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THE EFFICACY OF TERAZOSIN, FINASTERIDE, OR BOTH IN BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Background Men with benign prostatic hyperplasia can be treated with α_1 -adrenergic-antagonist drugs that relax prostatic smooth muscle or with drugs that inhibit 5α -reductase and therefore reduce tissue androgen concentrations. However, the effects of the two types of drugs have not been compared.

Methods We compared the safety and efficacy of placebo, terazosin (10 mg daily), finasteride (5 mg daily), and the combination of both drugs in 1229 men with benign prostatic hyperplasia. American Urological Association symptom scores and peak urinary-flow rates were determined at base line and periodically for one year.

Results The mean changes from base line in the symptom scores in the placebo, finasteride, terazosin, and combination-therapy groups at one year were decreases of 2.6, 3.2, 6.1, and 6.2 points, respectively ($P < 0.001$ for the comparisons of both terazosin and combination therapy with finasteride and with placebo). The mean changes at one year in the peak urinary-flow rates were increases of 1.4, 1.6, 2.7, and 3.2 ml per second, respectively ($P < 0.001$ for the comparisons of both terazosin and combination therapy with finasteride and with placebo). Finasteride had no more effect on either measure than placebo. In the placebo group, 1.6 percent of the men discontinued the study because of adverse effects, as did 4.8 to 7.8 percent of the men in the other three groups.

Conclusions In men with benign prostatic hyperplasia, terazosin was effective therapy, whereas finasteride was not, and the combination of terazosin and finasteride was no more effective than terazosin alone. (N Engl J Med 1996;335:533-9.)

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BENIGN prostatic hyperplasia is a proliferative process that involves both the stromal and epithelial elements of the prostate.^{1,2} Its clinical manifestations include obstructive and irritative urinary tract symptoms, urinary retention, urinary tract infection, and hematuria.³ In most men with this disorder, the goal of therapy is to relieve bothersome urinary symptoms.⁴

Until recently, prostatectomy and watchful waiting were the only widely accepted treatment options for men with benign prostatic hyperplasia, but recent studies have reported that both finasteride, a 5α -reductase inhibitor,⁵⁻⁷ and long-acting α_1 -adrenergic-antagonist drugs, such as terazosin,^{8,9} doxazosin,^{10,11} and tamsulosin,^{12,13} are safe and effective treatments for this disorder. These drugs are attractive options for many men with benign prostatic hyperplasia, because they have few adverse effects. However, there are no studies comparing these drugs in men with benign prostatic hyperplasia. We therefore studied terazosin, finasteride, the combination of both drugs, and placebo to evaluate their safety and efficacy in such men.

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*Members of the study group are listed in the Appendix.

METHODS

The protocol for this double-blind, placebo-controlled study was approved by the Cooperative Studies Evaluation Committee and the Human Rights Committee of the Cooperative Studies Program Coordinating Center, Department of Veterans Affairs (Perry Point, Md.), and all the men gave informed consent.

Recruitment and Determination of Eligibility

Men 45 to 80 years of age who had symptomatic benign prostatic hyperplasia and were attending the outpatient clinics at the participating Veterans Affairs medical centers were interviewed and screened by the study coordinators. Those who were willing to participate in the study and had no obvious reason to be excluded began a four-week, single-blind, lead-in period during which they received placebo and underwent a complete history taking and physical examination. The men's symptoms were assessed twice during this period with the American Urological Association Symptom Index, which assesses the occurrence of seven symptoms characteristic of benign prostatic hyperplasia during the preceding week, each scored on a scale from 0 (absent) to 5 (severe). The total score reflects the overall severity of the patient's condition (1 to 7, mild; 8 to 19, moderate; and 20 to 35, severe). This scoring system has been found to be reliable and valid when the period recalled is either one month or one week, and the system is sensitive to changes in symptoms.¹⁴⁻¹⁶

In addition, at each of the two visits uroflometry was performed with a Urodyne 1000 machine (Dantec Medical, Santa Clara, Calif.), residual urinary volume after voiding was determined ultrasonographically with an instrument measuring bladder volume, serum concentrations of prostate-specific antigen were measured, and routine tests of hematologic values and blood chemistry were performed. The base-line values given here for symptom scores, peak urinary-flow rates, and residual urinary volumes after voiding are the means of the two measurements made during the lead-in period. A urine specimen was analyzed by dipstick, and the spun sediment was inspected. Transrectal ultrasonography was performed to determine prostatic volume.¹⁷

Criteria for Eligibility and Exclusion

To be eligible for the study, a man had to have a mean symptom score of at least 8, a mean peak urinary-flow rate of no more than 15 ml per second and no less than 4 ml per second, with a minimal voided volume of 125 ml, and a mean residual volume after voiding of less than 300 ml. No threshold level of prostatic enlargement was required.

