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TOPIC PAPER

Nocturia improvement in the combination of Avodart® and tamsulosin (CombAT) study

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Abstract
Purpose The purpose of the study was to assess the impact of dutasteride plus tamsulosin combination therapy, compared with dutasteride or tamsulosin monotherapy, on nocturia in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) using data from the 4-year CombAT study.
Methods Nocturia was assessed using Question 7 of the International Prostate Symptom Score questionnaire. Efficacy measures included as follows: mean change in nocturia at 3-month intervals up to 48 months; proportion of patients with improvement/worsening in nocturia; nocturnal voiding frequency at baseline and study end, overall and by baseline subgroups; and nocturnal voiding frequency <2 at study end in patients with a baseline score ≥2.
Results In total, 4,722 patients with a mean age of 66 years were included. Mean nocturia improvements were significantly superior ($p \leq 0.01$) with combination therapy than with either monotherapy (adjusted mean change from baseline in IPSS Question 7 score at month 48: combination therapy −0.5, dutasteride −0.4, tamsulosin −0.3). Reduction in nocturia score with combination therapy was significantly ($p \leq 0.01$) better than tamsulosin monotherapy across all baseline subgroups tested, except for men with previous 5ARI use. Among those with a baseline IPSS Q7 score ≥2, more patients with combination therapy had a score <2 at month 48 (34 %) compared with dutasteride (30 %, $p = 0.018$) or tamsulosin (26 %, $p < 0.0001$).
Conclusions Combination therapy provided greater improvements and less worsening of nocturia compared with both dutasteride and tamsulosin monotherapies. These analyses are the first to show greater improvement with a 5ARI/α-blocker combination versus either agent alone for the management of nocturia in patients with LUTS/BPH.

Keywords Nocturia · Dutasteride · Tamsulosin · Combination drug therapy · Randomised controlled trial

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Introduction

Nocturia is among the most frequently reported and bothersome symptoms in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) [1, 2]. As defined by the International Continence Society (ICS), nocturia is the complaint that results in an individual having to wake at least once a night to void [3]. Available evidence suggests that waking only once per night to void is associated with minimal bother, whereas frequent voiding ≥2 per night can have a substantial impact on patients [4, 5]. Sleep disruption due to nocturia can have a negative impact on the patients' ability to function, can cause chronic fatigue, and eventually lead to marked reductions in quality of life (QoL) [1, 2]. Nocturia is also

associated with falls, fractures, and an increased risk of mortality [6, 7].

Current pharmacological treatments for LUTS/BPH include α_1-adrenoceptor antagonists (α_1-blockers) and 5α-reductase inhibitors (5ARIs), or a combination of both [8]. However, data on the impact of these different treatment options on nocturia are currently limited.

The CombAT study was a multicentre, randomised, double-blind, 4-year study that compared the efficacy and safety of combination therapy [5ARI (dutasteride) plus α_1-blocker (tamsulosin)] with both monotherapies in patients with moderate-to-severe LUTS/BPH and benign prostatic enlargement [9]. Combination therapy provided significantly greater LUTS improvements and was significantly superior at reducing the relative risk of BPH clinical progression, compared with both tamsulosin and dutasteride monotherapies. In addition, combination therapy was significantly superior to tamsulosin but not dutasteride at reducing the relative risk of acute urinary retention or BPH-related surgery at 4 years. Here, we present findings from post hoc analyses of changes in nocturia among patients participating in the 4-year CombAT study.

Patients and methods

Study design and patient population

CombAT was a multicentre, randomised, double-blind, parallel-group study involving 4,844 patients in 35 countries [9]. The study design was published previously [10]. Subjects eligible for inclusion in CombAT were men aged ≥50 years with a confirmed clinical diagnosis of BPH, an International Prostate Symptom Score (IPSS) ≥12, prostate volume ≥30 cc, prostate-specific antigen 1.5–10 ng/ml, maximum urinary flow rate (Q_{max}) >5 to ≤15 ml/s, and a minimum voided volume of ≥125 ml.

