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Benign Prostatic Hyperplasia

The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study

Claus G. Roehrborn[a,*], *Paul Siami*[b], *Jack Barkin*[c], *Ronaldo Damião*[d], *Kim Major-Walker*[e], *Indrani Nandy*[e], *Betsy B. Morrill*[e], *R. Paul Gagnier*[e], *Francesco Montorsi*[f] *on behalf of the CombAT Study Group*

[a] *Department of Urology, UT Southwestern Medical Center, Dallas, Texas, USA*
[b] *Deaconess Clinic, Evansville, Indiana, USA*
[c] *Department of Urology, University of Toronto, Toronto, Ontario, Canada*
[d] *Urology Department, State University of Rio de Janeiro, Rio de Janeiro, Brazil*
[e] *Research and Development, GlaxoSmithKline, Research Triangle Park, North Carolina, USA*
[f] *Department of Urology, Universita Vita Salute San Raffaele, Milan, Italy*

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Abstract

Background: Combination therapy with dutasteride and tamsulosin provides significantly greater benefit than either monotherapy for various patient-reported outcomes in men with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and prostatic enlargement.
Objective: To investigate whether combination therapy is more effective than either monotherapy in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression over 4 yr in men at increased risk of progression.
Design, setting, and participants: The Combination of Avodart® and Tamsulosin (CombAT) study was a 4-yr, multicenter, randomised, double-blind, parallel-group study in 4844 men ≥50 yr of age with a clinical diagnosis of BPH, International Prostate Symptom Score ≥12, prostate volume ≥30 cm^3, prostate-specific antigen 1.5–10 ng/ml, and maximum urinary flow rate (Q_{max}) >5 and ≤15 ml/s with minimum voided volume ≥125 ml.
Intervention: Oral daily tamsulosin, 0.4 mg; dutasteride, 0.5 mg; or a combination of both.
Measurements: The 4-yr primary end point was time to first AUR or BPH-related surgery. Secondary end points included BPH clinical progression, symptoms, Q_{max}, prostate volume, safety, and tolerability.
Results and limitations: Combination therapy was significantly superior to tamsulosin monotherapy but not dutasteride monotherapy at reducing the relative risk of AUR or BPH-related surgery. Combination therapy was also significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression. Combination therapy provided significantly greater symptom benefit than either monotherapy at 4 yr. Safety and tolerability of combination therapy was consistent with previous experience with dutasteride and tamsulosin monotherapies, with the exception of an imbalance in the composite term of cardiac failure among the three study arms. The lack of placebo control is a study limitation.
Conclusions: The 4-yr CombAT data provide support for the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement.
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* Corresponding author. Department of Urology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., J8 142, Moss Clinical Science Building, Dallas, TX 75390-9110, USA. Tel. +1 214 648 2941; Fax: +1 214 648 0365.
E-mail address: claus.roehrborn@utsouthwestern.edu (C.G. Roehrborn).

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1. Introduction

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) is a progressive disease [1–5]. Medical management of LUTS due to BPH with α-blockers and/or 5α-reductase inhibitors (5-ARIs) is the first-line treatment; these two drug classes have shown different abilities to influence likelihood of progression [6–8]. The 4-yr Combination of Avodart® and Tamsulosin (CombAT) study was initiated to investigate whether combination therapy with dutasteride and tamsulosin was more effective than either monotherapy in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression in men with moderate-to-severe LUTS due to BPH who were predicted to be at increased risk of progression by virtue of having a prostate volume $\geq$30 cm^3 *and* prostate-specific antigen (PSA) $\geq$1.5 ng/ml [9].

In this paper, we report the 4-yr results of CombAT relating to the risks of AUR, BPH-related surgery, overall clinical progression, and symptom progression, as well as symptom improvement, maximum urinary flow rate (Q_{max}) improvement and prostate volume and serum PSA changes.

2. Materials and methods

2.1. Study design

The design of the multinational, multicenter, randomised, double-blind, parallel-group CombAT study has been previously reported [9–11]. Briefly, eligible subjects were randomised to receive one of the following treatments orally once daily for a period of 4 yr: dutasteride 0.5 mg and tamsulosin 0.4 mg, dutasteride 0.5 mg and tamsulosin-matched placebo, or dutasteride-matched placebo and tamsulosin 0.4 mg. Details of AUR and BPH-related prostatic surgery episodes were recorded at every visit, and the occurrence of recurrent urinary tract infection or urosepsis and/or first episode of incontinence (overflow or urge) was assessed at baseline and every 3 mo. The International Prostate Symptom Score (IPSS) questionnaire (including question 8, BPH-related health status) was implemented at screening, baseline, and every 3 mo, and Q_{max} was measured at screening, baseline, and every 6 mo. Transrectal ultrasound (TRUS) was performed at screening and annually to document change in total prostate volume.

