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The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia

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ABSTRACT

BACKGROUND

Benign prostatic hyperplasia is commonly treated with alpha-adrenergic–receptor antagonists (alpha-blockers) or 5α-reductase inhibitors. The long-term effect of these drugs, singly or combined, on the risk of clinical progression is unknown.

METHODS

We conducted a long-term, double-blind trial (mean follow-up, 4.5 years) involving 3047 men to compare the effects of placebo, doxazosin, finasteride, and combination therapy on measures of the clinical progression of benign prostatic hyperplasia.

RESULTS

The risk of overall clinical progression — defined as an increase above base line of at least 4 points in the American Urological Association symptom score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection — was significantly reduced by doxazosin (39 percent risk reduction, P<0.001) and finasteride (34 percent risk reduction, P=0.002), as compared with placebo. The reduction in risk associated with combination therapy (66 percent for the comparison with placebo, P<0.001) was significantly greater than that associated with doxazosin (P<0.001) or finasteride (P<0.001) alone. The risks of acute urinary retention and the need for invasive therapy were significantly reduced by combination therapy (P<0.001) and finasteride (P<0.001) but not by doxazosin. Doxazosin (P<0.001), finasteride (P=0.001), and combination therapy (P<0.001) each resulted in significant improvement in symptom scores, with combination therapy being superior to both doxazosin (P=0.006) and finasteride (P<0.001) alone.

CONCLUSIONS

Long-term combination therapy with doxazosin and finasteride was safe and reduced the risk of overall clinical progression of benign prostatic hyperplasia significantly more than did treatment with either drug alone. Combination therapy and finasteride alone reduced the long-term risk of acute urinary retention and the need for invasive therapy.

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BENIGN PROSTATIC HYPERPLASIA IS THE main cause of lower urinary tract symptoms in older men.[1] These symptoms may adversely affect the quality of life and interfere with activities of daily living.[2-4] Less commonly, benign prostatic hyperplasia causes acute urinary retention, a need for surgery, urinary incontinence, recurrent urinary tract infection, or obstructive uropathy.[4,5]

The preferred medical treatment for many men with symptomatic benign prostatic hyperplasia is either an alpha-adrenergic–receptor antagonist (alpha-blocker), which reduces smooth-muscle tone in the prostate and bladder neck, or a 5α-reductase inhibitor, which reduces prostate volume by inducing epithelial atrophy.[6-9] Short-to-moderate-term clinical trials have demonstrated the effectiveness of alpha-blockers for the relief of symptoms and improvement of the urinary flow rate.[10-14] A four-year trial with the 5α-reductase inhibitor finasteride demonstrated that benign prostatic hyperplasia can be a progressive condition, leading to acute urinary retention and the need for surgery, and that finasteride reduced the risk of these outcomes by over 50 percent in men with symptomatic benign prostatic hyperplasia.[15] Combined medical therapy was not superior to single-drug therapy in alleviating symptoms and improving the urinary flow rate in two 12-month clinical trials.[16,17]

The Medical Therapy of Prostatic Symptoms (MTOPS) Study was designed to determine whether therapy with the alpha-blocker doxazosin or the 5α-reductase inhibitor finasteride, alone or in combination, would delay or prevent clinical progression of benign prostatic hyperplasia.

METHODS

STUDY DESIGN AND PARTICIPANTS

The study design has been described previously.[18] A total of 3047 men were recruited: 116 in the pilot study and 2931 in the full-scale study.[19] The institutional review board at each of the 17 clinical centers approved the study, and all men gave written informed consent.

Men at least 50 years of age who had an American Urological Association (AUA) symptom score of 8 to 35 (scores can range from 0 [no symptoms] to 35 [severe symptoms])[20] during the pilot phase — the range was subsequently changed to 8 to 30 during the full-scale study to allow for a 4-point worsening — and a maximal urinary flow rate between 4 and 15 ml per second, with a voided volume of at least 125 ml, were enrolled from 1993 to 1998. Excluded from randomization were men who had undergone a prior medical or surgical intervention for benign prostatic hyperplasia, those with a blood pressure of less than 90/70 mm Hg while they were supine, and those with a serum prostate-specific antigen (PSA) level of more than 10 ng per milliliter.

Men were randomly assigned in a double-blind, equal fashion with the use of the urn method[21] to receive one of the following: placebo, doxazosin, finasteride, or combination therapy. Merck and Pfizer donated active drugs and placebo tablets, which were designed to look and taste like doxazosin or finasteride. Randomization was stratified according to center. Men were instructed to take the medications once daily at bedtime. The dose of finasteride was 5 mg. The dose of doxazosin was doubled at one-week intervals, beginning with 1 mg daily for the first week, until the final daily dose of 8 mg was reached. Men who were unable to tolerate the 8-mg dose received a 4-mg dose; those not able to tolerate either an 8-mg or a 4-mg dose were counted as having discontinued doxazosin. Men who discontinued randomized treatment were followed for primary and secondary outcomes.

Vital signs, the AUA symptom score, maximal urinary flow rate, compliance with the treatment regimen, and adverse events were assessed every three months. Digital rectal examination, measurement of serum PSA, and urinalysis were performed annually. Prostate volume was assessed by transrectal ultrasonography,[22] once at base line and again at the end of year 5 or at the end-of-study follow-up, whichever came first.

