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Benign Prostatic Hyperplasia

The Influence of Baseline Parameters on Changes in International Prostate Symptom Score with Dutasteride, Tamsulosin, and Combination Therapy among Men with Symptomatic Benign Prostatic Hyperplasia and an Enlarged Prostate: 2-Year Data from the CombAT Study

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Abstract

Background: Knowledge of baseline factors that influence outcomes for men with benign prostatic hyperplasia (BPH) receiving medical therapy may help to improve outcomes and cost effectiveness.
Objectives: To examine the influence of baseline parameters on changes in International Prostate Symptom Score (IPSS) and maximum urinary flow rate (Q_{max}) in men with BPH receiving dutasteride, tamsulosin, or a combination of the two using 2-yr Combination of Avodart and Tamsulosin (CombAT) study data.
Design, setting, and participants: CombAT is an ongoing, 4-yr, multicentre, randomised, double-blind study in 4844 men aged ≥50 yr with clinical diagnosis of BPH, IPSS ≥12, prostate volume ≥30 cm^3, prostate-specific

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Lower urinary tract symptoms
IPSS
Q_{max}

antigen (PSA) 1.5–10 ng/ml, and Q_{max} >5 and ≤15 ml/s with minimum voided volume ≥125 ml.
Intervention: Daily tamsulosin 0.4 mg, dutasteride 0.5 mg, or the combination.
Measurements: Post hoc analyses of mean IPSS and Q_{max} changes from baseline by treatment group and by baseline prostate volume, PSA, age, body mass index (BMI), IPSS, IPSS quality of life (QoL) score, BPH Impact Index score, Q_{max}, and previous BPH medical therapy.
Results and limitations: Combination therapy was more effective than either monotherapy after 24 mo in improving IPSS in all baseline subgroups, with benefit onset varying by baseline prostate volume. Combination therapy was also more effective in improving Q_{max} versus tamsulosin in all subgroups and versus dutasteride in 10 of 18 subgroups. At 24 mo, dutasteride monotherapy resulted in significantly greater IPSS improvements versus tamsulosin in men with lower age, worse symptoms, worse QoL, less bother, higher BMI, greater Q_{max}, higher prostate volume, and higher PSA at baseline. Post hoc analyses, the lack of placebo control, and the exclusion of men with unsuccessful medical BPH treatment are study limitations.
Conclusions: Combination therapy with tamsulosin and dutasteride affords the greatest and the most rapid symptomatic benefit among men with higher baseline prostate volume and is effective regardless of previous BPH medical therapy. Dutasteride monotherapy is more effective than tamsulosin in men with higher baseline prostate volume or PSA and worse symptoms.

1. Introduction

Current guidelines on selection of the two commonly prescribed drug classes for symptomatic benign prostatic hyperplasia (BPH), the 5α-reductase inhibitors (5-ARIs) and alpha-blockers, lack detail on patient selection beyond the observation that 5-ARIs are less effective in improving symptoms among men without an enlarged prostate [1,2]. Combination therapy is considered an option for men ''in whom baseline risk of progression is significantly higher . . . patients with larger glands and higher PSA values,'' although ''at present, absolute threshold values cannot be given'' [2].

This lack of guidance on patient selection in part reflects a relative paucity of evidence on the differential effects of these therapies in different subgroups of men. Although the accumulated subject numbers in randomised trials of medical therapy are substantial, few data have been published on the patterns of effect of 5-ARIs and alpha-blockers and on where combination therapy would be most beneficial. Post hoc analyses from the Medical Therapy of Prostatic Symptoms Study (MTOPS) provided insight into which men may gain additional benefit of combination therapy over monotherapies alone [3]. These data demonstrated that men with a prostate volume ≥25 cm^3 had a significantly greater decrease in symptoms when they received finasteride in addition to doxazosin compared with doxazosin alone.

Although these data have significantly contributed to our understanding of the importance of prostate volume as a marker for treatment outcome, a number of questions remain outstanding. First, are there any other parameters that influence treatment outcomes with combination therapy versus monotherapies beyond prostate volume? Second, which parameters are of importance in influencing the symptomatic outcomes of 5-ARIs and alpha-blockers? Finally, what impact does a previous history of BPH medical therapy have on outcomes with combination therapy and with monotherapies?

The aim of the 4-yr Combination of Avodart and Tamsulosin (CombAT) study is to investigate whether combination therapy with the alpha-blocker tamsulosin and the dual 5-ARI dutasteride is more effective than either monotherapy alone for improvement of symptoms and for long-term clinical outcomes of acute urinary retention (AUR) and BPH-related prostatic surgery in men with moderate-to-severe symptoms of BPH and prostatic

enlargement. The design of the CombAT study [4] and data from the 2-yr, preplanned primary and secondary end point analyses have been previously reported [5]. In this paper, we report the outcomes of post hoc analyses of the influence of baseline parameters, including previous treatment status, on changes in International Prostate Symptom Score (IPSS) and maximum urinary flow rate (Q_{max}) with tamsulosin, with dutasteride, and with combination therapy.

2. Methods

2.1. Study design

The design of the CombAT study has been previously reported [4,5]. Briefly, CombAT is a multinational, multicentre, randomised, double-blind, parallel-group study in which eligible subjects were randomised to receive oral dutasteride 0.5 mg once daily and tamsulosin 0.4 mg once daily, dutasteride 0.5 mg once daily and tamsulosin matched placebo, or dutasteride matched placebo and tamsulosin 0.4 mg once daily for a period of 4 yr. The self-administered IPSS questionnaire was implemented at screening, at baseline, and every 3 mo, and Q_{max} measurements were obtained at screening, at baseline, and every 6 mo. Transrectal ultrasound (TRUS) was performed at screening and annually for calculation of total prostate volume by formula.