2.2. Study population

Men $\geq$50 yr of age with a BPH clinical diagnosis by medical history and physical examination, an IPSS $\geq$12 points, prostate volume $\geq$30 cm^3 by TRUS, total serum PSA $\geq$1.5 ng/ml, and Q_{max} >5 ml/s and $\leq$15 ml/s with a minimum voided volume $\geq$125 ml were eligible for inclusion. Principal exclusion criteria were total serum PSA > 10.0 ng/ml, history or evidence of prostate cancer, previous prostatic surgery, history of AUR within 3 mo prior to study entry, 5-ARI use within 6 mo (or dutasteride within 12 mo) prior to entry, or use of an α-blocker or phytotherapy for BPH within 2 wk prior to entry.

2.3. Study end point and statistical analyses

The primary end point at 4 yr was time to first event of AUR or BPH-related prostatic surgery, defined as the number of days from the date of first dose of randomised study drug to the date of the initial event. The proportion of subjects experiencing AUR or BPH-related surgery was a supportive end point to the primary analysis. To address multiplicity, secondary end points were analysed in a predefined hierarchy (Table 1). Additionally, all primary and secondary end points defined and initially tested at 2 yr were included as secondary end points at 4 yr and analysed according to the hierarchy at year 2 [10]: We report IPSS, Q_{max}, and prostate volume outcomes in this paper.

The intent-to-treat population was the primary population analysed, consisting of all subjects randomised to double-blind study treatment. The primary comparison was combination versus tamsulosin, for which the study was powered at 94%; a comparison of combination versus dutasteride was also performed. The primary analysis used a log rank test stratified by investigative site cluster. Superiority for combination versus tamsulosin and dutasteride was based on a two-sided p value at $\alpha = 0.01$. The relative risk (hazard ratio) for the treatment effect and associated two-sided 95% confidence intervals were estimated using a Cox proportional hazards model with treatment as the only covariate and stratified by investigative site cluster.

3. Results

3.1. Subject disposition and demographics

Of the 4844 men randomised to treatment, 3195 (66%) completed the month 48 visit (Fig. 1). A numerically higher rate of discontinuation was observed in the tamsulosin group (39%) compared with the combination (31%) or dutasteride (33%) groups, and more patients in the

Table 1 – Combination of Avodart® and Tamsulosin study secondary end-point hierarchy

Comparison of combination vs tamsulosin	Comparison of combination vs dutasteride
Time to BPH clinical progression*	Time to BPH clinical progression*
Time to AUR	The proportion of subjects with symptom deterioration of IPSS $\geq$4 points
The proportion of subjects with symptom deterioration of IPSS $\geq$4 points	Time to worsening of urinary incontinence
Time to BPH-related prostatic surgery	The proportion of subjects with BPH-related macroscopic haematuria
Time to worsening of urinary incontinence	Time to recurrent UTI
The proportion of subjects with BPH-related macroscopic haematuria	Time to BPH-related renal insufficiency
Time to recurrent UTI	Time to AUR
Time to BPH-related renal insufficiency	Time to BPH-related prostatic surgery
The proportion of subjects with BPH-related macroscopic haematospermia	The proportion of subjects with BPH-related macroscopic haematospermia

AUR = acute urinary retention; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; UTI = urinary tract infection.
* Defined as one of the following: symptom deterioration by IPSS $\geq$4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related UTI or urosepsis; BPH-related renal insufficiency.