Eligible patients entered a single-blind run-in period during which they received placebo for 4 weeks. Patients were then randomised (1:1:1 ratio) into one of the following treatment groups: tamsulosin 0.4 mg (plus dutasteride-matched placebo); dutasteride 0.5 mg (plus tamsulosin-matched placebo); combination therapy with dutasteride (0.5 mg) plus tamsulosin (0.4 mg). Patients self-administered their study treatment once daily for a period of 4 years and returned to the clinic for assessments every 3 months. The IPSS questionnaire was used to evaluate LUTS at baseline and during treatment.

Assessments and statistical analyses

The prevalence of nocturia was assessed with Question 7 of the IPSS, which asks: *During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?* Responses range from 0 to 5, as follows: none (0), 1 time (1), 2 times (2), 3 times (3), 4 times (4), 5 or more times (5).

Combination therapy was compared with dutasteride and tamsulosin monotherapies for the following outcome measures: mean changes in nocturia at each 3-month interval up to 48 months (using a generalised linear model); the proportion of patients with improvement or worsening (decrease/increase of ≥1 episode) in nocturia (Fisher's exact test), using the last observation carried forward (LOCF) approach; nocturnal voiding frequency at study end (48 months), overall and by various baseline subgroups (*t* tests or Fisher's exact test from the general linear model), using the LOCF approach; nocturnal voiding frequency <2 at study end in those patients with a baseline nocturia score ≥2 (Fisher's exact test), using the LOCF approach. Statistical significance was defined as $p \leq 0.05$. Safety data from the CombAT study have been reported previously [9].

Results

Patient demographics and baseline characteristics

In total, 4,813 patients had nocturia results at baseline, and 4,722 patients (98 %) had nocturia results at baseline and at ≥1 follow-up visit. Mean (SD) IPSS Question 7 score at baseline was 2.4 (1.24) in the combination therapy group, 2.4 (1.21) in the dutasteride group, and 2.4 (1.21) in the tamsulosin group. Patient demographics and baseline characteristics across each IPSS Question 7 score category are shown in Table 1. Overall IPSS score and BPH Impact Index (BII) rose according to increasing severity of nocturia, while Q_{max} decreased.

The majority of patients (80 %) had an IPSS Question 7 score of 1–3; 17 % patents had a score of 4 or 5 (Fig. 1). Only 3 % in each treatment group were free of nocturia at baseline. The proportion of patients in each group with a baseline IPSS Question 7 score of ≥2 was 76 % in the combination therapy and dutasteride groups and 75 % in the tamsulosin group.

Improvements in nocturia

At the end of the study (month 48), mean (SD) IPSS Question 7 scores were 1.8 (1.13) in the combination therapy group, 2.0 (1.16) in the dutasteride group, and 2.1 (1.19) in the tamsulosin group. Improvements in nocturia were significantly superior ($p \leq 0.01$) with combination therapy than with either monotherapy (adjusted mean

Table 1 Patient demographics and baseline characteristics by IPSS Question 7 score; data reported as mean (±SD)

Demographic parameter	IPSS Question 7 score						
	All	0	1	2	3	4	5
	Total $n = 4{,}813$	Total $n = 152$	Total $n = 1{,}023$	Total $n = 1{,}645$	Total $n = 1{,}196$	Total $n = 436$	Total $n = 361$
Age (years)	66.1 (7.0)	63.4 (6.6)	64.6 (6.9)	66.1 (7.0)	67.1 (7.0)	67.3 (6.7)	66.5 (7.3)
IPSS	16.4 (6.2)	12.0 (5.4)	13.1 (5.2)	15.4 (5.2)	18.0 (5.5)	21.3 (5.9)	21.4 (6.5)
Q_{max} (ml/s)	10.7 (3.6)	11.3 (3.7)	11.0 (3.8)[b]	10.8 (3.7)[e]	10.7 (3.5)[h]	10.5 (3.4)	10.4 (3.3)
Prostate volume (ml)	55.0 (23.5)	54.5 (22.4)	54.4 (22.8)[c]	54.5 (23.8)[f]	55.5 (23.1)[i]	56.7 (25.3)[k]	55.5 (23.8)
PSA (ng/ml)	4.0 (2.1)	4.0 (2.0)[a]	4.1 (2.0)[d]	3.9 (2.1)[g]	4.0 (2.1)[j]	3.9 (2.0)[k]	4.1 (2.2)[l]
BII	5.3 (3.0)	3.9 (2.6)	4.1 (2.6)	5.2 (2.9)	5.9 (3.0)	6.8 (3.3)[k]	5.9 (3.2)