2.2. Study population

Men aged ≥50 yr with a clinical diagnosis of BPH by medical history and physical examination were eligible for inclusion. Other principal inclusion criteria were an IPSS ≥12 points, a prostate volume ≥30 cm^3 by TRUS, a total serum PSA ≥1.5 ng/ml, and a Q_{max} >5 ml/s and ≤15 ml/s with a minimum voided volume ≥125 ml. Men with a total serum PSA >10.0 ng/ml were excluded. Use of a 5-ARI within the 6 mo (or dutasteride in the 12 mo) prior to the screening visit or use of an alpha-blocker or phytotherapy for BPH within the 2 wk prior to the screening visit were exclusion criteria. A history of unsuccessful treatment with tamsulosin, finasteride, or dutasteride, as defined by the investigator based on efficacy or tolerability, was also an exclusion criterion.

2.3. Study end point and statistical analyses

For the planned analyses at 2 yr, the primary end point was change in IPSS from baseline, with comparisons for combination versus dutasteride and for combination versus tamsulosin. Change in Q_{max} from baseline was a preplanned secondary end point. Although mean changes from baseline in IPSS and Q_{max} were prespecified in the study analysis plan for a range of subgroups, the statistical comparisons were post hoc analyses of the effect of baseline parameters on mean change in IPSS and Q_{max} from baseline to each postbaseline assessment up to and including the month 24 visit by treatment group. Baseline parameters analysed were prostate volume (tertiles: 30–<42, 42–<58, ≥58 cm^3; median: <49, ≥49 cm^3), PSA (tertiles: 1.5–<2.7, 2.7–<4.4, ≥4.4 ng/ml; median: <3.5, ≥3.5 ng/ml), age (median: <66, ≥66 yr), BMI (median: <26.8, ≥26.8 kg/m^2), IPSS (median: <16, ≥16; <20, ≥20), IPSS QoL score (median: <4, ≥4), BPH Impact Index (BII) score (median: <5, ≥5) and Q_{max} (median: <10.4, ≥10.4 ml/s).

Two analyses of outcomes by previous treatment use were also conducted using the following patient subgroups: men with or without a history of receiving an alpha-blocker, a 5-ARI, or phytotherapy prior to study entry; and men with or without a history of receiving an alpha-blocker. These analyses were conducted because they represent treatment effect in naïve versus non-naïve men as well as the common clinical scenario of patients with prior alpha-blocker use.

The primary population of subjects statistically analysed was the ''intent-to-treat'' (ITT) population, which consisted of all subjects randomised to double-blind study treatment. The last-observation-carried-forward (LOCF) approach was utilised. For all analyses, comparisons of changes from baseline to month 24 for combination therapy versus dutasteride, for combination therapy versus tamsulosin, and for dutasteride versus tamsulosin were conducted to further examine predictors of treatment response. Additionally, evaluations of treatment interaction by baseline variables were conducted. For all analyses, superiority was based on 2-sided p values <0.05, with no formal adjustments made for multiplicity of testing.

3. Results

3.1. Subject demographics and disposition

The study randomised 4844 men to treatment: these men constituted the ITT population. Of these, 3822 (79%) completed the month 24 visit [5]. Of the ITT population, 1829 (38%) had not received any previous medical therapy for BPH; 2397 (49%) had not received an alpha-blocker; 2444 (50%) had received an alpha-blocker; and 2943 (61%) had received an alpha blocker, a 5-ARI, or phytotherapy for BPH. Of the study population, 3446 (71%) had moderate symptoms (IPSS <20) and 1391 (29%) had severe symptoms. Baseline demographics by treatment group have been previously reported [5]; these were also broadly similar between groups of men divided by previous treatment use (Table 1). Men previously receiving medical therapy tended to have a higher baseline IPSS, BII, IPSS QoL score, prostate volume, and PSA. For men receiving prior alpha-blockers, the median time from previous use was 2.3 mo.

3.2. Changes in International Prostate Symptom Score by baseline prostate volume

At month 24, combination therapy resulted in a significantly greater improvement in IPSS versus dutasteride and tamsulosin in all prostate volume tertiles (Figs. 1 and 2a) and above and below the

Table 1 – Baseline characteristics of subjects in the Combination of Avodart and Tamsulosin (CombAT) study by previous medical therapy status (values are means unless otherwise stated).

	Treatment naïve (n = 1829)	Alpha-blocker naïve (n = 2397)	Previous alpha-blocker treatment (n = 2444)	Any previous BPH medical treatment (n = 2943)
Age (yr)	65.5	65.7	66.5	66.5
PSA (ng/ml)	3.9	3.9	4.1	4.1
Prostate volume (cm^3)	53.2	53.7	56.2	56.1
Q_{max} (ml/s)	10.9	11.0	10.5	10.6
IPSS	16.0	15.8	17.0	16.8
BPH Impact Index score	5.0	5.1	5.5	5.5
IPSS QoL score	3.5	3.5	3.7	3.7
Previous BPH medical treatment	–	5-ARI: 3% Phytotherapy: 19%	5-ARI: 19% Phytotherapy: 20%	Alpha-blocker: 83% 5-ARI: 18% Phytotherapy: 32%
Time since previous BPH medical therapy (mean; mo)	–	Phytotherapy: 13.5	Alpha-blocker: 8.6 Phytotherapy: 25.9	Alpha-blocker: 8.6 Phytotherapy: 20.0
Time since previous BPH medical therapy (median; mo)	–	Phytotherapy: 4.0	Alpha-blocker: 2.3 Phytotherapy: 9.8	Alpha-blocker: 2.3 Phytotherapy: 6.0

BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen; Q_{max} = maximum urinary flow rate; IPSS = International Prostate Symptom Score; QoL = quality of life; 5-ARI = 5α-reductase inhibitor.

median of 49 cm^3 (Table 2). Combination therapy resulted in significantly greater improvements in IPSS compared with dutasteride monotherapy at all time points across all volume tertiles. Compared with tamsulosin monotherapy, combination therapy was superior from month 21 in the lowest volume tertile (30–<42 cm^3; Fig. 1a), from month 6 in the middle-volume tertile (42–<58 cm^3; Fig. 1b), and from month 3 in the highest volume tertile (≥58 cm^3; Fig. 1c).

For the comparison between dutasteride and tamsulosin monotherapies, in the lowest volume tertile (30–<42 cm^3; Fig. 1a), tamsulosin was associated with a more rapid onset of symptom benefit, which was maintained until month 15. Thereafter, there was no significant difference between dutasteride and tamsulosin monotherapies in terms of symptom improvement. In the middle-volume tertile (42–<58 cm^3; Fig. 1b), a similar pattern was observed but there was no significant difference between dutasteride and tamsulosin from month 12. In the highest volume tertile (≥58 cm^3; Fig. 1c), tamsulosin was superior to dutasteride at the month 3 assessment, and there was no significant difference between the treatments for months 6, 9, and 12; thereafter, the symptom improvements for dutasteride were significantly greater than those for tamsulosin. When subgroups above and below the median prostate volume were examined at month 24, dutasteride treatment resulted in a significantly greater improvement in IPSS versus tamsulosin in men with a baseline prostate volume ≥49 cm^3 but not <49 cm^3 (Table 2). There was a significant treatment interaction by baseline prostate volume ($p < 0.001$).

3.3. *Changes in International Prostate Symptom Score by baseline prostate-specific antigen*

At month 24, combination therapy resulted in a significantly greater improvement in IPSS versus dutasteride and tamsulosin in all PSA tertiles, with the exception of the highest PSA tertile versus dutasteride (Fig. 2b). For the comparison between dutasteride and tamsulosin monotherapies, there was no significant difference between the treatments in the lowest two PSA tertiles; in the highest, significantly greater improvements in IPSS were observed for dutasteride versus tamsulosin. When subgroups above and below the median PSA were examined at month 24, dutasteride treatment resulted in a significantly greater improvement in IPSS versus tamsulosin in men with a baseline PSA ≥3.5 ng/ml but not <3.5 ng/ml (Table 2). There was a significant treatment interaction by baseline PSA ($p = 0.02$).

3.4. *Changes in maximum urinary flow rate by baseline prostate volume and prostate-specific antigen*

Combination therapy resulted in a significantly greater improvement in Q_{max} versus tamsulosin monotherapy for all prostate volume and PSA tertiles (Fig. 2c and d) and above and below the median prostate volume and the median PSA (Table 3). Compared with dutasteride, combination therapy