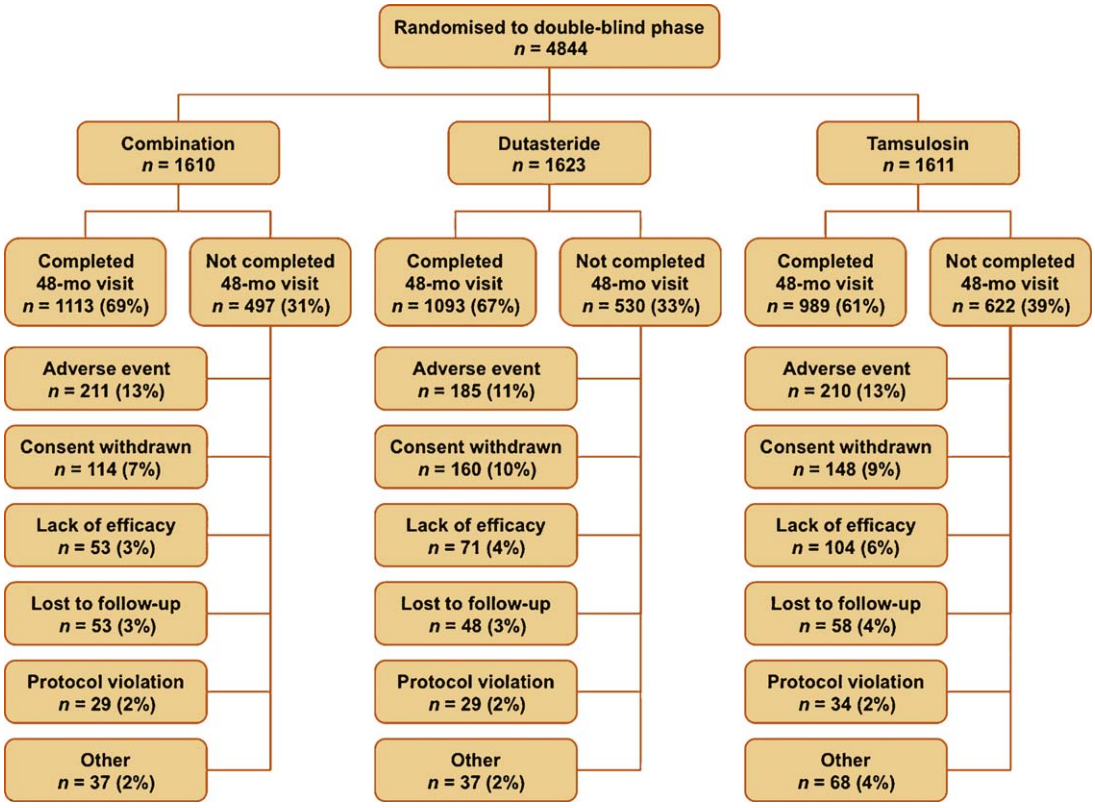


Fig. 1 – Subject disposition in the Combination of Avodart® and Tamsulosin study.

tamsulosin group withdrew due to lack of efficacy. Table 2 summarises the patient demographics and baseline characteristics: These were similar across treatment groups.

3.2. *Primary end point: acute urinary retention or benign prostatic hyperplasia-related prostatic surgery*

The time to first AUR or BPH-related surgery was significantly lower with combination therapy versus tamsulosin ($p < 0.001$); there was no significant difference between combination therapy and dutasteride ($p = 0.18$). Combination therapy reduced the relative risk of AUR or BPH-related surgery by 65.8% compared with tamsulosin and by 19.6% compared with dutasteride (Fig. 2). The cumulative incidence of AUR or BPH-related surgery during the study is shown in Fig. 3. Starting at 8 mo, a higher incidence of AUR or BPH-related surgery was seen in the tamsulosin arm compared with the combination and dutasteride arms; the margin of this difference increased with time to month 48.

When AUR and BPH-related surgery were considered separately, time to first event was significantly lower with

Table 2 – Baseline demographics and patient characteristics

	Combination ($n = 1610$)	Dutasteride ($n = 1623$)	Tamsulosin ($n = 1611$)
Mean age ± SD, yr	66.0 ± 7.05	66.0 ± 6.99	66.2 ± 7.00
White ethnicity (%)	1421 (88)	1433 (88)	1405 (87%)
Mean total IPSS score ± SD, points	16.6 ± 6.35	16.4 ± 6.03	16.4 ± 6.10
Prostate volume, cm^3			
Mean total ± SD	54.7 ± 23.51	54.6 ± 23.02	55.8 ± 24.18
Median total	48.9	48.4	49.6
Mean transition zone* ± SD	27.7 ± 20.20	30.3 ± 21.02	30.5 ± 24.47
Mean serum PSA ± SD, ng/ml	4.0 ± 2.05	3.9 ± 2.06	4.0 ± 2.08
Mean Q_{max} ± SD, ml/s	10.9 ± 3.61	10.6 ± 3.57	10.7 ± 3.66
Mean postvoid residual volume ± SD, ml	68.2 ± 66.12	67.4 ± 63.49	67.7 ± 65.14
Sexually active (%)	1176 (73)	1189 (73)	1164 (72%)
Previous α-blocker use (%)	805 (50)	820 (51)	819 (51%)
Previous 5α-reductase inhibitor use (%)	171 (11)	188 (12)	172 (11%)

IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; Q_{max} = maximum urinary flow rate; SD = standard deviation.
* In a subset of 656 men.