OUTCOMES

The primary outcome, described as overall clinical progression, was the first occurrence of an increase over base line of at least four points in the AUA symptom score, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence. An increase in the AUA symptom score of at least four points was measured relative to the score at the time of randomization and confirmed by readministration of the symptom-score questionnaire within four weeks. Acute urinary retention was defined as the inability to void (acute urinary retention in men with an obvious precipitating cause, such as anesthesia, was included as a primary outcome only after a voiding trial without a catheter was unsuccessful). Renal insufficiency had to be due to benign prostatic hyperplasia, defined as a follow-up

serum creatinine level at any time of at least 1.5 mg per deciliter (133 μmol per liter) and at least a 50 percent increase relative to the base-line level at any time. Recurrent urinary tract infection was defined as two or more urinary tract infections within one year or urosepsis. Incontinence was defined as self-reported socially or hygienically unacceptable urinary incontinence. Outcome events were reviewed by a clinical review committee whose members were unaware of the men's treatment assignments.[18]

Secondary outcomes were changes over time in the AUA symptom score and the maximal urinary flow rate. Other outcomes were the cumulative incidence of invasive treatments related to benign prostatic hyperplasia (transurethral prostatectomy, transurethral incision of the prostate, laser therapy, stenting, open prostatectomy, and transurethral microwave therapy) and changes over time in the PSA level and prostate volume.

The rate of loss to follow-up was below the hazard rate of 5 percent per year assumed during the design of MTOPS and used for the power and sample-size calculation (rate per 100 patient-years in the placebo group, 2.5; in the doxazosin group, 2.2; in the finasteride group, 3.3; and in the combination-therapy group, 2.4).

STATISTICAL ANALYSIS

Analyses of primary and secondary outcomes followed the intention-to-treat principle.[23] The life-table method was used to estimate the cumulative incidence of outcome events.[24] Data on men who had invasive therapy related to benign prostatic hyperplasia or prostate or bladder cancer — considered competing risk events — before progression were censored on the date of the event in the analysis of the progression of benign prostatic hyperplasia. Pairwise differences between cumulative incidence curves were tested with use of the Mantel (log-rank) test.[24] A log-rank test with a resulting P value of less than 0.0157 was required for each pairwise comparison of an active therapy with placebo with respect to the progression of benign prostatic hyperplasia in order to maintain an overall type I error level of 0.05, after adjustment for multiple comparisons and interim analyses. This criterion plus the enrollment of 3047 men provided the study with 81 percent power to detect a 33 percent reduction in the incidence of progression of benign prostatic hyperplasia in an active-therapy group, taking into account a rate of loss to follow-up of 5 percent per year. A Bonferroni-adjusted criterion of a P value of less than 0.0167 was used in pairwise comparisons of active therapies (not specified by the protocol) with respect to the progression of benign prostatic hyperplasia. Nominal (unadjusted) two-sided P values of less than 0.05 were considered to indicate statistical significance in all other tests.

Estimates of risk reduction, as well as the association of risk with prespecified base-line covariates, were evaluated with use of a proportional-hazards model.[24] The assumption of proportionality was evaluated with use of Lin's goodness-of-fit test.[25] Estimates of absolute risk were obtained from crude event rates (the number of events per 100 person-years) and Poisson regression models.[26] In univariate Poisson models, the strength of the association of risks was a base-line covariate as measured by the entropy (explained variation in R^2), computed as the ratio of the model or Wald χ^2 to twice the negative of the likelihood of the model without covariates.[27] The numbers of patients who would need to be treated to prevent one adverse outcome (number needed to treat) over a four-year period were calculated as the inverse of the difference in life-table estimates of the cumulative incidence probability at four years. The nonparametric Wei–Lachin test was used for pairwise comparisons of treatment groups with respect to changes over time in the AUA symptom score, maximal urinary flow rate, and PSA level.[28] Differences between active therapy and placebo with respect to adverse events were assessed on the basis of the statistical significance of incidence density ratios.[29] Results of the analysis at the year-4 landmark, examined during interim monitoring, are also presented.

RESULTS

BASE-LINE CHARACTERISTICS

Of 4391 men who were screened for eligibility, 3047 were enrolled. There were no significant differences among the groups in base-line demographic characteristics or features related to benign prostatic hyperplasia (Table 1).

OVERALL CLINICAL PROGRESSION, THE PRIMARY OUTCOME

Over a mean follow-up of 4.5 years in all four groups in the full-scale study (6.0 years in the pilot phase), 351 primary outcome events occurred: 128 in the placebo group, 85 in the doxazosin group, 89 in the finasteride group, and 49 in the combination-therapy group. These events were distributed as follows:

Table 1. Base-Line Characteristics of 3047 Men with Benign Prostatic Hyperplasia.*