BII BPH impact index, *IPSS* International Prostate Symptom Score, Q_{max} maximum urinary flow rate, *PSA* prostate-specific antigen, *SD* standard deviation

[a] $n = 151$, [b] $n = 1{,}022$, [c] $n = 1{,}021$, [d] $n = 1{,}019$, [e] $n = 1{,}644$, [f] $n = 1{,}640$, [g] $n = 1{,}639$, [h] $n = 1{,}195$, [i] $n = 1{,}189$, [j] $n = 1{,}184$, [k] $n = 435$, [l] $n = 358$

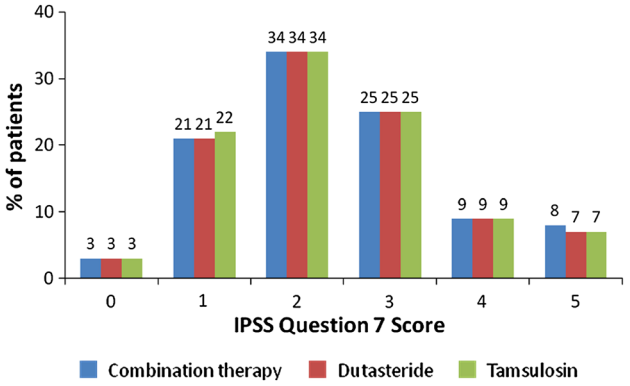


Fig. 1 Distribution of IPSS Question 7 scores at baseline for patients treated with dutasteride, tamsulosin, or combination therapy ($n = 4{,}722$ patients)

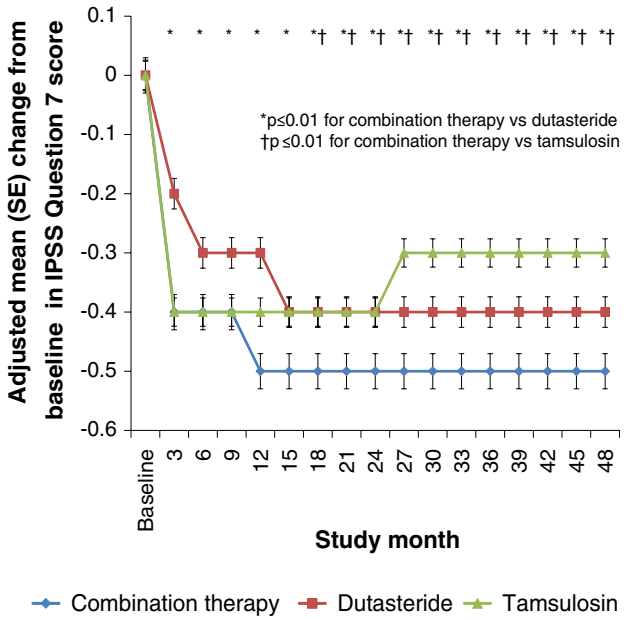


Fig. 2 Mean (SE) change from baseline in IPSS Question 7 score (LOCF)

change from baseline in IPSS Question 7 score: combination therapy, −0.5; dutasteride, −0.4; tamsulosin, −0.3). Superiority of combination began at month 3 versus dutasteride and month 18 versus tamsulosin (Fig. 2).