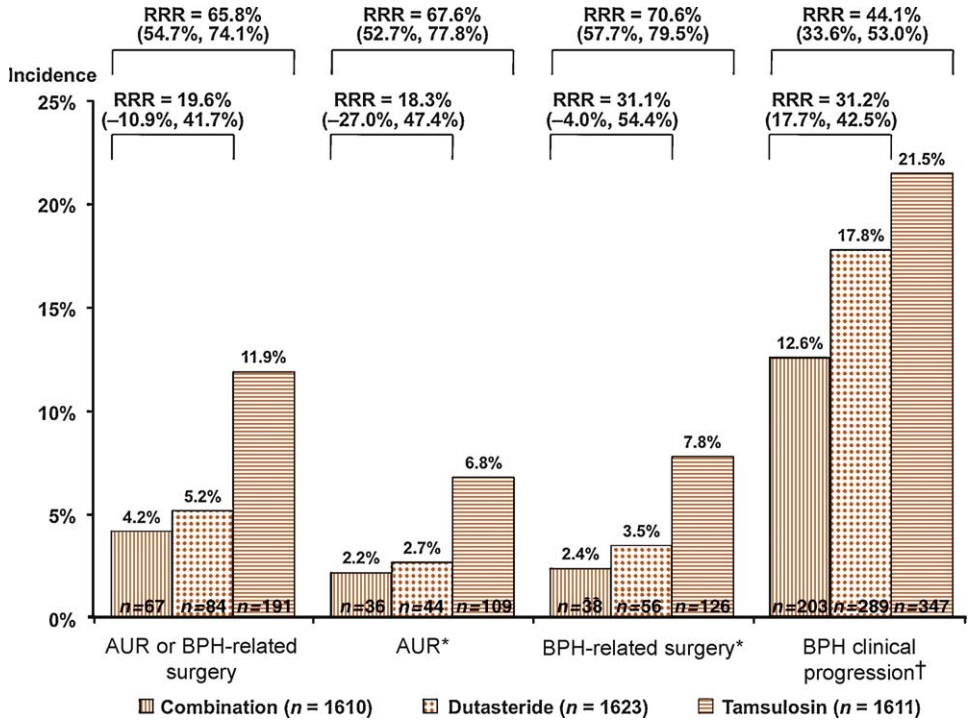
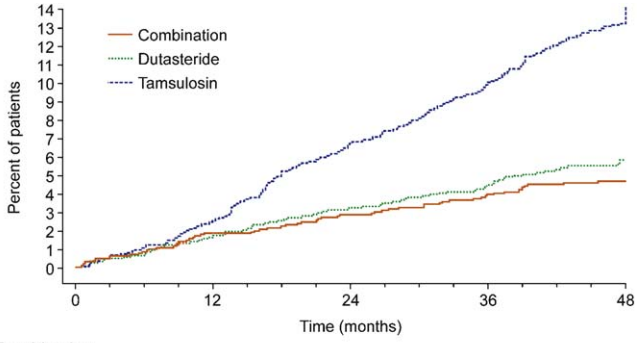


Fig. 2 – Four-year incidences of acute urinary retention (AUR) or benign prostatic hyperplasia (BPH)-related surgery (primary end point), AUR, BPH-related surgery, and BPH clinical progression and reduction in relative risk (RRR) (and 95% confidence intervals) with combination therapy versus each monotherapy.
***The first occurrence of the individual event; therefore, it may not have been the first contributing component of the overall AUR or BPH-related surgery primary end point.**
†Defined as one of the following: symptom deterioration by International Prostate Symptom Score ≥4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related urinary tract infection or urosepsis; BPH-related renal insufficiency.

combination therapy versus tamsulosin ($p < 0.001$). Compared with tamsulosin, combination therapy reduced the relative risk of AUR by 67.6% and BPH-related surgery by 70.6% (Fig. 2 and Table 3). Compared with dutasteride, the reduction in relative risk with combination therapy was 18.3% for AUR and 31.1% for BPH-related surgery, and the difference in time to event between treatment groups was not significant ($p = 0.37$ and $p = 0.074$, respectively).



Combination				
Cumulative no. of events	29	43	58	67
No. at risk	1610	1457	1347	1274
Dutasteride				
Cumulative no. of events	27	49	65	84
No. at risk	1623	1484	1365	1277
Tamsulosin				
Cumulative no. of events	40	102	146	191
No. at risk	1611	1464	1307	1176

Fig. 3 – Kaplan-Meier estimates of time to the first episode of acute urinary retention or benign prostatic hyperplasia-related prostatic surgery.

3.3. *Secondary end points*

3.3.1. *Benign prostatic hyperplasia clinical progression*

Time to first BPH clinical progression was significantly different in favour of combination therapy versus tamsulosin and dutasteride ($p < 0.001$ for both comparisons). Combination therapy reduced the relative risk of BPH clinical progression by 44.1% compared with tamsulosin and 31.2% compared with dutasteride (Fig. 2).