Characteristic	All Men (N=3047)	Placebo (N=737)	Doxazosin (N=756)	Finasteride (N=768)	Combination Therapy (N=786)
Age — yr					
Mean	62.6±7.3	62.5±7.5	62.7±7.2	62.6±7.3	62.7±7.1
Median	62.0	62.0	63.0	62.0	62.0
Race or ethnic group — no. (%)†					
White	2509 (82.3)	607 (82.4)	624 (82.5)	643 (83.7)	635 (80.8)
Black	270 (8.9)	67 (9.1)	65 (8.6)	61 (7.9)	77 (9.8)
Hispanic	223 (7.3)	52 (7.1)	57 (7.5)	47 (6.1)	67 (8.5)
Other	45 (1.5)	11 (1.5)	10 (1.3)	17 (2.2)	7 (0.9)
AUA symptom score‡					
Mean	16.9±5.9	16.8±5.9	17.0±5.8	17.6±5.9	16.8±5.8
Median	17.0	17.0	17.0	17.0	16.0
Prostate volume — ml§					
Mean	36.3±20.1	35.2±18.8	36.9±21.6	36.9±20.6	36.4±19.2
Median	31.0	30.6	31.1	31.0	31.4
Maximal urinary flow rate — ml/sec					
Mean	10.5±2.6	10.5±2.6	10.3±2.5	10.5±2.5	10.6±2.5
Median	10.6	10.6	10.4	10.5	10.7
Post-voiding residual volume — ml					
Mean	68.1±82.9	69.6±82.1	69.2±88.2	66.2±80.0	67.5±81.1
Median	39.0	41.0	40.0	39.0	39.0
Serum PSA — ng/ml					
Mean	2.4±2.1	2.3±2.0	2.4±2.1	2.4±2.1	2.3±1.9
Median	1.6	1.5	1.6	1.5	1.6
Serum creatinine — mg/dl¶					
Mean	1.1±0.2	1.1±0.1	1.1±0.1	1.1±0.1	1.1±0.1
Median	1.0	1.1	1.1	1.0	1.0

* Plus–minus values are means ±SD. There were no significant differences in base-line characteristics among the groups. PSA denotes prostate-specific antigen.
† Race or ethnic group was assigned by the local investigator.
‡ Scores for the American Urological Association (AUA) symptom score can range from 0 (no symptoms) to 35 (severe symptoms).
§ Prostate volume was measured by transrectal ultrasonography.
¶ To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

approximately 78 percent took the form of an increase over base line in the AUA symptom score of at least 4 points, 12 percent acute urinary retention, and 9 percent incontinence. Recurrent urinary tract infection or urosepsis developed in only five men. No men had renal insufficiency as a result of benign prostatic hyperplasia.

Over the duration of the study, the rate of overall clinical progression among men in the placebo group was 4.5 per 100 person-years (Table 2 and Fig. 1). As compared with placebo, doxazosin reduced the risk of progression by 39 percent, to 2.7 per 100 person-years (P<0.001), and finasteride by 34 percent, to 2.9 per 100 person-years (P=0.002). The reduction in risk associated with doxazosin did not differ significantly from that associated with finasteride. As compared with placebo, combination therapy reduced the risk of overall clinical progression by 66 percent, to 1.5 per 100 person-years (P<0.001), a significantly greater reduction than was induced by either drug alone (P<0.001 for each pairwise comparison of combination therapy with monotherapy, with 1 degree of freedom).

The four-year cumulative incidence (among the 75 percent of men who had at least four years of follow-up data) of overall clinical progression was 17 percent in the placebo group (95 percent confidence interval, 14 to 20) (Table 2 and Fig. 1). As compared with placebo, doxazosin reduced the cumulative incidence to 10 percent (95 percent confidence interval, 8 to 12; P<0.001), finasteride to 10 percent (95 percent confidence interval, 8 to 13; P=0.002), and combination therapy to 5 percent (95 percent confidence interval, 4 to 7; P<0.001). Combination

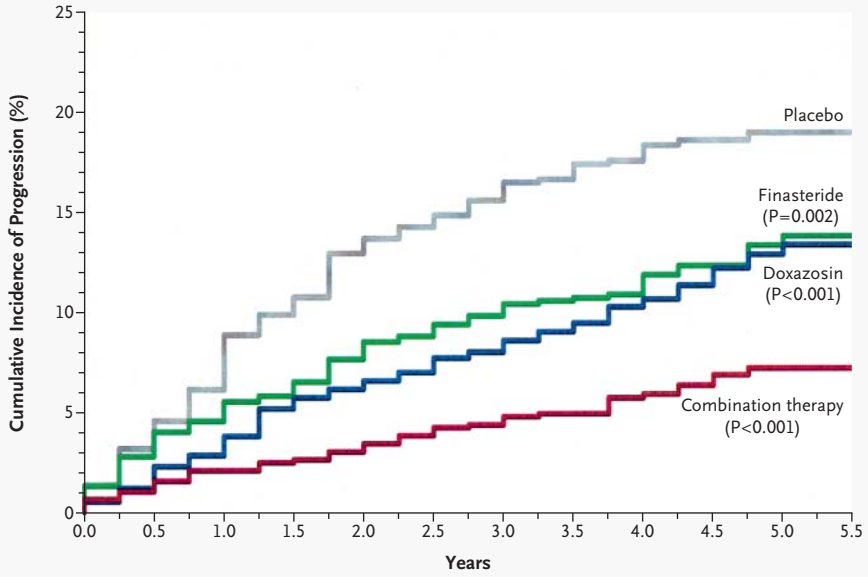
Table 2. Clinical Progression of Benign Prostatic Hyperplasia and Reduction in Risk with Doxazosin, Finasteride, and Combination Therapy, as Compared with Placebo.*