In each baseline nocturia category, combination therapy also resulted in a numerically greater proportion of patients with overall improvement at month 48, compared with both dutasteride and tamsulosin alone (Table 2). Among those with significant nocturia at baseline (score ≥2), significantly more patients in the combination therapy group (60 %) showed improvement by at least one IPSS Q7 point at month 48 than in the dutasteride (54 %; $p = 0.006$) or tamsulosin (48 %; $p < 0.001$) groups. Also, among those with a baseline IPSS Q7 score ≥2, more subjects who received combination therapy had a score <2 at month 48 (34 %) compared with those who received dutasteride (30 %, $p = 0.018$) or tamsulosin (26 %, $p < 0.0001$) monotherapy.

Worsening/no change in nocturia

Compared with tamsulosin monotherapy, combination therapy resulted in a significantly ($p \leq 0.01$) smaller proportion of patients with worsening nocturia (Table 2). A smaller proportion of patients with worsening nocturia was also noted for combination therapy versus dutasteride, with the difference approaching statistical significance ($p = 0.014$). The proportion of patients who experienced 'no change' of nocturia symptoms was similar (with no statistically significant differences) across the three treatment groups (Table 2).

Table 2 **(a)** IPSS Q7 score at baseline and month 48 (LOCF) and **(b)** distribution of patients with improvement, no change or worsening in IPSS Q7 score at month 48, by baseline IPSS Q7 score (LOCF)

Baseline score		Endpoint					
Frequency	*N*	0	1	2	3	4	5
(a)							
Combination therapy							
0	50	34	12	4	0	0	0
1	337	47	192	62	22	10	4
2	527	27	206	221	57	8	8
3	387	13	79	153	107	24	11
4	147	4	30	45	45	16	7
5	121	3	43	18	18	14	19
Dutasteride							
0	52	24	19	7	1	1	0
1	328	38	183	74	23	3	7
2	549	26	193	240	55	20	15
3	396	8	72	144	121	43	8
4	140	3	29	39	41	22	6
5	113	1	24	32	17	17	22
Tamsulosin							
0	48	21	18	7	2	0	0
1	341	34	170	94	25	15	3
2	542	13	162	232	95	22	18
3	391	15	57	131	126	45	17
4	141	5	20	43	39	20	14
5	112	2	29	33	16	10	22

Baseline score		Endpoint (month 48)		
Frequency	*N*	Improvement *N* (%)	No change *N* (%)	Worsening *N* (%)
(b)				
Combination therapy				
0	50	0 (0)	34 (68)	16 (32)
1	337	47 (14)	192 (57)	98 (29)
2	527	233 (44)	221 (42)	73 (14)
3	387	245 (63)	107 (28)	35 (9)
4	147	124 (84)	16 (11)	7 (5)
5	121	102 (84)	19 (16)	0 (0)
All	1,569	751 (48)	589 (38)	229 (15)
Dutasteride				
0	52	0 (0)	24 (46)	28 (54)
1	328	38 (12)	183 (56)	107 (33)
2	549	219 (40)	240 (44)	90 (16)
3	396	224 (57)	121 (31)	51 (13)
4	140	112 (80)	22 (16)	6 (4)
5	113	91 (81)	22 (19)	0 (0)
All	1,578	684 (43)^	612 (39)	282 (18)†
Tamsulosin				
0	48	0 (0)	21 (44)	27 (56)
1	341	34 (10)	170 (50)	137 (40)*
2	542	175 (32)*	232 (43)	135 (25)*
3	391	203 (52)*	126 (32)	62 (16)*
4	141	107 (76)	20 (14)	14 (10)
5	112	90 (80)	22 (20)	0 (0)
All	1,575	609 (39)*	591 (38)	375 (24)*

Note that patients with a score of 0 cannot experience improvement, and patients with a score of 5 cannot experience worsening

