPE-associated BOO [McConnell *et al.* 2003; Roehrborn *et al.* 2002, 2010]. In general, the greater the prostate volume before 5α-RI therapy, the greater the induced reduction in symptoms [Oelke *et al.* 2013]. In contrast with tamsulosin, dutasteride has been proved to reduce episodes of AUR and need for BPH-related surgical operations compared with placebo [Chughtai *et al.* 2012].

Due to its slow onset of action, dutasteride should be prescribed as long-term medication. Based on study findings, long-term 4-year use of dutasteride in men with moderate-to-severe LUTS and prostate volume of at least 30 cm^3, led to an overall mean reduction in IPSS score of 6.5 points, regardless of baseline age, severity of symptoms or prostate volume [Roehrborn *et al.* 2005]. Interestingly, improvement in both voiding and storage LUTS was consistent and sustained during the 4 years of dutasteride administration, and the longer the treatment duration, the greater the relief in symptoms. Similarly, prostate volume reduction has also been proved to be consistent and durable throughout 4 years of dutasteride treatment [Roehrborn *et al.* 2005].

Dutasteride is generally well-tolerated. Most common complications related to its use comprise sexual dysfunction, which includes reduced sexual desire, erectile dysfunction and, less frequently, various disorders of ejaculatory function, such as retrograde ejaculation, anejaculation or reduced ejaculatory volume, fatigue and gynecomastia [Keam and Scott, 2008; Roehrborn *et al.* 2002]. Nevertheless, the low incidence of treatment-related adverse events and the satisfactory treatment effect of dutasteride lead to low withdrawal rates, according to available literature [Gravas and Oelke, 2010; Keam and Scott, 2008; Schulman *et al.* 2006]. A higher incidence of high-grade prostate cancer has been observed in two trials assessing the role of finasteride and dutasteride on chemoprevention of prostate cancer [Andriole *et al.* 2010; Thompson *et al.* 2003]. While there is no established causal relationship between 5α-RI use and high-grade prostate tumors, patients under 5α-RI treatment should be regularly followed-up using PSA and any confirmed increase in PSA value should be further evaluated [Oelke *et al.* 2013].

Rationale for combined use

The rationale behind combined use of an α1-blocker and a 5α-RI to control BPH-related LUTS relies on the potential synergistic effect of these two pharmaceutical agents due to their different modes of action. The theoretical synergy in efficacy and the impact on treatment-related adverse events needed to be clarified by trial results.

The first randomized, placebo-controlled trials that evaluated the therapeutic effect of combined α1-blocker and 5α-RI use revealed combination treatment superiority over 5α-RI monotherapy but not over α1-blocker monotherapy [Debruyne *et al.* 1998; Kirby *et al.* 2003; Lepor *et al.* 1996]. Criticism of these studies focused mainly on their relatively short duration of follow-up. Thus, MTOPS, a randomized, double-blind, placebo-controlled trial, was designed to provide long-term data on combination treatment thanks to its 4-year follow-up period [McConnell *et al.* 2003]. MTOPS findings demonstrated that combination therapy with doxazosin and finasteride was superior to either α1-blocker or 5α-RI monotherapy in improving BPH-related symptoms. The MTOPS trial also showed that the risk of symptom deterioration was by far the main progression event in men with LUTS and it was significantly reduced by the combination and single-agent therapies (α1-blocker or 5α-RI) compared with placebo. The risks of AUR and the need for invasive therapy were significantly reduced by combination therapy and finasteride but not by doxazosin [McConnell *et al.* 2003].

The Combination of Avodart and Tamsulosin (CombAT) trial was a multicenter, randomized, double-blind, placebo-controlled trial that assessed the efficacy of combination therapy with tamsulosin OCAS 0.4 mg and dutasteride 0.5 mg per day *versus* monotherapy with tamsulosin or dutasteride alone (Table 1). The study was conducted over 4 years in men with moderate-to-severe BPE/BPH-related LUTS who were, according to the inclusion criteria set, more likely to be at risk for BPH progression [Siami *et al.* 2007]. Specifically, eligible patients had to be at least 50 years of age, with a clinical diagnosis of BPH, moderate-to-severe LUTS as indicated by a baseline total IPSS score of ⩾12 points, prostate volume of at least 30 cm^3 measured using transrectal ultrasound (TRUS), and a total PSA value of at least 1.5 ng/ml at screening [Siami *et al.* 2007]. The inclusion criteria of the Combat Study were based on the findings of the MTOPS study that showed that the baseline prostate volume (31 ml or greater) and PSA (1.6 ng/dl or greater) were important predictors of the risk of clinical BPH progression [Crawford *et al.* 2006]. No placebo arm was included in the CombAT design, as it was judged unethical to provide no treatment to patients at risk for disease progression.