Event	Placebo (N=737)		Doxazosin (N=756)		Finasteride (N=768)		Combination (N=786)	
	Rate/100 person-yr		Rate/100 person-yr	Risk Reduction (95% CI)	Rate/100 person-yr	Risk Reduction (95% CI)	Rate/100 person-yr	Risk Reduction (95% CI)
Duration of study								
Clinical progression of benign prostatic hyperplasia†	4.5		2.7	39 (20 to 53)	2.9	34 (14 to 50)	1.5	66 (54 to 76)
≥4-Point increase in AUA symptom score	3.6		1.9	45 (25 to 60)	2.5	30 (6 to 48)	1.3	64 (48 to 75)
Retention	0.6		0.4	35 (–31 to 67)	0.2	68 (21 to 87)	0.1	81 (44 to 93)
Incontinence	0.3		0.3	–32 (–227 to 46)	0.3	–9 (–183 to 57)	0.1	65 (–28 to 90)
Urinary tract infection or urosepsis	0.1		0.1	Insufficient data	0.0	Insufficient data	<0.1	Insufficient data
Invasive therapy due to benign prostatic hyperplasia‡	1.3		1.3	3 (–48 to 37)	0.5	64 (34 to 80)	0.4	67 (40 to 82)
	Cumulative No. of Events	Cumulative Incidence (95% CI)	Cumulative No. of Events	Cumulative Incidence (95% CI)	Cumulative No. of Events	Cumulative Incidence (95% CI)	Cumulative No. of Events	Cumulative Incidence (95% CI)
		%		%		%		%
At 4 yr								
Clinical progression of benign prostatic hyperplasia†	122	17 (14 to 20)	73	10 (8 to 12)	78	10 (8 to 13)	42	5 (4 to 7)
≥4-Point increase in AUA symptom score	97	14 (11 to 17)	55	7 (5 to 9)	65	9 (7 to 11)	36	5 (3 to 6)
Retention	18	2 (1 to 4)	9	1 (0 to 2)	6	<1 (0 to 1)	4	<1 (0 to 1)
Incontinence	6	<1 (0 to 1)	7	<1 (0 to <1)	7	<1 (0 to 1)	1	<1 (0 to <1)
Urinary tract infection or urosepsis	1	<1 (0 to <1)	2	<1 (0 to <1)	0	0 (0 to <1)	1	<1 (0 to <1)
Invasive therapy due to benign prostatic hyperplasia‡	37	5 (3 to 7)	26	3 (2 to 5)	14	2 (0 to 3)	12	1 (0 to 2)

* CI denotes confidence interval, and insufficient data that there were insufficient data to obtain a meaningful estimate of risk reduction.
† Clinical progression of benign prostatic hyperplasia was defined as the occurrence of any of the following: an increase from base line of at least 4 points in the American Urological Association (AUA) symptom score, acute urinary retention, urinary tract infection or urosepsis, incontinence, or an increase in the serum creatinine level, attributable to benign prostatic hyperplasia, of at least 1.5 mg per deciliter and to a value at least 50 percent above base-line values.
‡ Invasive therapy was defined as the need for any of the following invasive therapies: transurethral prostatectomy, transurethral incision of the prostate, transurethral microwave therapy, laser therapy, stenting, or open prostatectomy.

therapy was more effective than either drug alone or placebo ($P<0.001$ for the pairwise comparison with doxazosin, $P<0.001$ for the comparison with finasteride, and $P<0.001$ for the comparison with placebo, each with 1 degree of freedom).

Univariate analysis showed that the risk of overall clinical progression increased with increasing base-line serum PSA levels and base-line prostate volume in the placebo group ($P<0.001$) and the doxazosin group ($P\leq0.006$), but not in the finasteride group ($P>0.05$) or the combination-therapy group ($P>0.05$) (data not shown). The number needed to treat to prevent one instance of overall clinical progression was 8.4 for combination therapy, 13.7 for doxazosin, and 15.0 for finasteride. In a preplanned secondary analysis, among men who had serum PSA levels of more than 4.0 ng per milliliter (20 percent of men who underwent randomiza-



No. at Risk												
Placebo	737	712	670	631	612	588	575	555	492	337	218	84
Doxazosin	756	735	715	698	675	660	641	627	565	387	259	98
Finasteride	768	737	699	675	659	634	617	599	530	379	257	105
Combination therapy	786	762	747	733	726	715	697	683	599	426	280	112

Figure 1. Cumulative Incidence of Progression of Benign Prostatic Hyperplasia.

Progression was defined by an increase of at least 4 points over base line in the American Urological Association symptom score, acute urinary retention, urinary incontinence, renal insufficiency, or recurrent urinary tract infection. P values are for the comparison with placebo.

tion) or a base-line prostate volume of more than 40 ml on transrectal ultrasonography (30 percent of men who underwent randomization), the number needed to treat was 4.7 and 4.9, respectively, for combination therapy and 7.2 for both subgroups for finasteride therapy.

INDIVIDUAL PROGRESSION EVENTS

Symptoms

An increase in the AUA symptom score of more than 4 points above base-line values was the most common individual event included in the composite end point of progression (Table 2). As compared with the risk in the placebo group (3.6 per 100 person-years), the risk was reduced by 45 percent in the doxazosin group (P<0.001), 30 percent in the finasteride group (P=0.016), and 64 percent in the combination-therapy group (P<0.001). The differences between finasteride and doxazosin and between combination therapy and doxazosin were not significant.