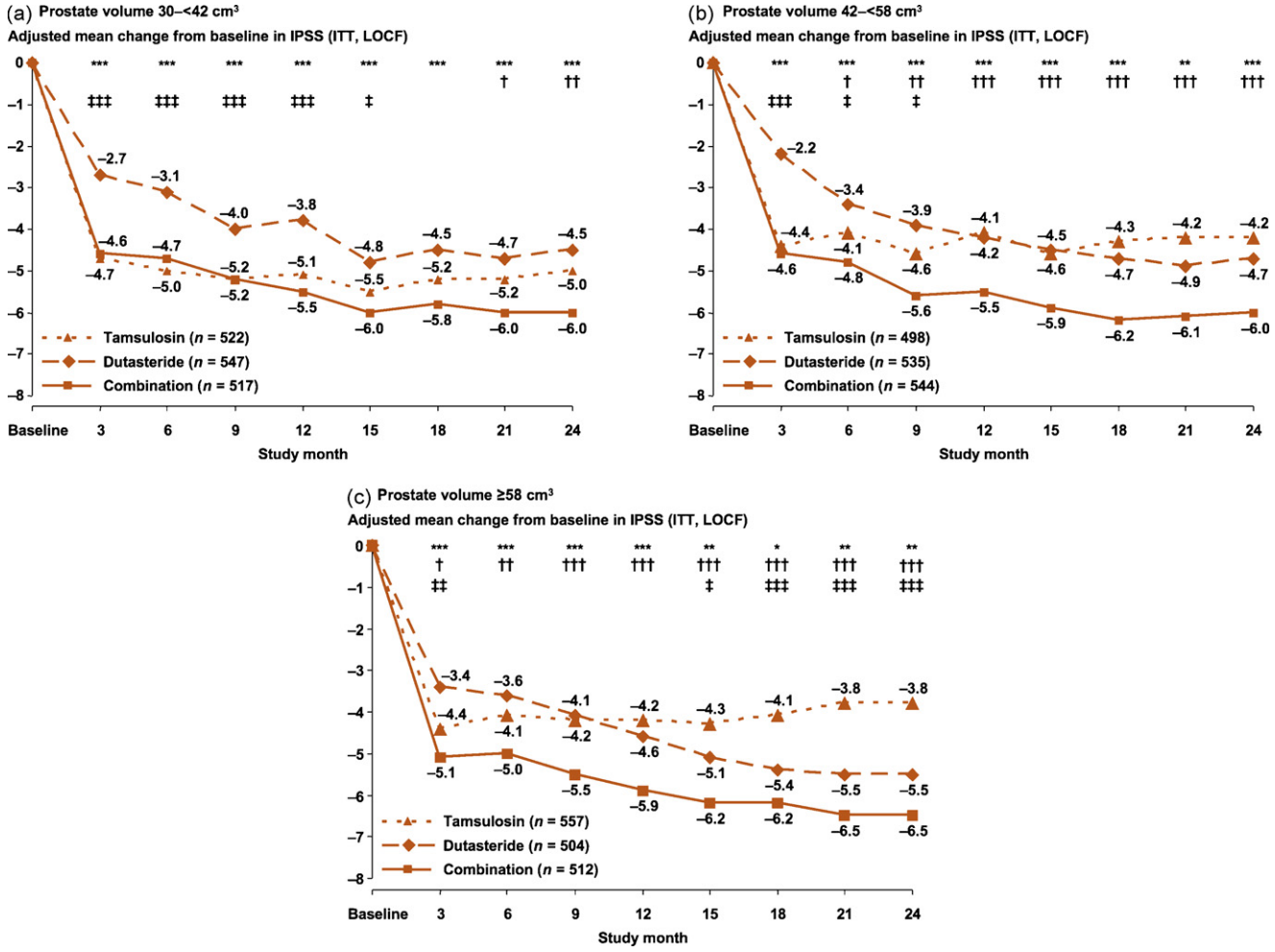

Fig. 1 – Adjusted mean change in International Prostate Symptom Score (IPSS) from baseline, by visit and by treatment group, for baseline prostate volume tertiles: (a) Prostate volume 30–<42 cm³; (b) prostate volume 42–<58 cm³; (c) prostate volume ≥58 cm³.

ITT = intent to treat; LOCF = last observation carried forward.

* $p < 0.05$ combination versus dutasteride.

** $p < 0.01$ combination versus dutasteride.

*** $p < 0.001$ combination versus dutasteride.

† $p < 0.05$ combination versus tamsulosin.

†† $p < 0.01$ combination versus tamsulosin.

††† $p < 0.001$ combination versus tamsulosin.

‡ $p < 0.05$ dutasteride versus tamsulosin.

‡‡ $p < 0.01$ dutasteride versus tamsulosin.

‡‡‡ $p < 0.001$ dutasteride versus tamsulosin.

was associated with significantly greater improvements in only the highest prostate volume and PSA tertiles, as well as above the median prostate volume and median PSA. For the comparison between dutasteride and tamsulosin monotherapies, significantly greater improvements in Q_{max} were observed for dutasteride treatment versus tamsulosin in all prostate volume and PSA tertiles except for the middle prostate volume tertile. Dutasteride treatment also resulted in significantly greater improvements in Q_{max} at month 24 versus tamsulosin in men with a baseline prostate volume and PSA both above and below the median values (Table 3). There was a significant treatment by baseline prostate volume interaction ($p = 0.002$).

3.5. *Changes in International Prostate Symptom Score and in maximum urinary flow rate by previous benign prostatic hyperplasia treatment status*

At month 24, combination therapy resulted in significantly greater improvements in IPSS versus