Four year results of CombAT trial showed a sustained superior therapeutic effect of combination treatment *versus* monotherapies. Compared with monotherapies with tamsulosin or dutasteride, combination treatment led to greater symptoms reduction (−6.3 *versus* −3.8 *versus* −5.3 IPSS points), higher quality of life (−1.5 *versus* −1.1 *versus* −1.3 points in BPH-related health status) and higher Q_{max} (2.4 *versus* 0.7 *versus* 2.0 ml/s) [Roehrborn *et al.* 2010]. Moreover, dutasteride plus tamsulosin combination therapy was associated with lower risk of AUR or BPH-related surgery in comparison with each monotherapy, providing slower disease progression [Roehrborn *et al.* 2010] (data presented in Table 1). In terms of patient-reported quality of life using the BPH Impact Index, IPSS question 8 and the Patient Perception of Study Medication questionnaire, results have shown that, at 4 years, improvement in quality of life and treatment satisfaction was higher in the combination therapy group

Table 1. Presentation of the CombAT and CONDUCT studies on the combination treatment with tamsulosin and dutasteride.

	CombAT			Conduct	
Study design	Multinational, multicenter, double-blind, randomized, parallel-group study			Multinational, multicenter, open-label, randomized, parallel-group study	
Inclusion criteria	Age >50 years, IPSS ⩾12, PV ⩾30cc[3], PSA 1.5–10 ng/ml, Q_{max} 5–15 ml/s			Age >50 years, IPSS 8–19, PV ⩾30 cm[3], PSA 1.5–10 ng/ml	
Study arms	Tamsulosin 0.4 mg, dutasteride 0.5 mg, Tamsulosin 0.4 mg + dutasteride 0.5 mg			FDC tamsulosin 0.4 mg + dutasteride 0.5 mg, WW with initiation of tamsulosin 0.4 mg if IPSS did not improve after randomization over the baseline value	
Study outcomes	Time to AUR or BPH-related surgery. Time to BPH clinical progression (defined as one of the following: IPSS increase ⩾4 points, BPH-related AUR, incontinence, rUTI, RF)			IPSS change from baseline to month 24. Various-points IPSS improvements, Time to and proportion of patients with BPH progression (IPSS rise ⩾3 points, BPH-related AUR, rUTI, incontinence or RF). BII score change from baseline, IPSS-Q8 and responses to two questions of the PPST questionnaire	
Number of participants	4844 (Combination 1610, dutasteride 1623, tamsulosin 1611)			742 (FDC 369, WW-All 373)	
Baseline characteristics	Combination	Dutasteride	Tamsulosin	FDC	WW-All
Age (*years*)	66.0 ± 7.05	66.0 ± 6.99	66.2 ± 7.00	66.3 ± 7.78	66.2 ± 7.34
IPSS score	16.6 ± 6.35	16.4 ± 6.03	16.4 ± 6.10	13.2 ± 4.06	12.9 ± 3.95
PV (*cm³*)	54.7 ± 23.51	54.6 ± 23.02	55.8 ± 24.18	51.0 ± 18.17	52.6 ± 19.57
Q_{max} (*ml/s*)	10.9 ± 3.61	10.6 ± 3.57	10.7 ± 3.66	NA	NA
PVR (*ml*)	68.2 ± 66.12	67.4 ± 63.49	67.7 ± 65.14	NA	NA
PSA (*ng/ml*)	4.0± 2.05	3.9 ± 2.06	4.0 ± 2.08	3.9 ± 2.00	3.7 ± 1.91
Results	**Risk reduction (Combination *versus* tamsulosin and dutasteride alone)** Time to AUR or BPH-related surgery (65.8%¥, 19.6%) Time to AUR (67.6%¥, 18.3%) Time to BPH-related surgery (70.6%¥, 31.1%) Time to BPH clinical progression (44.1%¥, 31.2%†) Time to first IPSS increase ⩾4 points (41.3%¥, 35.2%†) Time to first BPH-related AUR (69.6%¥, 29.7%) Time to first BPH-related incontinence episode (25.8%, 16.0%) Time to BPH-related rUTI (40.0%, 39.1%) Time to BPH-related RF (87.0%¥, 48.9%)			**(FDC *versus* WW-All)** Mean IPSS change from baseline –5.4 *versus* –3.6 # IPSS improvement by ⩾3 points: 77% *versus* 64%# IPSS improvement by ⩾25%: 73% *versus* 60%# Clinical progression: 29% *versus* 18%# Mean BII change from baseline: –2.4 *versus* –1.6# IPSS-Q8 change from baseline: –1.5 *versus* –1.1# PPST-Q1: 87% *versus* 86% PPST-Q2: 68% *versus* 65%	
Treatment-related adverse events	Erectile dysfunction, loss of antegrade ejaculation and decreased libido were the most frequently reported adverse events in combination treatment group *versus* tamsulosin and dutasteride groups (9% *versus* 7% *versus* 5%, 4% *versus* <1% *versus* 1% and 4% *versus* 3% and 2%, respectively).			Erectile dysfunction and retrograde ejaculation were the most frequently reported adverse events in FDC *versus* WW-All group (8% *versus* 0% and 5% *versus* 4%). Drug-related adverse events and serious adverse events were more frequent in the FDC than the WW-All group (24% *versus* 10% and 10% *versus* 8%, respectively).	