Men were excluded if they were unwilling or unable to give informed consent or if they had taken an experimental drug less than four weeks before being screened; if they had taken an α -adrenergic-agonist drug, a cholinergic agonist or antagonist drug, a topical β -adrenergic-antagonist drug for glaucoma, or any anti-hypertensive drug except a diuretic or an angiotensin-converting-enzyme inhibitor within two weeks before the lead-in period; or if they had taken an estrogen, androgen, or drug causing androgen inhibition within the preceding three months. Other criteria for exclusion were an episode of unstable angina pectoris, a myocardial infarction, a transient ischemic attack, or a cerebrovascular accident in the past six months; insulin-dependent diabetes mellitus; orthostatic hypotension (defined as a difference of more than 20 mm Hg between the systolic blood pressure measured when the man was standing and that measured when he was supine, independent of concomitant changes in pulse or symptoms of postural hypotension) or a history of syncope; a blood pressure of less than 90/70 mm Hg when the man was sitting; a history of carcinoma of the prostate, pelvic irradiation, or urethral stricture; surgery for benign prostatic hyperplasia or bladder-neck obstruction; current evidence of prostatic carcinoma; active urinary tract disease, cystoscopy, or biopsy of the prostate within the previous two weeks; a history of recurrent urinary tract infections or an in-

fection of the urinary tract, including asymptomatic bacteriuria, within the preceding two months; prior pelvic surgery that was likely to interfere with normal bladder function; any progressive disorder that might prevent the evaluation of drug efficacy and safety; clinically important renal or hepatic impairment (as evidenced by a serum creatinine concentration greater than 2.0 mg per deciliter [177 μ mol per liter] or a serum alanine aminotransferase concentration more than 1.5 times the upper limit of normal); and a serum concentration of prostate-specific antigen above 10 ng per milliliter.

In response to telephone calls from the study sites, the men at each site were randomly assigned by a central computer in equal proportions to receive terazosin and finasteride placebo (the terazosin group), finasteride and terazosin placebo (the finasteride group), both terazosin and finasteride (the combination-therapy group), and terazosin and finasteride placebos (the placebo group) for one year.

Treatments

The following titration schedule was used for all men receiving terazosin or its matching placebo: days 1 to 3, 1 mg; days 4 to 7, 2 mg; days 8 to 14, 5 mg; and day 15 through the completion of the study, 10 mg. All the medication kits provided for the option to reduce the dose of terazosin or its matching placebo in a blinded manner. Terazosin (or its matching placebo) was administered at bedtime. All the men receiving finasteride or its matching placebo received a single daily dose of 5 mg at bedtime.

The principal investigator at each site was permitted to reduce the daily dose of terazosin from 10 to 5 mg in the event of an adverse effect attributed to that drug. Men in the finasteride group (i.e., those receiving finasteride and terazosin placebo) who had an adverse effect thought to be due to terazosin received terazosin placebo at a reduced dose in a new medication kit. The study medication was discontinued in the event of a serious adverse effect attributed to finasteride or a serious adverse effect that persisted despite a reduction in the dose of terazosin.

Follow-up of Patients

The men were reevaluated after 2, 4, 8, 13, 19, 26, 32, 39, 45, and 52 weeks of therapy. A small proportion of men who returned for the 52-week visit were not evaluated at some intermediate visits. At each visit pills were counted to assess compliance, the men were interviewed about adverse effects, and their vital signs were determined. American Urological Association symptom scores and residual urinary volumes after voiding were determined and uroflometry was performed at 2, 4, 13, 26, 39, and 52 weeks. Blood samples were obtained at 4, 26, and 52 weeks for hematologic analysis and studies of blood chemistry. Transrectal ultrasonography was performed at 26 and 52 weeks. Serum concentrations of prostate-specific antigen were measured at base line and 52 weeks.