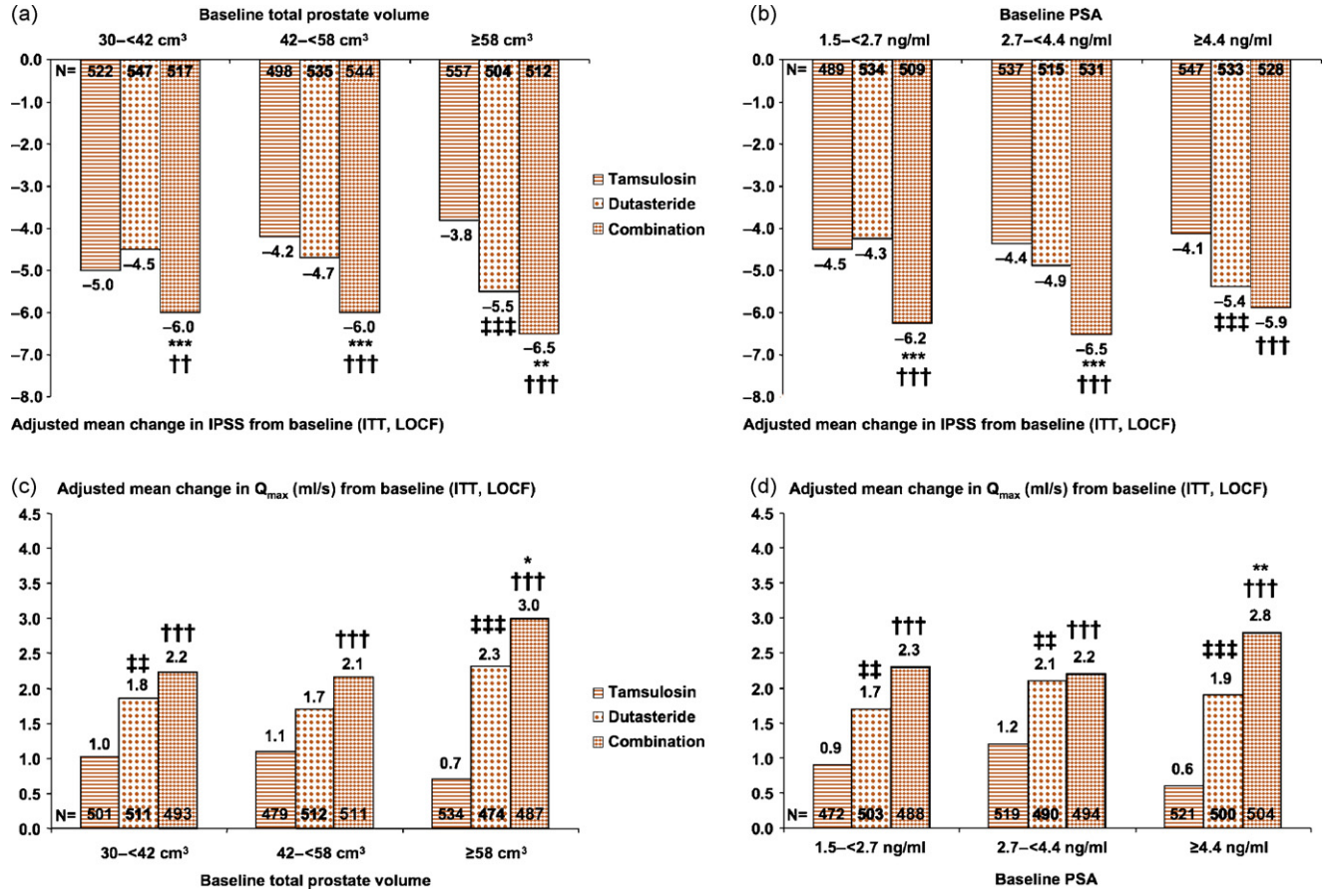

Fig. 2 – Adjusted mean changes in International Prostate Symptom Score (IPSS) from baseline to month 24 (a) by prostate volume and (b) by prostate-specific antigen (PSA) tertiles. Adjusted mean changes in maximum urinary flow rate (Q_{max}) from baseline to month 24 (c) by prostate volume and (d) by PSA tertiles.
ITT = intent to treat; LOCF = last observation carried forward.
* ***p*** **< 0.05 combination versus dutasteride.**
** ***p*** **< 0.01 combination versus dutasteride.**
*** ***p*** **< 0.001 combination versus dutasteride.**
†† ***p*** **< 0.01 combination versus tamsulosin.**
††† ***p*** **< 0.001 combination versus tamsulosin.**
‡‡ ***p*** **< 0.01 dutasteride versus tamsulosin.**
‡‡‡ ***p*** **< 0.001 dutasteride versus tamsulosin.**

tamsulosin and dutasteride in naïve and in previously treated men (Fig. 3a). Dutasteride therapy was significantly more effective than tamsulosin in improving IPSS in previously treated men (any BPH medical therapy or alpha-blocker therapy).

Combination therapy resulted in significantly greater improvements in Q_{max} versus tamsulosin and dutasteride in naïve and in previously treated men, with the exception of the change in Q_{max} versus dutasteride in alpha-blocker–naïve and treatment-naïve men (Fig. 3b). Dutasteride therapy was significantly more effective than tamsulosin in improving Q_{max} in previously treated men and in treatment-naïve men.

3.6. *Changes in International Prostate Symptom Score and in maximum urinary flow rate by other baseline parameters*

Combination therapy resulted in significantly greater improvements in IPSS in all subgroups versus tamsulosin and dutasteride at month 24 (Table 2). Combination therapy was therefore more effective than either monotherapy in patients with moderate or severe symptoms and regardless of baseline QoL or bother. Tamsulosin treatment was not associated with significantly greater improvements versus dutasteride within any subgroup; dutasteride treatment had a significantly greater effect versus

Table 2 – Adjusted mean changes from baseline to month 24 in International Prostate Symptom Score (IPSS) by baseline parameters.

Baseline parameter (first and second subgroups)	Treatment group	First subgroup	Second subgroup
Median age (<66 yr, n = 2263; ≥66 yr, n = 2578)	Tam	−4.1	−4.5
	Dut	−4.9‡	−4.9
	Comb	−6.5***†††	−5.9***†††
Median BMI (<26.8 kg/m^2, n = 2396; ≥26.8 kg/m^2, n = 2427)	Tam	−4.6	−4.0
	Dut	−5.1	−4.6‡
	Comb	−6.2***†††	−6.1***†††
IPSS (<20, n = 3446; ≥20, n = 1391)	Tam	−2.8	−8.3
	Dut	−3.1	−9.5‡‡
	Comb	−4.2***†††	−11.2***†††
Median IPSS (<16, n = 2340; ≥16, n = 2497)	Tam	−1.8	−6.7
	Dut	−2.1	−7.6‡
	Comb	−3.0***†††	−9.2***†††
Median IPSS QoL (<4, n = 2293; ≥4, n = 2540)	Tam	−3.0	−5.5
	Dut	−3.4	−6.2‡
	Comb	−4.6***†††	−7.6***†††
Median BII (<5, n = 2068; ≥5, n = 2764)	Tam	−2.9	−5.4
	Dut	−3.6‡	−5.9
	Comb	−4.5**†††	−7.4***†††
Median Q_{max} (<10.4 ml/s, n = 2412; ≥10.4 ml/s, n = 2425)	Tam	−4.6	−4.1
	Dut	−4.9	−4.9‡‡
	Comb	−6.2***†††	−6.1***†††
Median prostate volume (<49 cm^3, n = 2423; ≥49 cm^3, n = 2403)	Tam	−4.8	−3.9
	Dut	−4.5	−5.3‡‡‡
	Comb	−6.1***†††	−6.3**†††
Median PSA (<3.5 ng/ml, n = 2405; ≥3.5 ng/ml, n = 2408)	Tam	−4.6	−4.1
	Dut	−4.6	−5.1‡‡‡
	Comb	−6.3***†††	−6.0**†††