(Continued)

Table 1. (Continued)

	CombAT	Conduct
	Drug-related adverse events were more frequent in combination treatment group *versus* tamsulosin and dutasteride groups (28%[¥†] *versus* 21% *versus* 19%). Drug-related adverse events leading to study withdrawal were more frequent, but not significantly different, in the combination treatment group *versus* either monotherapies (6% *versus* 4% *versus* 4%).	Adverse events leading to study/drug discontinuation were more frequent in the FDC group (7% *versus* 5%).

IPSS, International Prostate Symptom Score; Q_{max}, maximal urinary flow rate; PSA, prostate-specific antigen; AUR, acute urinary retention; rUTI, recurrent urinary tract infections; RF, renal failure; PV, prostatic volume; PVR, post-void residual volume; FDC, fixed-dose combination; WW, watchful waiting; WW-All, WW with initiation of tamsulosin 0.4 mg if IPSS improvement after randomization was not met; PPST, patient perception of study treatment.
[¥]Significant over tamsulosin.
[†]Significant over dutasteride.
[#]Significant over WW-All group.

compared with either monotherapy group [Montorsi *et al.* 2010].

A *post hoc* analysis of the CombAT data, performed at the end of the study, evaluated the effects of combined therapy with dutasteride and tamsulosin on voiding and storage symptoms compared with those of either monotherapy [Montorsi *et al.* 2011]. It was found that that combined therapy provided significantly greater improvements in both storage and voiding symptoms compared with dutasteride or tamsulosin alone. At 4 years, the mean reduction in the storage and voiding subscore was significantly greater in the combined therapy group *versus* the dutasteride (adjusted mean difference −0.43 and −0.51, respectively) and tamsulosin (adjusted mean difference −0.96 and –1.60, respectively) monotherapy groups. The improvement in the storage and voiding subscore with combined therapy was significantly better than dutasteride from 3 months. Similarly, the improvement in the storage and voiding subscore with combined therapy was significantly better than tamsulosin from 12 and 6 months, respectively.

Moreover, analysis of 4-year CombAT data showed that combination treatment led to significant nocturia improvement in terms of number of nocturnal voiding episodes over either monotherapy [Oelke *et al.* 2014]. However, assessment of nocturia was based on IPSS question 7 rather than use of voiding diaries, and improvement was relatively modest and rather clinically insignificant compared with the monotherapies (adjusted mean change from baseline in IPSS question 7 score: −0.5 for combination treatment *versus* −0.4 and −0.3 for dutasteride and tamsulosin groups, respectively). Another subanalysis of CombAT data revealed sustained superior therapeutic effect of combination treatment over tamsulosin monotherapy in improving LUTS, regardless of patients' ethnic background. Even though racial differences in 5-AR activity, prostate volume, PSA levels and LUTS severity have been proved, no difference was found between Asian and White men in terms of clinical response to treatment [Chung *et al.* 2012].