Acute Urinary Retention

As compared with the rate of acute urinary retention in the placebo group (18 events; rate, 0.6 per 100 person-years), the rate in both the finasteride group (6 events; rate, 0.2 per 100 person-years; risk reduction, 68 percent; P=0.009) and the combination-therapy group (4 events; rate, 0.1 per 100 person-years; risk reduction, 81 percent; P<0.001) was significantly lower, as was the cumulative incidence of this complication (Table 2 and Fig. 2A). Although doxazosin delayed the time to acute urinary retention, it did not significantly reduce the cumulative incidence, as compared with placebo (P=0.23) (Table 2 and Fig. 2A). In all groups, the risk of acute urinary retention increased with increasing serum PSA levels (P=0.001 in the placebo group, P<0.001 in the doxazosin group, P=0.01 in the finasteride group, and P=0.003 in the combination-therapy group), with a very low risk among men with base-line PSA levels of 1.1 ng per milliliter or less (data not shown).

Urinary Incontinence

The rates of urinary incontinence and recurrent urinary tract infection or urosepsis were too low in each of the groups to permit meaningful analyses, in comparison either with placebo or with one another (Table 2).

Renal Insufficiency

There were no cases of renal insufficiency related to benign prostatic hyperplasia in any of the groups.

INVASIVE THERAPY FOR BENIGN PROSTATIC HYPERPLASIA

Most types of invasive therapy for benign prostatic hyperplasia (84 percent) were endoscopic (e.g., transurethral prostatectomy) or open surgeries; the remainder were minimally invasive (e.g., transurethral microwave therapy). The indication for and the use of invasive therapies were not standardized by the protocol and thus may have varied from site to site. Forty men in the placebo group received invasive therapy for benign prostatic hyperplasia (rate, 1.3 per 100 person-years). Treatment with finasteride and combination therapy significantly reduced the risk of receiving invasive therapy, by 64 percent (P<0.001) and 67 percent (P<0.001), respectively, as compared with placebo (Table 2 and Fig. 2B). In contrast, doxazosin did not significantly reduce the cumulative incidence of invasive therapy.

With the exception of the finasteride group, the risk of undergoing invasive therapy increased with increasing serum PSA levels (P=0.02 for the placebo group, P<0.001 for the doxazosin group, and P=0.007 for the combination-therapy group). The number needed to treat to prevent 1 patient from undergoing invasive therapy was 25.9 for combination therapy, 60.1 for doxazosin, and 29.0 for finasteride. It was reduced to 23.1 and 15.9 by combination therapy in men with initial serum PSA levels of more than 4.0 ng per milliliter and in those with a prostate volume on transrectal ultrasonography of more than 40 ml at base line.

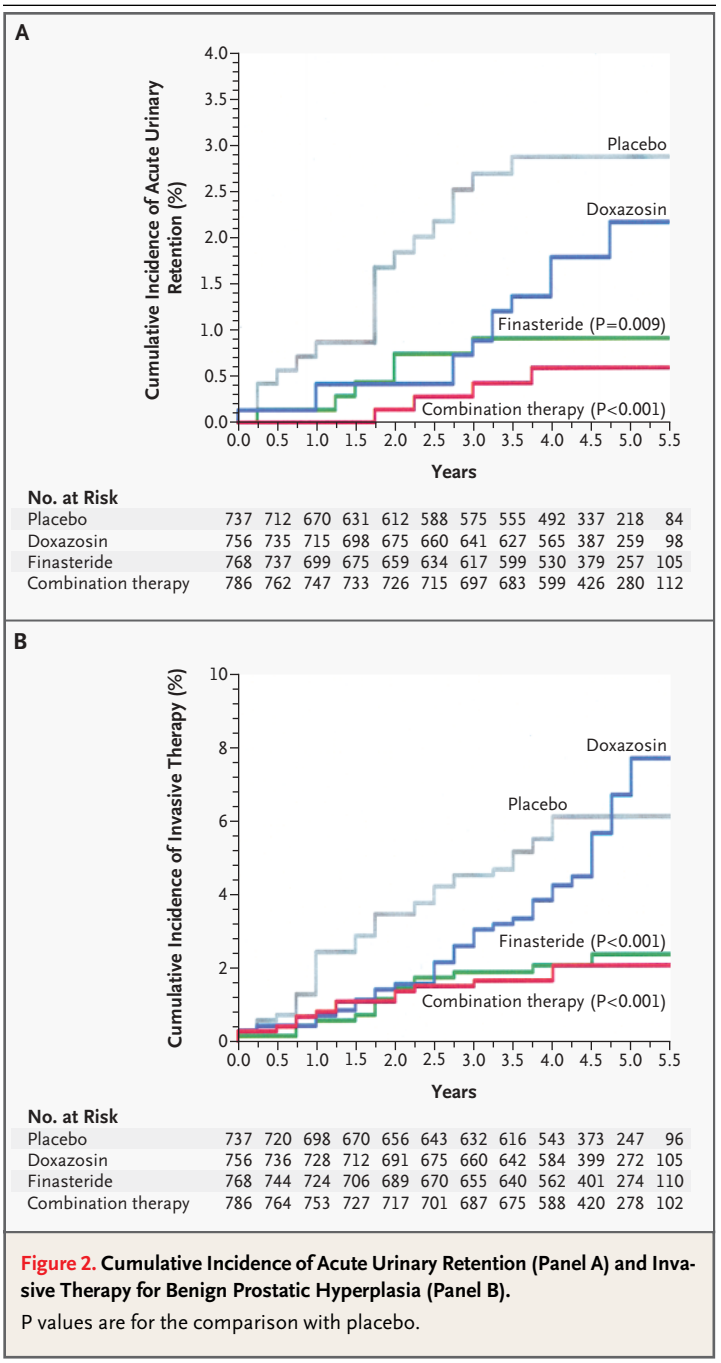


Figure 2. Cumulative Incidence of Acute Urinary Retention (Panel A) and Invasive Therapy for Benign Prostatic Hyperplasia (Panel B).