Tam = tamsulosin; Dut = dutasteride; Comb = combination; BMI = body mass index; QoL = quality of life; BII = Benign Prostatic Hyperplasia Impact Index; Q_{max} = maximum urinary flow rate; PSA = prostate-specific antigen.
** $p < 0.01$ combination versus dutasteride.
*** $p < 0.001$ combination versus dutasteride.
††† $p < 0.001$ combination versus tamsulosin.
‡ $p < 0.05$ dutasteride versus tamsulosin.
‡‡ $p < 0.01$ dutasteride versus tamsulosin.
‡‡‡ $p < 0.001$ dutasteride versus tamsulosin.

tamsulosin in men with a lower age, worse IPSS, worse QoL, less bother, higher BMI, and greater Q_{max}. All treatment groups showed a greater degree of symptom improvement in subjects with worse baseline IPSS scores.

Combination therapy resulted in significantly greater improvements in Q_{max} in all subgroups versus tamsulosin (Table 3). Combination therapy was also associated with greater Q_{max} improvements versus dutasteride in older men, in those with a higher BMI, in those with worse QoL and bother, and in those with a lower Q_{max}. It was also associated with greater Q_{max} improvements in both moderate and severe symptom groups and in those with an IPSS ≥16, the median. Dutasteride had significantly greater effects versus tamsulosin in all subgroups examined. In men with a baseline Q_{max} ≥10.4 ml/s, combination and dutasteride monotherapy, but not tamsulosin monotherapy, was associated with an increase in Q_{max}.

4. Discussion

These post hoc analyses of 2-yr data from the CombAT study provide insights into the patterns of effect of tamsulosin and dutasteride monotherapies and of their combination in men with symptomatic BPH and an enlarged prostate (≥30 cm^3). In this group of men, combination therapy with dutasteride and tamsulosin resulted in significantly greater improvements in IPSS at month 24 versus either monotherapy, regardless of baseline prostate volume. It is evident from the more detailed analysis of IPSS improvements by baseline prostate volume and time that both parameters affected treatment response to tamsulosin and dutasteride monotherapies: this is also reflected in the pattern of benefit of combination therapy over either monotherapy.

As prostate volume or PSA increases, it is evident that the Q_{max} improvement observed with combination therapy is derived increasingly from dutaste-

Table 3 – Adjusted mean changes from baseline to month 24 in maximum urinary flow rate (Q_{max}; ml/s) by baseline parameters.

Baseline parameter (first and second subgroups)	Treatment group	First subgroup	Second subgroup
Median age (<66 yr, *n* = 2263; ≥66 yr, *n* = 2578)	Tam	0.9	0.9
	Dut	1.9‡‡‡	1.9‡‡‡
	Comb	2.4†††	2.5*†††
Median BMI (<26.8 kg/m^2, *n* = 2396; ≥26.8 kg/m^2, *n* = 2427)	Tam	0.8	1.0
	Dut	1.9‡‡‡	2.0‡‡‡
	Comb	2.2†††	2.6*†††
IPSS (<20, *n* = 3446; ≥20, *n* = 1391)	Tam	0.9	1.0
	Dut	1.9‡‡‡	2.0‡‡
	Comb	2.4*†††	2.6*†††
Median IPSS (<16, *n* = 2340; ≥16, *n* = 2497)	Tam	0.8	1.0
	Dut	2.0‡‡‡	1.9‡‡‡
	Comb	2.4†††	2.5*†††
Median IPSS QoL (<4, *n* = 2293; ≥4, *n* = 2540)	Tam	0.8	1.0
	Dut	1.9‡‡‡	2.0‡‡‡
	Comb	2.3†††	2.6**†††
Median BII (<5, *n* = 2068; ≥5, *n* = 2764)	Tam	1.0	0.8
	Dut	2.0‡‡‡	1.8‡‡‡
	Comb	2.4†††	2.4*†††
Median Q_{max} (<10.4 ml/s, *n* = 2412; ≥10.4 ml/s, *n* = 2425)	Tam	2.0	−0.2
	Dut	3.1‡‡‡	0.8‡‡‡
	Comb	3.6*†††	1.3†††
Median prostate volume (<49 cm^3, *n* = 2423; ≥49 cm^3, *n* = 2403)	Tam	1.0	0.9
	Dut	1.8‡‡‡	2.0‡‡‡
	Comb	2.1†††	2.8**†††
Median PSA (<3.5 ng/ml, *n* = 2405; ≥3.5 ng/ml, *n* = 2408)	Tam	1.0	0.9
	Dut	1.8‡‡‡	2.0‡‡‡
	Comb	2.3†††	2.6*†††

Tam = tamsulosin; Dut = dutasteride; Comb = combination; BMI = body mass index; IPSS = International Prostate Symptom Score; QoL = quality of life; BII = Benign Prostatic Hyperplasia Impact Index; Q_{max} = maximum urinary flow rate; PSA = prostate-specific antigen.
* $p < 0.05$ combination versus dutasteride.
** $p < 0.01$ combination versus dutasteride.
††† $p < 0.001$ combination versus tamsulosin.
‡‡ $p < 0.01$ dutasteride versus tamsulosin.
‡‡‡ $p < 0.001$ dutasteride versus tamsulosin.

ride and less from tamsulosin. This phenomenon was also observed in the MTOPS study, in which a combination of finasteride and doxazosin produced no significant benefit for Q_{max} in men with a prostate volume <25 cm^3 but produced increasing benefits at higher volumes, with resulting superiority for combination therapy over doxazosin monotherapy in men with a prostate volume ≥25 cm^3 [3].