In conclusion, CombAT results demonstrated that dutasteride plus tamsulosin combination is superior to either monotherapy in terms of symptoms and Q_{max} improvement from the ninth month of treatment, and superior to tamsulosin after the eighth month of treatment for disease progression-related events, such as AUR and need for surgical treatment [Roehrborn *et al.* 2010]. After 4 years, combination therapy led to a reduction in relative risk of AUR by 68%, need for surgery by 71%, and worsening of symptoms by 41% compared with tamsulosin [Roehrborn *et al.* 2010]. To prevent one case of urinary retention and/or surgical treatment 13 patients need to be treated [number needed to treat (NNT)] for 4 years with dutasteride and tamsulosin combination therapy compared with tamsulosin monotherapy while the absolute risk reduction (risk difference) was 7.7%. Furthermore, men with baseline prostate volume $\geqslant$ 40 cm^3 and baseline PSA levels $\geqslant$ 1.5 ng/ml experienced the greatest benefit from combination therapy than tamsulosin monotherapy in terms of reduced risk for AUR, BPH-related surgical intervention,

progression of disease and symptoms deterioration [Roehrborn *et al.* 2011].

A retrospective analysis of two nationally representative databases showed that each month of delay in adding a 5α-RI to α-blocker monotherapy led to an increased likelihood of progression at the end of 1 year [Naslund *et al.* 2009]. These data suggest that if combination therapy is indicated, simultaneous initiation of the 5α-RI and the α-blocker or the early addition of 5α-RI to α-blocker should be considered.

The safety analysis of CombAT trial reported that combination treatment had significantly higher rates of treatment-related adverse events in comparison to either monotherapies (28% *versus* 21% and 19%), a finding explained by the synergistic effect of the use of two drugs, although no difference was found in withdrawal rates due to treatment-related side effects between combination therapy (6%), tamsulosin (4%) or dutasteride monotherapy (4%) [Roehrborn *et al.* 2010]. Erectile and ejaculatory dysfunction was more frequent in the combination than in the monotherapy arms due to the synergistic effect of two drug classes, although this was not accompanied by higher drop-out rates. Moreover, a decline in treatment-related side effects was observed over the trial duration, with a 1-year rate of 12% compared with a 2% 4-year rate [Barkin, 2011].

Fixed-dose combination therapy

In 2010, the pharmaceutical company GlaxoSmithKline (GSK) received approval for a single-capsule containing 0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride, in the form of soft gelatin capsule and modified release pellets. Therapeutic indications comprise treatment of moderate-to-severe BPH symptoms and reduction in the risk of AUR and surgery in patients with moderate-to-severe BPH symptoms [GlaxoSmithKline Duodart® SPC].

Between December 2010 and October 2013, the CONDUCT trial was conducted. CONDUCT was a an international, multicenter, randomized, open-label, parallel-group phase IV study aiming to investigate whether immediate treatment in eligible men with a FDC of 0.5 mg dutasteride and 0.4 mg tamsulosin offers faster and more profound symptom reduction than that offered by watchful waiting (WW) plus initiation of tamsulosin if symptoms did not improve (WW-All). Moreover, both groups received lifestyle advice on dietary habits, fluid management and bladder training exercises [Roehrborn *et al.* 2015].

Study inclusion criteria comprised age ⩾50 years, a confirmed BPH diagnosis, LUTS of moderate degree, baseline prostate volume ⩾30 cm^3 measured by TRUS and baseline total serum PSA level of ⩾1.5 ng/ml. Patients were excluded if total serum PSA value was >10.0 ng/ml, they had history or evidence of prostate cancer, and were under any current, or prior, BPH-related treatment. Men with moderate LUTS were included in CONDUCT because patients with severe LUTS should ideally receive active treatment, rather than experience a treatment delay of at least 4 weeks based on the protocol design. Nevertheless, even though according to the CONDUCT design almost 50% of its participants would be excluded from the CombAT trial, study participants were closer to the breadth of patients evaluated in general urological practice.

The study primary endpoint was IPSS change from baseline at 2 years. Secondary endpoints comprised several degrees of IPSS improvements and the time to, and proportion of patients with, BPH clinical progression. Other study outcomes included change in BII score from baseline, rating of IPSS question 8 and responses to two patient perception of study treatment (PPST) questions.

In total, 742 patients were initially randomized in the trial (369 patients in the FDC group and 373 in the WW group) and 592 of them completed the 24-month study. In 61% of patients in WW group tamsulosin was administered, with the vast majority (83%) of men receiving treatment within the first 6 study months, mainly due to symptom deterioration according to IPSS.

CONDUCT results revealed that FDC administration resulted in greater improvement in symptoms than WW with addition of tamsulosin if symptoms were not improved (−5.4 *versus* −3.6 IPSS points at month 24, $p < 0.001$). The relationship of changes in symptom scores with patient global ratings of improvement has been investigated [Barry *et al.* 1995]. Based on this, the observed −5.4 IPSS points adjusted mean reduction in FDC group would be considered as moderate improvement in symptoms by patients while the change of −3.6 units seen in the WW-All group would be interpreted as mild LUTS improvement by patients (Table 1).