Symptom deterioration was the most common progression event in each treatment group. Time to first symptom deterioration was significantly different in favour of combination therapy compared with tamsulosin and dutasteride ($p < 0.001$ for both comparisons). Combination therapy reduced the relative risk of symptom deterioration of IPSS ≥4 points by 41.3% versus tamsulosin and 35.2% versus dutasteride (Table 3).

3.3.2. *Change in International Prostate Symptom Score and benign prostatic hyperplasia-related health status (question 8)*

The adjusted mean change in IPSS from baseline to year 4 was −6.3 points for combination therapy versus −3.8 points ($p < 0.001$) for tamsulosin and −5.3 points ($p < 0.001$) for dutasteride (Fig. 4). Superiority of combination therapy

Table 3 – Incidence of individual benign prostatic hyperplasia (BPH) clinical progression events*, BPH-related surgery and acute urinary retention at 4 yr, and risk reduction with combination therapy versus each monotherapy over the duration of the study

	At 4 yr						Duration of study	
	Combination (n = 1610)		Dutasteride (n = 1623)		Tamsulosin (n = 1611)		Reduction in relative risk (95% CI)	
	No. of events	Incidence (95% CI)	No. of events	Incidence (95% CI)	No. of events	Incidence (95% CI)	Combination vs dutasteride	Combination vs tamsulosin
BPH clinical progression events								
Symptom deterioration by IPSS ≥4 points	139	8.6% (7.3, 10.0)	212	13.1% (11.4, 14.7)	229	14.2% (12.5, 15.9)	35.2% (19.7, 47.7)	41.3% (27.5, 52.5)
p value	–	–	–	–	–	–	<0.001	<0.001
BPH-related AUR	26	1.6% (1.0, 2.2)	37	2.3% (1.6, 3.0)	82	5.1% (4.0, 6.2)	29.7% (−16.1, 57.4)	69.6% (52.7, 80.4)
p value	–	–	–	–	–	–	0.17	<0.001
BPH-related urinary incontinence	49	3.0% (2.2, 3.9)	60	3.7% (2.8, 4.6)	65	4.0% (3.1, 5.0)	16.0% (−22.5, 42.4)	25.8% (−7.5, 48.8)
p value	–	–	–	–	–	–	0.37	0.11
Recurrent BPH-related UTI or urosepsis	3	0.2% (0.0, 0.4)	5	0.3% (0.0, 0.6)	5	0.3% (0.0, 0.6)	39.1% (−155.0, 85.4)	40.0% (−151.2, 85.7)
p value	–	–	–	–	–	–	0.49	0.48
BPH-related renal insufficiency	1	<0.1% (0.0, 0.2)	2	0.1% (0.0, 0.3)	7	0.4% (0.1, 0.8)	48.9% (−464.5, 95.4)	87.0% (−5.9, 98.4)
p value	–	–	–	–	–	–	0.58	0.024
BPH-related surgery	38	2.4% (1.6, 3.1)	56	3.5% (2.6, 4.3)	126	7.8% (6.5, 9.1)	31.1% (−4.0, 54.4)	70.6% (57.7, 79.5)
p value	–	–	–	–	–	–	0.074	<0.001
AUR	36	2.2% (1.5, 3.0)	44	2.7% (1.9, 3.5)	109	6.8% (5.5, 8.0)	18.3% (−27.0, 47.4)	67.6% (52.7, 77.8)
p value	–	–	–	–	–	–	0.37	<0.001

AUR = acute urinary retention; BPH = benign prostatic hyperplasia; CI = confidence interval; IPSS = International Prostate Symptom Score; UTI = urinary tract infection.

* The first occurrence of the individual event; therefore, it may not have been the first contributing component of overall BPH clinical progression.