Overall, the pattern of effect of tamsulosin and dutasteride monotherapies by prostate volume tertiles adds to observations from previous studies that recruited men with, on average, a lower prostate volume than in the CombAT study. Although the mean baseline symptom scores in the Veterans Affairs Cooperative Study (VA-Coop), the Prospective European Doxazosin and Combination Therapy (PREDICT) study, the alfuzosin, finasteride, and combination (ALFIN) study, and MTOPS were similar to that of the CombAT study (15–17 points), the mean prostate volume was lower at 36–41 cm^3 [6–9]. In the 6-mo ALFIN study, which lacked placebo control, alfuzosin treatment resulted in significantly greater improvements in symptoms compared with finasteride [8]. In the 1-yr VA-Coop and PREDICT studies, finasteride therapy resulted in small, statistically insignificant symptom improvements over placebo, in contrast with the significant improvements observed with alpha-blocker therapy [6,7]. Similarly, in the large-scale MTOPS study, at the same time point, finasteride therapy was also equivalent to placebo and inferior to doxazosin; however, after 4 yr of therapy, it was superior to placebo but inferior to doxazosin therapy for improvement in symptoms [9]. The comparative symptomatic benefits of alpha-blockers and of finasteride in these studies are akin to the observations in the population of men with the lowest prostate volumes recruited in the CombAT study.

The patterns of effect of alpha-blocker and 5-ARI monotherapies underlie the pattern of effect of combination therapy. After 1 yr of therapy in the

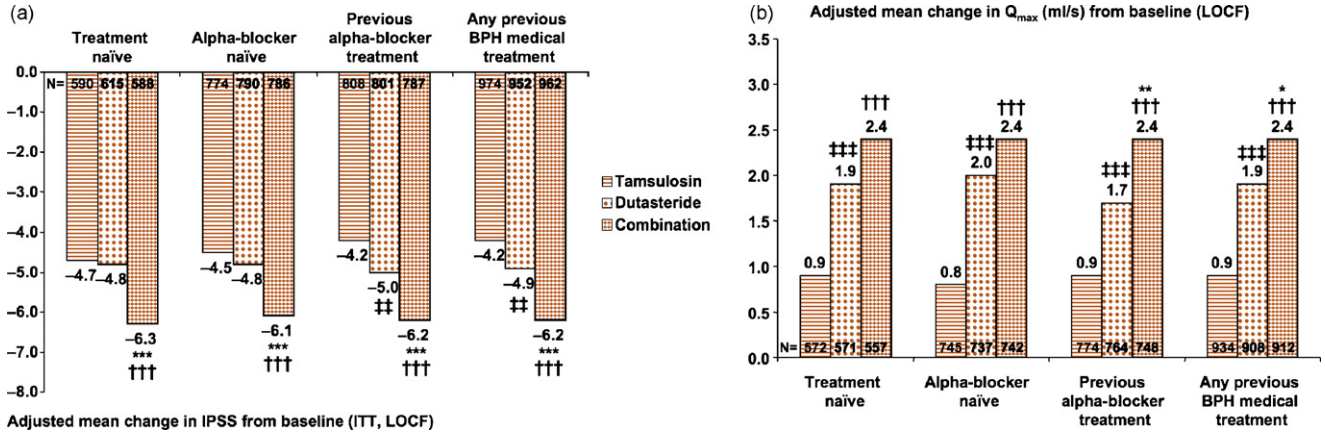

Fig. 3 – (a) Adjusted mean changes in International Prostate Symptom Score (IPSS) from baseline to month 24 by previous treatment status; (b) adjusted mean changes in maximum urinary flow rate (Q_{max}) from baseline to month 24 by previous treatment status.

ITT = intent to treat; LOCF = last observation carried forward; BPH = benign prostatic hyperplasia.

* ***p* < 0.05 combination versus dutasteride.**

** ***p* < 0.01 combination versus dutasteride.**

*** ***p* < 0.001 combination versus dutasteride.**

††† ***p* < 0.001 combination versus tamsulosin.**

‡‡ ***p* < 0.01 dutasteride versus tamsulosin.**

‡‡‡ ***p* < 0.001 dutasteride versus tamsulosin.**

VA-Coop, PREDICT, and MTOPS studies, combination therapy did not improve symptoms to a significantly greater extent than alpha-blocker therapy [6,7,9]; however, at 4 yr, combination therapy was superior to both alpha-blocker and 5-ARI monotherapies in the MTOPS study [9]. When these improvements at 4 yr were analysed by baseline prostate volume groupings of <25, 25–<40, and ≥40 cm^3, the symptom benefit of combination therapy over finasteride alone was evident in all prostate volume groups. Compared with doxazosin, the benefit was evident in the highest two volume groups but not in the <25 cm^3 group [3]. The applicability of these results to a combination of finasteride (as opposed to dutasteride) and an alpha-blocker in men with symptomatic BPH and an enlarged prostate (≥30 cm^3) can only be speculated. Although a 1-yr comparison of finasteride and dutasteride in such men did not find any statistically significant differences in symptomatic outcomes [10], these two 5-ARIs have never been compared in long-term therapy, either as monotherapy or in combination with an alpha-blocker.