Statistical Analysis

The primary outcome variables were American Urological Association symptom scores and peak urinary-flow rates during the year of follow-up. The statistical analyses were based on the intention-to-treat principle; that is, the results for all men for whom any follow-up data were available were included in the analyses of the treatment groups to which the men had been assigned. Repeated-measures analyses of covariance were used to assess the significance of differences between groups with regard to each primary outcome variable over the entire follow-up period.¹⁸ Bonferroni's adjustment was used to take into account the three primary pairwise comparisons: those of finasteride with terazosin, finasteride with combination therapy, and terazosin with combination therapy.¹⁹ A similar analysis was performed of the following secondary pairwise comparisons: finasteride with placebo, terazosin with placebo, and combination therapy with placebo. All statistical tests were two-tailed.

RESULTS

Of 1686 men screened, 1229 (73 percent) met the criteria for entry into the study and were enrolled from December 1992 through March 1994. The follow-up was completed by March 1995. The majority of the men (87 percent) were white; 11 percent were black; 1 percent were Asian or Pacific Islanders; and 0.5 percent were Native Americans. The base-line characteristics of the men in each group are shown in Table 1. There were no significant differences between the treatment groups with regard to any of these characteristics.

Of the 1229 men who entered the study, 222 (18 percent) were not receiving the study medication at the end of one year (Table 2). In the four groups, from 49 men (16 percent) to 67 men (22 percent) did not complete the study. There were no significant differences between groups except in the frequency of withdrawal from the study due to adverse effects, which was significantly lower ($P < 0.05$) in the placebo group than in any other group.

Compliance and Safety during Follow-up

The mean degree of compliance with the study medication, as determined by pill counts, ranged from 94 to 98 percent in the four treatment groups. The reported adverse effects are shown in Table 3. Dizziness was significantly more frequent in the terazosin and the combination-therapy groups than in the finasteride and the placebo groups. Impotence and decreased libido were significantly more frequent in the finasteride and the combination-therapy groups than in the terazosin and the placebo groups. The men in the combination-therapy group had significantly more ejaculatory abnormalities than the men in any other group. There were no clinically or statistically significant changes in hematologic or blood chemical values in any treatment group.

TABLE 1. BASE-LINE CHARACTERISTICS OF 1229 MEN WITH BENIGN PROSTATIC HYPERPLASIA, ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	PLACEBO (N=305)	FINASTERIDE (N=310)	TERAZOSIN (N=305)	COMBINATION (N=309)
Age (yr)	65±7	65±7	65±6	65±7
Prostatic volume (cm ³)	38.4±1.3	36.2±1.0	37.5±1.1	37.2±1.1
White race (%)	79	79	81	80
American Urological Association symptom score†	15.8±5.5	16.2±5.4	16.2±5.5	15.9±5.7
Peak urinary-flow rate (ml/sec)	10.4±2.6	10.6±2.5	10.5±2.6	10.4±2.7
Serum prostate-specific antigen (ng/ml)	2.4±2.1	2.2±1.8	2.2±1.9	2.3±2.0

*Plus-minus values are means ±SD.

†Scores are assigned on a scale from 0 to 35, as described in the Methods section.

During the study more men required dose reductions in the terazosin group and the combination-therapy group (11 percent each) than in the finasteride and the placebo groups (2 percent each). At the end of the study, 80 percent of the men in the terazosin group were receiving 10 mg of terazosin, 11 percent were receiving reduced doses, and 9 percent were receiving none. In the combination-therapy group, 80 percent of the men were receiving 10 mg of terazosin, 11 percent were receiving 5 mg, and 9 percent were receiving none. Among the men in the finasteride group, 92 percent were receiving 5 mg of finasteride, and 8 percent were receiving none.

Outcome

In the terazosin and combination-therapy groups, symptom scores were significantly lower at all fol-

TABLE 2. FOLLOW-UP OF THE MEN WITH BENIGN PROSTATIC HYPERPLASIA, ACCORDING TO TREATMENT GROUP.

OUTCOME	PLACEBO (N=305)	FINASTERIDE (N=310)	TERAZOSIN (N=305)	COMBINATION (N=309)	ALL GROUPS (N=1229)
					no. of men
Completed the study treatment	254	243	256	254	1007 (82)
Discontinued study treatment	51	67	49	55	222 (18)
Adverse event	5	15	18	24	62 (28)
Absolute indication for surgery*	4	5	2	2	13 (6)
Unrelated medical problem	10	10	4	8	32 (14)
Death	3	7	2	2	14 (6)
Loss to follow-up	3	9	9	5	26 (12)
Other	26	21	14	14	75 (34)

*In the judgment of the principal investigator.