P values are for the comparison with placebo.

OTHER OUTCOMES

Symptom Score

Significant improvements over time in the AUA symptom score occurred in all active-treatment groups as compared with the placebo group (P< 0.001 for doxazosin, P=0.001 for finasteride, and P<0.001 for combination therapy). The four-year mean reduction in symptom score was 4.9 in the placebo group, 6.6 in the doxazosin group, 5.6 in the finasteride group, and 7.4 in the combination-therapy group (median reductions are shown in Table 3). The improvement in the symptom score was significantly greater in the combination-therapy group than in the finasteride group (P<0.001) or the doxazosin group (P=0.006) and in the doxazosin group than in the finasteride group (P=0.001).

Table 3. Median Change from Base-Line Values of Selected Serial Measurements.

Variable	Placebo		Doxazosin		Finasteride		Combination Therapy		P Value					
	No. of Men	Median Change	No. of Men	Median Change	No. of Men	Median Change	No. of Men	Median Change	Doxazosin vs. Placebo	Finasteride vs. Placebo	Combination Therapy vs. Placebo	Doxazosin vs. Combination Therapy	Finasteride vs. Combination Therapy	Finasteride vs. Doxazosin
AUA symptom score*														
Year 1	656	–4.0	677	–6.0	686	–4.0	700	–6.0	<0.001	0.777	<0.001	0.077	<0.001	<0.001
Year 4	534	–4.0	582	–6.0	565	–5.0	598	–7.0	<0.001	0.047	<0.001	0.035	<0.001	0.002
Over study duration†	—	—	—	—	—	—	—	—	<0.001	0.001	<0.001	0.006	<0.001	0.001
Maximal urinary flow rate (ml/sec)														
Year 1	653	1.3	675	3.0	678	1.8	697	3.6	<0.001	0.031	<0.001	0.002	<0.001	<0.001
Year 4	519	1.4	567	2.5	551	2.2	574	3.7	<0.001	0.047	<0.001	0.002	<0.001	0.089
Over study duration†	—	—	—	—	—	—	—	—	<0.001	<0.001	<0.001	<0.001	<0.001	0.025
Serum PSA (% change from base line)‡														
Year 1	670	0	697	0	695	–46	724	–47	0.024	<0.001	<0.001	<0.001	0.524	<0.001
Year 4	618	15	655	13	631	–50	673	–50	0.555	<0.001	<0.001	<0.001	0.925	<0.001
Over study duration†	—	—	—	—	—	—	—	—	0.291	<0.001	<0.001	<0.001	0.683	<0.001

* Scores for the American Urological Association (AUA) symptom score can range from 0 (no symptoms) to 35 (severe symptoms).
† P values were calculated with use of the Wei–Lachin test of stochastic ordering computed for all follow-up–visit measurements.
‡PSA denotes prostate-specific antigen.

Urinary Flow Rate

Maximal urinary flow rate improved over time in all active-treatment groups as compared with placebo ($P<0.001$ for each pairwise comparison) (Table 3). At four years, the mean improvement was 4.0 ml per second in the doxazosin group, 3.2 ml per second in the finasteride group, and 5.1 ml per second in the combination-therapy group.

Serum PSA Levels

At four years, serum PSA levels had increased by a median of 15 percent in the placebo group and by 13 percent in the doxazosin group (Table 3). As compared with base-line values, the four-year median decrease in serum PSA levels was 50 percent in both the finasteride and combination-therapy groups (Table 3).

Prostate Volume

Prostate volume in the 1148 men who were receiving placebo or doxazosin increased by a median of 24 percent (mean [±SD], 29±36) after an average follow-up of 4.5 years. The 427 men who were receiving finasteride or combination therapy and who had large prostate volumes at base line had a median decrease in volume of 19 percent (mean, 12±30) during the same period of follow-up.

ADVERSE EVENTS

The most common adverse events that occurred more frequently in the doxazosin group than in the placebo group were dizziness, postural hypotension, and asthenia (Table 4). The most common adverse events that occurred more frequently in the finasteride group than in the placebo group were erectile dysfunction, decreased libido, or abnormal ejaculation (Table 4). The individual adverse effects in the combination-therapy group were similar to those for each drug alone, with the exception of abnormal ejaculation, peripheral edema, and dyspnea, all of which occurred more frequently in patients taking both drugs (Table 4).

Among all men who were receiving active therapy, 27 percent had discontinued doxazosin and 24 percent had discontinued finasteride by the end of the study. Eighteen percent of the men who were receiving combination therapy had discontinued both drugs by the end of the study. Most often, treatment was discontinued because of adverse effects. Breast cancer was diagnosed in four men who received finasteride alone or in combination with doxazosin.

DISCUSSION

Benign prostatic hyperplasia and lower urinary tract symptoms can affect the quality of life in older men. However, in some men, benign prostatic hyperplasia can cause acute urinary retention, a need for surgery, urinary incontinence, urinary tract infections, and other complications.[4] Treatment with an alpha-blocker or a 5α-reductase inhibitor can ameliorate symptoms and improve urinary flow rate,[8,10,14] and finasteride substantially reduces the risk of acute urinary retention and the need for surgical treatment.[15,30,31]

Two 12-month clinical trials have evaluated combination therapy with an alpha-blocker and finasteride for benign prostatic hyperplasia. The Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study compared terazosin, finasteride, and combination therapy with placebo,[16] whereas the Prospective European Doxazosin and Combination Therapy Trial compared doxazosin, finasteride, and combination therapy with placebo.[17] Both trials found no benefit of combination therapy over monotherapy. However, these trials assessed primarily longitudinal changes in the AUA symptom score and maximal urinary flow rate, rather than the effect of medical therapy on the clinical progression of benign prostatic hyperplasia and the long-term reduction in the risk of associated complications.