In subjects treated with combination therapy in the CombAT study, improvements in symptoms and in Q_{max} were unaffected by prior BPH medical therapy status, with a very consistent pattern of effect across all patient subgroups. This suggests that, in this population of men with an enlarged prostate, the initiation of combination therapy affords the greatest degree of benefit for symptoms compared with monotherapies, regardless of previous BPH medical therapy status. These data are, to our knowledge, unique, as two early combination studies have not reported outcomes by previous treatment status [6,7] and the MTOPS study exclusively recruited men without a history of BPH medical therapy [11]. The CombAT study was not designed to evaluate whether an add-on strategy would result in similar outcomes to implementing combination therapy in treatment-naïve patients or to determine when such a strategy should be implemented. It is clear from the findings of these post hoc analyses, however, that combination therapy provides superior symptom benefit versus either monotherapy in all patients, regardless of previous treatment status.

In the CombAT study population, tamsulosin therapy was not associated with significantly greater improvements in IPSS or Q_{max} compared with dutasteride therapy in any subgroup at 24 mo. Conversely dutasteride showed greater IPSS improvements versus tamsulosin in certain subgroups, most notably in those with symptoms above the median (IPSS 16), a prostate volume above the median (49 cm^3), PSA above the median (3.5 ng/ml), and IPSS QoL score ≥4. These data suggest that, in addition to prostate volume being a driver of the

long-term symptom effects of dutasteride and tamsulosin, men with an IPSS ≥16 (and impaired QoL) and prostate enlargement could particularly benefit from dutasteride versus tamsulosin over a 2-yr period. Additionally, in all subgroups, dutasteride was associated with significantly greater improvements in Q_{max} compared with tamsulosin. It has been previously suggested that the degree of benefit of tamsulosin on symptoms appears disproportionate to its effects on Q_{max}, implying a therapeutic effect beyond reductions in bladder outlet resistance [12].

Data from studies such as Symptom Management After Reducing Therapy (SMART-1) suggest that following a period of combination therapy (6–9 mo), it may be possible to withdraw the alpha-blocker and to maintain the patient on long-term 5-ARI therapy, particularly those with moderate, as opposed to severe, symptoms [13]. Although the CombAT study does not address this issue directly, it does suggest that in those men with a larger prostate volume or a greater PSA, the contribution of the alpha-blocker to long-term symptom control is more modest. However, regardless of baseline symptom score, prostate volume, or PSA, over the 2 yr of this analysis, men who received combination therapy had the greatest degree of symptom benefit versus either monotherapy. Thus, although alpha-blocker withdrawal can be considered in men at elevated risk of BPH progression, as recruited into the CombAT study, combination therapy provides the greatest long-term symptom benefit.

A limitation of these statistical analyses of effects by subgroup is that they were not predefined [14] and that, on the basis of chance alone, 1 in every 20 significant test results could be expected at the 0.05 level. The use of median and tertile analyses, however, meant that a suitable level of power remained for these analyses (89% to detect a one-unit IPSS difference for median analyses and 74% for tertile analyses), and for the influence of baseline prostate volume on IPSS, a statistically significant treatment interaction was observed. Given the biological plausibility of these results and corroborating evidence from other datasets, we believe that these observations have validity.

Another consideration is the exclusion of men with a history of unsuccessful treatment with tamsulosin, finasteride, or dutasteride, which may have introduced potential selection bias to the analyses. Unsuccessful treatment was an investigator-defined criterion encompassing any degree of lack of success in terms of efficacy or tolerability. It would not have been considered ethical to enrol such patients in a long-term study and, furthermore, may likely have increased patient withdrawal rates. Finally, the absence of a double placebo arm in the study due to ethical reasons may also be considered a study limitation [5].

5. Conclusions

In men with symptomatic BPH and an enlarged prostate (≥30 cm^3), combination therapy was more effective than tamsulosin or dutasteride monotherapies alone in improving IPSS and Q_{max} after 2 yr, regardless of baseline prostate volume, PSA, age, BMI, IPSS, IPSS QoL score, BII score, Q_{max}, or prior medical treatment status. Baseline prostate volume had a significant impact on the onset of benefit for combination therapy over tamsulosin and dutasteride monotherapies, with earlier benefit over alpha-blocker therapy observed for men with a higher baseline prostate volume. Comparisons between dutasteride and tamsulosin monotherapies demonstrate significantly greater improvements in IPSS after 2 yr for dutasteride in men with a lower age, worse symptoms, worse BPH-related QoL, less bother, higher BMI, greater Q_{max}, higher prostate volume, or higher PSA at baseline.

These data support the use of combination medical therapy as the initial management strategy in men considered at risk for progression of BPH, as determined by higher prostate volume and/or PSA. This must be balanced against the increased rate of adverse events observed with combination medical therapy as well as against pharmacoeconomic considerations. Data from the remaining 2 yr of the CombAT study will provide information on the incidences of AUR and BPH-related surgery in the three arms as well as provide further insight into the pattern of symptom changes.

Author contributions: Claus G. Roehrborn had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Roehrborn, Castro, Wilson.
Analysis and interpretation of data: Roehrborn, Castro, Wilson, Montorsi.
Drafting of the manuscript: Roehrborn.
Critical revision of the manuscript for important intellectual content: Roehrborn, Siami, Barkin, Damião, Becher, Miñana, Castro, Wilson, Montorsi.
Statistical analysis: Roehrborn, Castro, Wilson.
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