TABLE 3. INCIDENCE OF SELECTED ADVERSE EVENTS IN THE MEN WITH BENIGN PROSTATIC HYPERPLASIA, ACCORDING TO TREATMENT GROUP.

ADVERSE EVENT	PLACEBO (N=305)	FINASTERIDE (N=310)	TERAZOSIN (N=305)	COMBINATION (N=309)	P VALUE*
Dizziness	22 (7)	26 (8)	79 (26)	66 (21)	<0.001
Asthenia	21 (7)	23 (7)	42 (14)	43 (14)	0.002
Impotence	14 (5)	29 (9)	18 (6)	29 (9)	0.05
Rhinitis	14 (5)	8 (3)	20 (7)	24 (8)	0.02
Headache	10 (3)	19 (6)	18 (6)	16 (5)	0.38
Ejaculatory abnormality	4 (1)	6 (2)	1 (0.3)	21 (7)	<0.001
Decreased libido	4 (1)	14 (5)	8 (3)	15 (5)	0.05
Syncope	0	3 (1)	3 (1)	5 (2)	0.20
Sinusitis	4 (1)	4 (1)	6 (2)	7 (2)	0.73
Postural hypotension	3 (1)	7 (2)	23 (8)	27 (9)	<0.001

*P values were calculated by the chi-square test for the overall difference among the four treatment groups.

low-up visits than at base line and were significantly lower than in the placebo and the finasteride groups (Fig. 1). There were significant changes from base line in both the finasteride and the placebo groups, but no differences between groups. The symptom scores in the terazosin group and the combination-therapy group reached their nadirs in 13 weeks and did not change significantly thereafter. The absolute mean changes in the symptom scores at 52 weeks were decreases of 2.6 points in the placebo group, 3.2 points in the finasteride group, 6.1 points in the terazosin group, and 6.2 points in the combination-therapy group.

At all follow-up visits, the mean peak urinary-flow rates were significantly higher in the terazosin and combination-therapy groups than in the placebo and finasteride groups (Fig. 2). The increases in these rates were greatest at four weeks in the terazosin and combination-therapy groups, and they did not change thereafter. The absolute mean changes in the

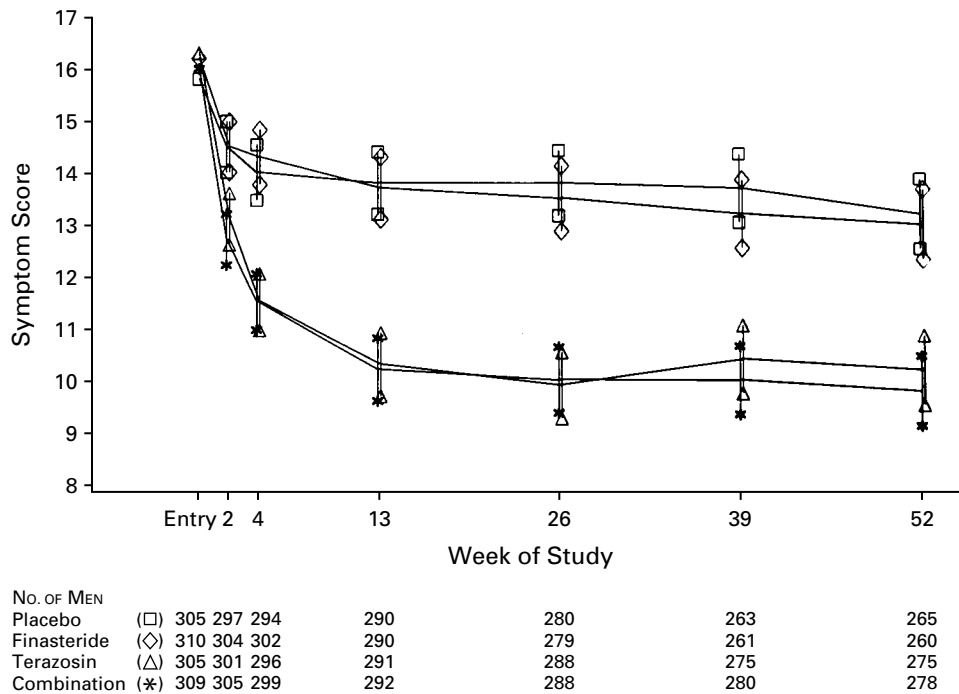


Figure 1. American Urological Association Symptom Scores in Men with Benign Prostatic Hyperplasia, According to Treatment Group.