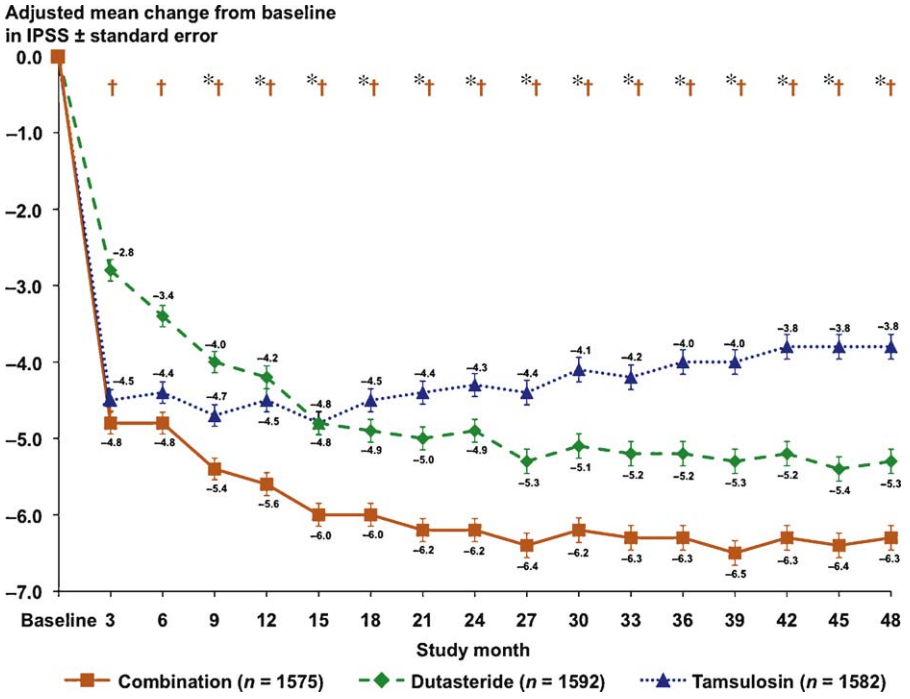


Fig. 4 – Mean adjusted change in International Prostate Symptom Score (IPSS; plus or minus standard error) from baseline by visit and treatment group.
***$p < 0.001$ for combination versus tamsulosin.**
†$p < 0.001$ for combination versus dutasteride.

versus tamsulosin was seen from month 9 and versus dutasteride from month 3, and it was maintained for the study duration ($p < 0.001$ for all comparisons). The adjusted mean difference in symptom improvement between combination therapy and tamsulosin increased during the study, from 1.8 points at month 24 to 2.5 points at month 48. In contrast, it tended to be maintained between the combination and dutasteride groups, from 1.3 points at month 24 to 0.96 point at month 48. For subjects who completed the study, the adjusted mean change in IPSS from baseline to year 4 was −7.3 points for combination therapy versus −4.9 points ($p < 0.001$) for tamsulosin and −6.4 points ($p < 0.001$) for dutasteride. The adjusted mean changes from baseline in BPH-related health status at month 48 were −1.5, −1.1, and −1.3 points in the combination, tamsulosin, and dutasteride groups, respectively. The decrease for combination therapy was significantly greater versus either monotherapy ($p < 0.001$).

3.3.3. *International Prostate Symptom Score responders (≥25% and ≥3-point improvement)*

The proportions of men with an IPSS response ≥25% at month 48 were 67%, 52%, and 61% in the combination, tamsulosin, and dutasteride groups, respectively ($p < 0.01$ for combination versus each monotherapy). At month 48, the proportions of men with a ≥3-point IPSS improvement were 71%, 59% and 66% in the combination, tamsulosin, and dutasteride groups, respectively ($p < 0.01$ for combination versus each monotherapy).

3.3.4. *Maximum urinary flow rate*

At month 48, the adjusted mean increase in Q_{max} from baseline was 2.4 ml/s for combination therapy versus 0.7 ml/s ($p < 0.001$) for tamsulosin and 2.0 ml/s ($p = 0.05$) for dutasteride (Fig. 5). These changes in Q_{max} resulted in mean values at month 48 of 13.3, 11.5, and 12.8 ml/s in the combination, tamsulosin, and dutasteride groups, respectively.

3.3.5. *Total and transition zone prostate volume*

At month 48, the adjusted mean percentage change from baseline in total prostate volume was −27.3% for combination therapy, +4.6% ($p < 0.001$) for tamsulosin, and −28.0% ($p = 0.42$) for dutasteride. At month 48, the adjusted mean percentage change from baseline in transition zone volume in a subset of 656 men was −17.9% for combination therapy, +18.2% ($p < 0.001$) for tamsulosin, and −26.5% ($p = 0.053$) for dutasteride.

3.4. *Safety and tolerability*

Table 4 summarises the adverse events data. The occurrence of drug-related adverse events was significantly greater in the combination group. However, withdrawal rates due to drug-related adverse events were similar across the treatment groups (6% in the combination group and 4% in both the dutasteride and tamsulosin groups). There were no reports of "floppy iris syndrome" [12] or malignant breast tumours in any treatment group.