* $p \leq 0.01$; ^ $p = 0.011$;
† $p = 0.014$ versus combination therapy

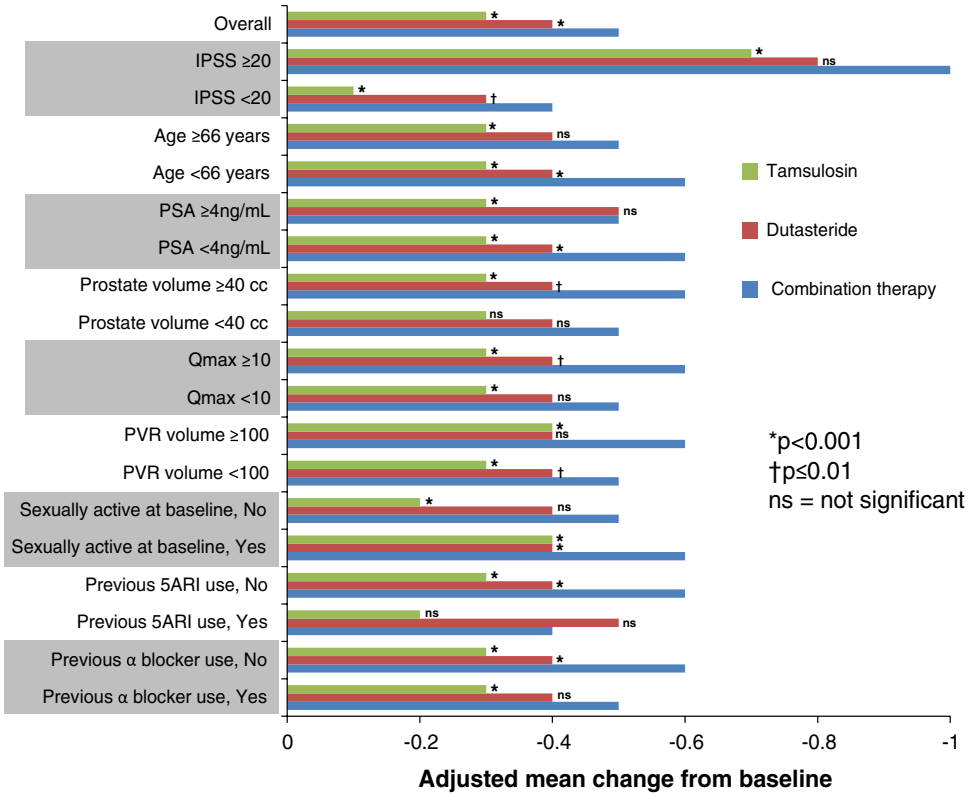


Fig. 3 Mean change from baseline in IPSS Question 7 score by various baseline subgroups (LOCF)

Treatment impact on nocturia score by baseline subgroups

At month 48, mean reduction in nocturia score with combination therapy (dutasteride plus tamsulosin) was significantly ($p \leq 0.01$) better than tamsulosin monotherapy across all baseline subgroups tested, except in the subgroup of men who had previous 5ARI use (Fig. 3). For the comparisons of combination therapy and dutasteride monotherapy, reduction in nocturia was significantly ($p \leq 0.01$) better in favour of dutasteride plus tamsulosin for the following subgroups analysed: IPSS <20, age <66 years, PSA <4 ng/ml, Q_{max} ≥10 ml/s, PVR volume <100 ml, men who were sexually active at baseline, men with no previous 5ARI use and men with no previous α-blocker use (Fig. 3).

Proportional contribution of IPSS constituent questions at baseline and month 48

The proportion of the total IPSS score contributed by each individual question was calculated at baseline and end of the study (month 48) (Fig. 4). In the combination and dutasteride groups, improvement in IPSS Q7 was less than for the other IPSS questions, as indicated by the relatively larger contribution of IPSS Q7 to the total score at month 48 than at baseline. In the tamsulosin group, the relative contributions of all IPSS questions were largely unchanged between baseline and month 48.