Our trial demonstrated that doxazosin, finasteride, and the two drugs combined each reduced the risk of overall clinical progression of benign prostatic hyperplasia, defined as worsening of symptoms, acute urinary retention, incontinence, urinary tract infection, or renal insufficiency. Combination therapy was significantly more effective than either drug alone.

Among the components of the composite primary outcome, a confirmed increase from base line in the AUA symptom score of at least 4 points was the most frequent event. This outcome has clinical importance, since in men with benign prostatic hyperplasia, bothersome symptoms are the most common reason for invasive therapy.[32,33] In a 12-month study, the mean increase of 2.7 points in the AUA symptom score was perceived by the patients as a global sense of worsening of their condition.[34] Patients with higher base-line scores required an increase of only 1.2 points, whereas those with lower initial scores needed a 3.3-point increase to have the same level of worsening.[34] A 4-point increase was considered indicative of a global sense of worsening of their condition by most patients. Combination treatment was more effective than either doxazosin or finasteride alone in decreasing the risk of symptomatic progression.

Table 4. The Ten Most Frequent Adverse Events Reported among the Groups.*

Variable	Placebo	Doxazosin	Finasteride	Combination Therapy
Total no. of person-yr	3489	3652	3600	3832
		rate/100 person-yr of follow-up		
Adverse event				
Erectile dysfunction	3.32	3.56	4.53†	5.11†
Dizziness	2.29	4.41†	2.33	5.35†
Postural hypotension	2.29	4.03†	2.56	4.33†
Asthenia	2.06	4.08†	1.56	4.20†
Decreased libido	1.40	1.56	2.36†	2.51†
Abnormal ejaculation	0.83	1.10	1.78†	3.05†
Peripheral edema	0.66	0.88	0.72	1.25†
Dyspnea	0.57	0.93	0.56	1.20†
Allergic reaction	0.46	0.85†	0.58	0.73
Somnolence	0.37	0.82†	0.39	0.78†

* The numbers shown are the rates per 100 person-years of follow-up (incidence density) as of September 30, 2002.
† P<0.05 for the comparison with the placebo group.

We found that combination therapy and finasteride alone were equally effective in reducing the risk of acute urinary retention and the need for invasive therapy, with the magnitude of the reduction similar to that observed with 5α-reductase inhibitors in clinical trials lasting two years[9,30,31,35] and four years.[15] Treatment with doxazosin alone slightly delayed the time to acute urinary retention and invasive therapy but failed to reduce the risk of these events over the duration of the study. This finding suggests that continued growth of the prostate in the doxazosin-monotherapy group eventually overcame the reduction in prostatic urethral obstruction achieved by relaxation of prostatic smooth-muscle tone by the alpha-blocker.[1]

In contrast, the reduction in the risk of acute urinary retention and the need for invasive therapy throughout the study may be attributed to a reduction in prostate size. Acute urinary retention does not always require surgery. The success of a voiding trial (with removal of the catheter) depends on the circumstances of the retention episode. Of all such events recorded in the placebo group in another

four-year study, 17 percent of the men had subsequent episodes of retention after a successful voiding trial and 75 percent eventually underwent surgery.[36] In another randomized study, only 29 percent of men in the placebo group had a successful voiding trial after an episode of retention.[37]

In our study, urinary tract infections were rare, suggesting that lower urinary tract symptoms and benign prostatic hyperplasia are not clinically significant risk factors for these infections. Similarly, the concern that untreated benign prostatic hyperplasia may lead to renal insufficiency was not substantiated in this trial.

Previous clinical trials evaluating the safety of alpha-blockers and combination therapy have been brief — one year or less.[16,17,38] We demonstrated the long-term safety of doxazosin, finasteride, and combination therapy, with incidence rates of the typical adverse effects similar to those reported in prior studies. The discrepancy between the number of cases of breast cancer in our trial and those in two other clinical trials of finasteride suggests that it was due to chance alone. In the four-year Long-Term Efficacy and Safety Study, in which more than 3000 men were randomly assigned to receive either finasteride or placebo, two cases of breast cancer were observed in the placebo group and none in the finasteride group.[15] In an interim assessment, the Prostate Cancer Prevention Trial, involving approximately 18,000 men who were randomly assigned to receive finasteride or placebo, found no significant difference in the number of reported cases of breast cancer after approximately five years of follow-up[39] (and Ford L, National Cancer Institute: personal communication).