Improvement was observed from month 1 until the end of trial, and FDC resulted in a shifting of symptom score from the moderate to the mild category from month 9 onwards, while no improvement in symptom severity category was observed in WW patients. Furthermore, FDC treatment significantly reduced the relative risk of clinical progression (mainly characterized as worsening in symptoms) by 43.1% when compared with WW-All, with an absolute risk reduction of 11.3% (NNT = 9).

With regard to quality of life parameters, greater improvement was observed in the FDC group in comparison with the WW-All group, from month 1 through month 24, according to BII questionnaire and IPSS question 8. No difference was found in treatment satisfaction between the two groups at the end of trial. Regarding adverse events, erectile dysfunction and retrograde ejaculation were the most common across both groups (Table 1). In all, serious or drug-related adverse events and adverse events that led to study withdrawal or study discontinuation were more prevalent in the FDC group, which had a higher incidence during the first 6 months of therapy which declined thereafter. The higher incidence of adverse events in the FDC group can be attributed to the synergistic effect of two active components in FDC therapy, and by the longer exposure of FDC patients to study medication (mean overall exposure 639.8 days) in comparison with patients in the WW group who started tamsulosin (mean overall exposure 566.3 days). None of the patients in the FDC group was diagnosed with prostate cancer.

Overall, the CONDUCT trial verified the effectiveness of the FDC of dutasteride and tamsulosin in managing men with moderate LUTS, treatment naïve, who are at risk for disease progression. Sustained efficacy of FDC therapy over the course of treatment, satisfaction with its use, and acceptable safety profile were proved.

Cost-effectiveness of the FDC and adherence

Cost-effectiveness of FDC treatment has been evaluated in various national health systems. Cost analysis studies from Canada showed that FDC treatment with dutasteride and tamsulosin is more cost-effective than concurrent administration of dutasteride and tamsulosin for BPH management [Ismaila *et al.* 2013; Sayani *et al.* 2014]. Findings from a Greek study revealed that even though FDC use would increase the overall BPH-associated budget, cost would be compensated for by a reduction in BPH-related treatment. Specifically, 4 years of FDC use would lead to 1758 less TURPs and 972 less episodes of AUR [Geitona *et al.* 2014]. Furthermore, FDC has been also proved to be more cost-effective than monotherapy, according to results of studies conducted in Spain, Scandinavia and the UK. The incremental costs of combination therapy are greatest in the first years of treatment but the benefits accrue over time. Therefore, FDC treatment has a high probability of being more cost-effective than various forms of monotherapy [Antoñanzas *et al.* 2011; Bjerklund Johansen *et al.* 2012; Walker *et al.* 2013].

Patients' nonadherence to medical treatment of male LUTS represents a significant problem [Nichol *et al.* 2009]. Combination therapies seem to result in better compliance compared with monotherapies [Lin *et al.* 2012; Nichol *et al.* 2009]. Less-frequent dosage enhances adherence and technical adherence interventions are usually directed at simplifying the medication regimen [Van Dulmen *et al.* 2007]. Therefore, a potential advantage of the FDC of tamsulosin with dutasteride may be the improvement of patients' adherence.

Conclusion

Combination treatment with dutasteride and tamsulosin is significantly superior to tamsulosin and dutasteride monotherapy in terms of symptom improvement and reduction of relative risk of BPH clinical progression in men with enlarged prostates. Combination therapy has been shown to be a safe treatment and the adverse events observed were consistent with previous experience with dutasteride and tamsulosin monotherapies, but the frequency of adverse events was higher for combination therapy. Recent results on FDC treatment complement older data in BPH patients at risk of progression with only moderate symptoms and who are naïve to treatment. Combination therapy should only be used when long-term treatment (more than 12 months) is intended.

Based on this evidence, guidelines from the major societies (including the EAU and the AUA) recommend the use of combination treatment with an α1-blocker and a 5α-RI in men with moderate-to-severe BPH/BPE-related LUTS, enlarged prostate and reduced Q_{max}, who are those at risk for disease progression [Oelke *et al.* 2013; McVary

et al. 2011]. Nevertheless, further studies are needed to provide additional data on optimal patient selection, the role of FDC as add-on treatment compared with FDC as first-line treatment, and cost-effectiveness.

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