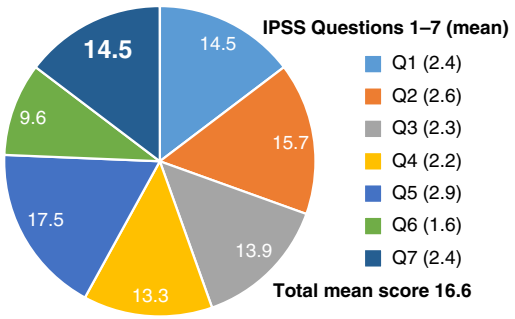
Discussion

In these secondary analyses of data from the CombAT study, treatment with dutasteride plus tamsulosin (combination therapy) was associated with a statistically significant improvement in mean nocturnal voids compared with either dutasteride or tamsulosin monotherapy. The improvement with combination therapy was greater relative to tamsulosin than to dutasteride (adjusted mean change from baseline in IPSS Question 7 score: combination therapy, −0.5; dutasteride, −0.4; tamsulosin, −0.3). In addition, a greater proportion of patients experienced improvement and a lower proportion experienced worsening with combination therapy across the range of baseline IPSS Q7 scores. Although the improvements in nocturia with combination therapy were statistically significant as compared with either monotherapy, the net benefits were relatively modest (on average <0.2 episodes per night compared with dutasteride and <0.3 episodes per night compared with tamsulosin). Dutasteride plus tamsulosin was statistically superior to tamsulosin monotherapy both overall and across all baseline subgroups tested, except in the relatively small subgroup of men with previous 5ARI use.

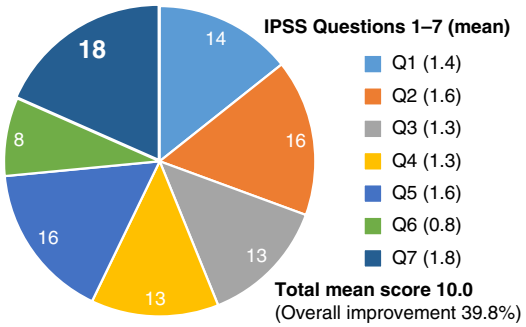
These analyses are the first to show a benefit for a 5ARI plus an α-blocker versus either agent alone for the management of nocturia in patients with BPH. Previous studies, including a secondary analysis of MTOPS,