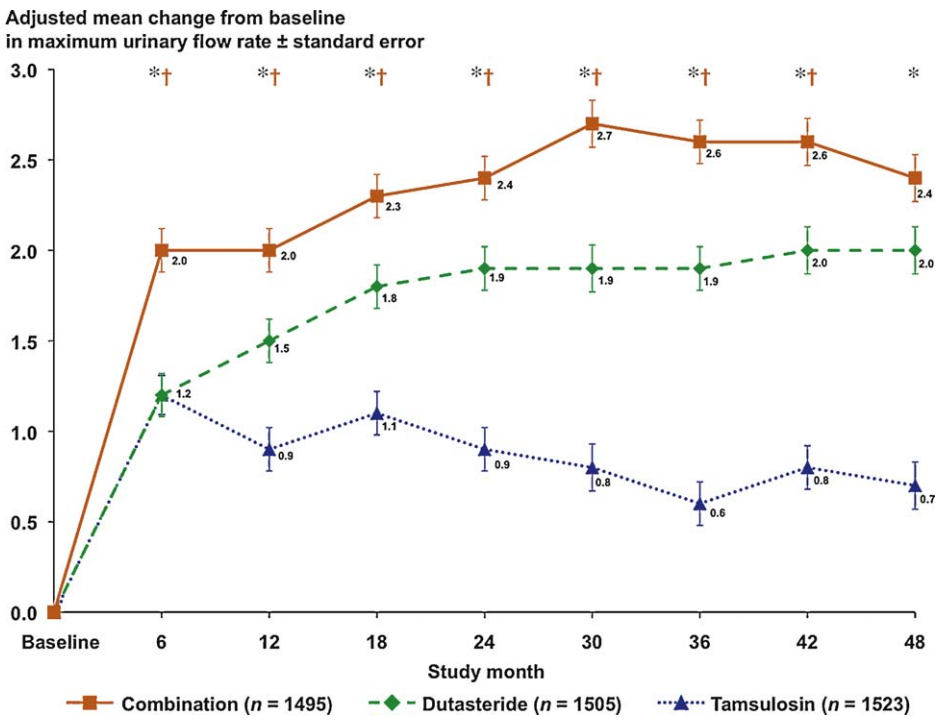


Fig. 5 – Mean adjusted change in maximum urinary flow rate (plus or minus standard error) from baseline by visit and treatment group.
***$p < 0.001$ for combination versus tamsulosin.**
†$p \leq 0.006$ for combination versus dutasteride.

There was no difference in overall cardiovascular events across treatment groups, although the incidence of the composite term *cardiac failure* was higher in the combination (14 of 1610; 0.9%) and tamsulosin monotherapy (10 of 1611; 0.6%) groups than in the dutasteride group (4 of 1623; 0.2%). The cardiac failure event rates (≤1%) in all three treatment arms of CombAT are lower than the event rate in the placebo arm at year 2 of the pivotal phase 3 BPH studies (1.3%) (α-blocker use was not permitted in these studies).

Prostate cancer was reported as an adverse event in 142 men: 37 (2.3%) in the combination group, 42 (2.6%) in the dutasteride group, and 63 (3.9%) in the tamsulosin group. Serum PSA decreased from baseline by a median of 57.1% and 56.0% in the combination and dutasteride groups, respectively, and increased by 18.4% in the tamsulosin group. At month 48, the median change from baseline in postvoid residual volume was −10.0 ml in the combination group compared with −7.0 ml in the dutasteride group and

Table 4 – Adverse events

	Combination, % (n = 1610)	Dutasteride, % (n = 1623)	Tamsulosin, % (n = 1611)
Any adverse event	73	73	72
Any serious adverse event	19	21	22
Any drug-related adverse event	28*	21	19
Any serious drug-related adverse event	<1	<1	<1
Any adverse event leading to study withdrawal	13	12	14
Any drug-related adverse event leading to study withdrawal	6	4	4
Drug-related adverse events occurring in ≥1% of subjects in any treatment group			
Erectile dysfunction	9	7	5
Retrograde ejaculation	4	<1	1
Altered (decreased) libido	4	3	2
Ejaculation failure	3	<1	<1
Semen volume decreased	2	<1	<1
Loss of libido	2	1	1
Dizziness	2	<1	2
Gynaecomastia	2	2	<1
Nipple pain	1	<1	<1
Breast tenderness	1	1	<1

* Combination vs dutasteride and tamsulosin $p < 0.001$.

0.0 ml in the tamsulosin group; the difference between combination and tamsulosin was statistically significant ($p < 0.001$).