In the placebo and doxazosin groups, base-line prostate volume, serum PSA level, maximal urinary flow rate, and severity of symptoms individually predicted the risk of clinical progression of benign prostatic hyperplasia and invasive therapy (R^2 values ranged from 0.67 percent to 5.24 percent). In the combination-therapy group, these four base-line covariates did not predict the risk of progression, and only the serum PSA level predicted the risk of invasive therapy and acute urinary retention. The prognostic value of base-line serum PSA level to predict the likelihood of acute urinary retention and the need for surgery has been demonstrated previously.[40,41] However, we also demonstrated the value of the base-line serum PSA level in predicting the risk of the clinical progression of benign prostatic hyperplasia. This benefit may be due to the ability of the PSA level to predict prostate growth.[41]

The absence of a direct relation in the combination-therapy group between the risk of overall progression and the base-line serum PSA level was further evidence of the effectiveness of the combination therapy in reducing the risk of progression, particularly for men with high base-line PSA levels. Since the risk of progression in men in the placebo group tended to be low for those with a low PSA level, the benefit of combination therapy was not as substantial in the low-PSA subgroup as in the high-PSA subgroup, as shown by the results of the analysis of the number needed to treat.

In summary, in this placebo-controlled trial, combination therapy with doxazosin and finasteride significantly reduced the risk of overall clinical progression of benign prostatic hyperplasia more than did either drug alone. Combination therapy and finasteride monotherapy reduced the long-term risk of acute urinary retention and the need for invasive therapy related to benign prostatic hyperplasia. Combination therapy resulted in a greater improvement in the AUA symptom score and the maximal urinary flow rate than did either drug alone. Our results indicate that long-term treatment with combination therapy is both safe and the most effective therapy for patients with lower urinary tract symptoms and benign prostatic hyperplasia, and its use is appropriate in men with an increased risk of progression.

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APPENDIX

The following institutions and investigators participated in the MTOPS Study: *Sponsor:* National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md. — J.W. Kusek, L.M. Nyberg, J.P. Briggs; *Steering committee chairman:* J.D. McConnell, University of Texas Southwestern Medical Center, Dallas; *Clinical centers* (principal investigators and study coordinators are listed first and second, respectively, after each institution): University of Colorado, Denver — E.D. Crawford, K. Homan, R. Donohue, D. Parker, K. Easterday, K. Robertson; New York Presbyterian Hospital, New York — S. Kaplan, M. Wentland, L. Hardy; University of Texas Southwestern Medical Center, Dallas — C. Roehrborn, A. Ahrens, J. McConnell, D. Hall, D. Cutts, S. Carter, K. Waldrep; Walter Reed Army Medical Center, Washington, D.C. — N. Schenkman, K. Sanetrik, S. Sihelnik, B. Zorn, D. McLeod, J. Moul, K. Peay, A. Szkutnik, J. Travis; University of Washington, Seattle — M. Brawer, D. Earl, M. Mayo; New York University School of Medicine, New York — C. Dixon, S. Hirschfield, H. Lepor, D. Hoffman, D. Brassil, M. Castro, P. Kramer; Baylor College of Medicine, Houston — K. Slawin, V. Pavlik, R. Morton, Jr., B. Miles, S. Harrison, R. Valdez; Brooke Army Medical Center, Fort Sam Houston, Tex. — J. Foley, A. Jones, I. Thompson, A. Morey, E. Canby-Hagino, R. Dobbs, Jr., T. Rozanski, G. Sloat; University of California at San Diego, La Jolla — J. Ramsdell, Z. Parman, J. Schmidt, M. Albo, H. Guy, D. Eskew, D. Sparks; Henry Ford Hospital, Detroit — M. Menon, C. David, A. Kirkemo, A. Diokno, D. Burks, H. Stricker, J. Peabody, R. Littleton, B. Leemon, B. Steinert, J. Kuzara, M. Peabody; Mayo Foundation, Rochester, Minn. — M. Lieber, J. Smith, D. Patterson, M. Blute, C. Van Oort, D. Fitch, D. Mann, K. Hyland, H. Wieland; Northwestern University, Chicago — K. McVary, E. Perez, J. Grayhack, W. Bushman, K. Haldes, M. Manzera; Vanderbilt University, Nashville — J. Smith, Jr., B. Hughes, D. Milam, P. Sisk; Washington University, St. Louis — G. Andriole, J. Faust, C. Sundaram, C. Nicolai, A. Johnson, N. Shelley; Yale University, New Haven, Conn. — H. Foster, T. Martin, K. Anderson, C. Puklin, D. Chodkowshi, S. Alfano, K. Sopp; Emory University, Atlanta — H. Clarke, B. Lopez, L. Tenover, S. Elmer, K. Lachenmeyer; University of Iowa, Iowa City — K. Kreder, M. Fearing, W. See, B. Ziegler, S. Schultz, T. Tuftee; University of Maryland, Baltimore — S. Jacobs, M. Hershner, M. Naslund, B. Greene, G. Markowitz; *Diagnostic center:* University of Colorado Health Sciences Center, Denver — G.J. Miller (deceased), M.S. Lucia, R. Lepoff, C. Covey-Magnuson, G. Johnson, K. Torkko; *Biostatistical coordinating center:* George Washington University Biostatistics Center, Rockville, Md. — O. Bautista, P. Burrows, R. Gersnoviez, R. Bain, S. Greenhouse (deceased), M. Manyak, J. Bamdad, W. Mason, H. Sherif, M. Temprosa, N. Minkoff; *External advisory board:* M. Barry (chair), R. Bruskewitz, A. Cockett, M. Litwin, J. Mostwin, D. Reda, R. Roberts, S. Rous, W. Williford; *Behavioral consultants:* University of Alabama, Birmingham — D. Smith-West, P. Greene; *Ex-Officio members of the steering committee:* Merck Research Laboratories: E. Round, G. Gormley; Pfizer: S. Mallen, R. Siegel, E. Grossman.

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