(a) Combination therapy

Combination therapy baseline
% contribution to mean

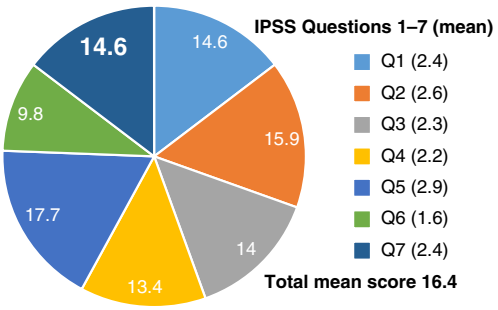


Combination therapy endpoint
% contribution to mean

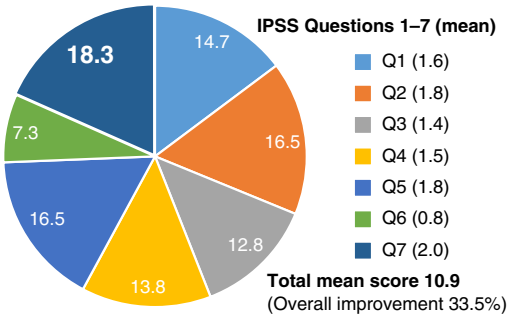


(b) Dutasteride

Dutasteride baseline
% contribution to mean

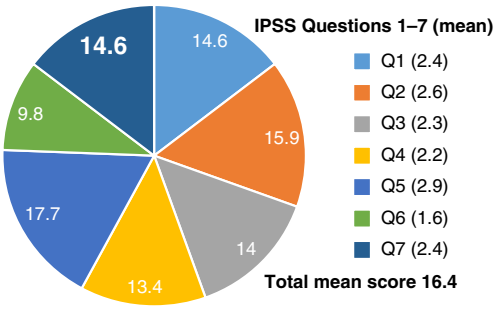


Dutasteride endpoint
% contribution to mean



(c) Tamsulosin

Tamsulosin baseline
% contribution to mean



Tamsulosin endpoint
% contribution to mean

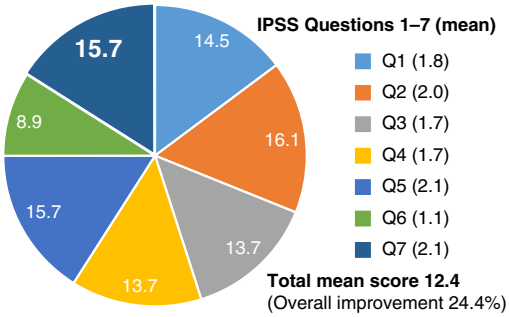


Fig. 4 Proportional contribution of individual IPSS questions to total IPSS score at baseline and end of the treatment (month 48). **a** Combination therapy, **b** Dutasteride, **c** Tamsulosin

have shown a benefit for 5ARI plus α-blocker combination therapy compared with 5ARI alone, but not compared with α-blocker monotherapy [11, 12]. However, it should be noted that the patient population in CombAT differed from that in MTOPS, in particular with regard to inclusion criteria for prostate volume and PSA level. The 5ARI and α-blocker studied were also different between the two trials.

Waking to void ≥2 times per night can have a substantial impact on patients' QoL [4, 5]. Among subjects with a baseline IPSS Question 7 score ≥2, a greater proportion of those treated with combination therapy reported improvement at study end compared with men who received either monotherapy. Also, significantly more of these patients treated with combination therapy had a score of <2 at study end compared with either monotherapy.

Interpretation of the findings presented here is limited by the post hoc nature of the analyses. In addition, nocturia was assessed as overall night-time voiding based on IPSS Q7, rather than through use of voiding diaries (as recommended by the ICS). Nocturnal polyuria or other urological and non-urological disorders were therefore not excluded. Also, as there was no placebo arm in this study, the placebo effect on nocturnal voiding frequency remains unknown for the specific CombAT study population. A pooled analysis of three randomised, controlled phase III trials comparing the effects of dutasteride and placebo on nocturia has recently shown significant differences in favour of the 5ARI, with a difference of 0.2 nocturnal voiding episodes [13]. This treatment difference is similar to that observed with the α-blocker, silodosin, in another recent pooled analysis of data from phase III studies [14]. Tamsulosin has also been shown to be statistically superior to placebo for reducing nocturnal voiding frequency [15]. Since statistically significant differences versus placebo have been shown in favour of both types of monotherapies, it seems reasonable to suggest that the combination of dutasteride plus tamsulosin would result in significant differences if compared with placebo.

Conclusions

After 48 months of treatment, combination therapy (dutasteride plus tamsulosin) led to greater improvements and less worsening of nocturia symptoms, compared with both dutasteride and tamsulosin monotherapies. These analyses are the first to show greater improvement with a 5ARI plus an α-blocker versus either agent alone for the management of nocturia in patients with BPH. Prospective studies specifically designed to assess nocturia are required to confirm these findings, as well as to assess the ultimate benefits for QoL and other outcomes associated with nocturia.

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Conflict of interest Matthias Oelke has been a speaker, advisor, and/or trial participant for Allergan, Apogepha, Astellas, Bayer, Ferring, GlaxoSmithKline, Lilly, Mundipharma, Pfizer and Recordati. Claus G. Roehrborn has been a speaker, advisor, and/or trial participant for GlaxoSmithKline. Carlos D'Ancona has been a speaker and trial participant for GlaxoSmithKline and Astellas. Timothy H. Wilson, Ramiro Castro, and Michael Manyak are employees of GlaxoSmithKline.

Ethical standard The CombAT study was approved by the appropriate ethics committees and performed in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki and later amendments. All participants provided written informed consent prior to inclusion in the study.

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