4. Discussion

In men with moderate-to-severe LUTS due to BPH, dutasteride and tamsulosin combination therapy significantly reduced the relative risk of AUR or BPH-related surgery over 4 yr by 66% compared with tamsulosin monotherapy. No significant difference was observed between combination therapy and dutasteride, which is concordant with other data [7]. Furthermore, combination therapy significantly reduced the relative risk of BPH clinical progression and symptom deterioration of IPSS $\geq$4 points (the most frequent progression event) versus both monotherapies. Taken together with the 2-yr results [10], these data support use of dutasteride and tamsulosin combination therapy as a treatment option in men with LUTS due to BPH and prostatic enlargement at increased risk of progression to provide rapid and durable symptom benefit and reduce the long-term risk of BPH progression.

The significantly greater improvements in IPSS from month 3 versus dutasteride and from month 9 versus tamsulosin reported at 2 yr [10] were maintained through month 48. However, although the level of symptom benefit observed with both combination therapy and dutasteride monotherapy was maintained between years 2 and 4, a reduction was observed in the tamsulosin arm that may be driven by the prostate volume increase observed in this arm during the study. The difference in symptom benefit between combination therapy and dutasteride at 4 yr, however, highlights that tamsulosin remains a significant contributor to long-term symptom benefits when used in combination, particularly in the first 9 mo of therapy, after which point the relative contribution of dutasteride becomes increasingly greater. This suggests that dutasteride allows tamsulosin to maintain its maximum effect on symptoms by preventing the prostate growth that occurred with tamsulosin monotherapy.

Combination therapy also significantly improved Q_{max} at month 48 compared with tamsulosin but not with dutasteride. The Q_{max} improvement at month 24 [10] was maintained at month 48 in the combination and dutasteride groups but decreased in the tamsulosin group. The level of Q_{max} improvement with tamsulosin at month 48 is of similar magnitude to that observed in the placebo arm at month 24 in the phase 3 BPH studies [13].

At month 48, the adjusted mean percentage decrease in total prostate volume with combination therapy and dutasteride was similar to what was observed at month 24 [10] and also to what has been previously reported for dutasteride [13,14]. A similar and consistent trend in transition zone volume was also observed in the subset of men who underwent these measurements. In contrast, adjusted mean percentage increases of 4.6% in total prostate volume and 18.2% in transition zone volume were observed in the tamsulosin arm after 4 yr. The lesser observed increase in total prostate volume in the tamsulosin group is likely due to unilateral regression to the mean induced by the requirement for total prostate volume $\geq$30 cm^3 at baseline with no such limitation for transition zone volume.

Across treatment groups, 61–69% of patients completed the visit at month 48; this is as would be expected in long-term trials and comparable with the 68% completion rate reported at 2 yr in the phase 3 BPH studies [13]. Combination therapy was generally well tolerated during the 4-yr study, and the most common types of adverse events reported with combination therapy were consistent with previous experience for dutasteride and tamsulosin monotherapies. The significantly greater rate of drug-related adverse events in the combination group was mostly driven by an increased incidence of ejaculatory disorders consistent with previous data [10]. However, withdrawal rates due to drug-related adverse events were similar across the treatment groups.

An earlier study of combination therapy in men with LUTS and BPH, the Medical Therapy of Prostatic Symptoms (MTOPS) study, showed significant benefit for finasteride and doxazosin combination therapy versus either monotherapy in reducing the relative risks of overall clinical progression of BPH, AUR, and need for invasive therapy during mean follow-up of 4.5 yr [7]. The MTOPS study did not have minimum enrolment criteria for PSA or prostate volume; mean prostate volume was 36.3 cm^3 and PSA was 2.4 ng/ml [7].

The absence of a placebo arm due to ethical reasons may be considered a study limitation. Because all patients were aware they were receiving active therapy, there is theoretical potential for enhanced reporting of subjective outcomes. However, previous comparison of IPSS improvement at 2 yr in the dutasteride arm of CombAT found only a marginal difference between that reported in the phase 3 placebo-controlled studies [10,13]. Furthermore, this potential limitation would apply to all study arms and would be unlikely to affect clinical outcomes.

5. Conclusions

The 4-yr data from the CombAT study provide support for the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement at increased risk of progression. Safety and tolerability of combination therapy was consistent with previous experience with dutasteride and tamsulosin monotherapies, with the exception of the imbalance in cardiac failure.

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.

Study concept and design: Roehrborn, Damião, Montorsi.
Acquisition of data: Barkin, Damião, Major-Walker, Gagnier.
Analysis and interpretation of data: Roehrborn, Siami, Barkin, Damião, Nandy, Morrill, Gagnier.
Drafting of the manuscript: Roehrborn, Siami, Barkin, Damião, Gagnier.

Critical revision of the manuscript for important intellectual content: Roehrborn, Siami, Barkin, Damião, Major-Walker, Gagnier, Montorsi.
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