Scores are expressed as adjusted means and 95 percent confidence intervals. The results of primary pairwise comparisons (with Bonferroni's adjustment) are as follows: finasteride and terazosin, $P < 0.001$; finasteride and combination therapy, $P < 0.001$; and terazosin and combination therapy, $P = 1.00$. The results of secondary pairwise treatment comparisons are as follows: finasteride and placebo, $P = 0.63$; terazosin and placebo, $P < 0.001$; and combination therapy and placebo, $P < 0.001$.

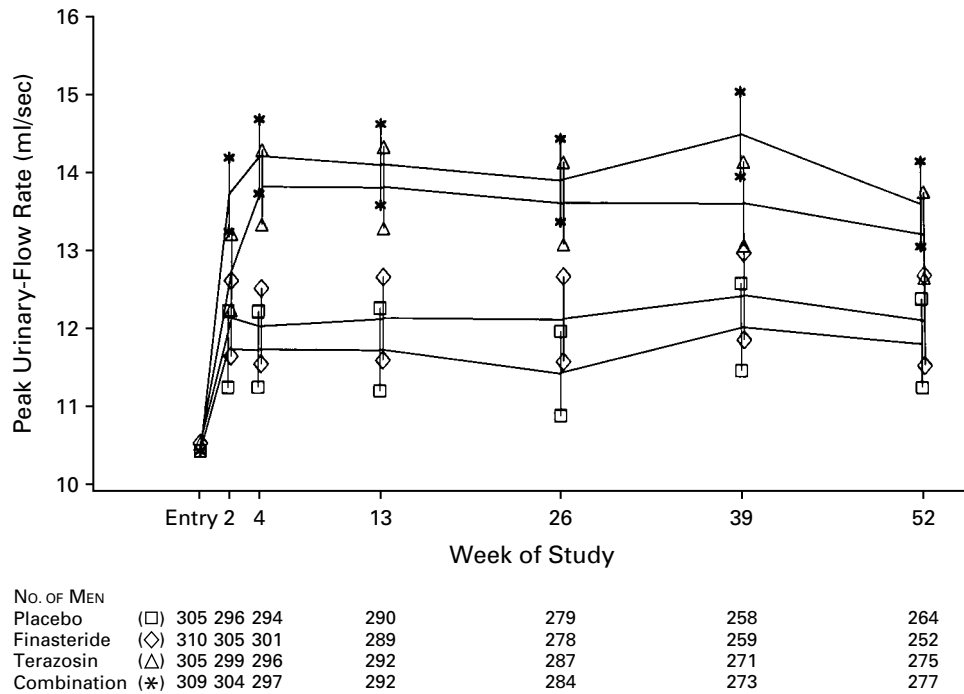


Figure 2. Peak Urinary-Flow Rates in Men with Benign Prostatic Hyperplasia, According to Treatment Group.

Rates are expressed as adjusted means and 95 percent confidence intervals. The results of primary pairwise comparisons (with Bonferroni's adjustment) are as follows: finasteride and terazosin, $P < 0.001$; finasteride and combination therapy, $P < 0.001$; and terazosin and combination therapy, $P = 0.15$. The results of secondary pairwise treatment comparisons are as follows: finasteride and placebo, $P = 0.07$; terazosin and placebo, $P < 0.001$; and combination therapy and placebo, $P < 0.001$.

peak urinary-flow rate at 52 weeks in the placebo, finasteride, terazosin, and combination-therapy groups were increases of 1.4, 1.6, 2.7, and 3.2 ml per second, respectively.

The base-line prostatic volume was 38.4 cm³ in the placebo group, 36.2 cm³ in the finasteride group, 37.5 cm³ in the terazosin group, and 37.2 cm³ in the combination-therapy group. The mean change from base line at 52 weeks was an increase of 0.5 cm³ in the placebo group, a decrease of 6.1 cm³ in the finasteride group, an increase of 0.5 cm³ in the terazosin group, and a decrease of 7.0 cm³ in the combination-therapy group. The changes in prostatic volume were significantly greater in the finasteride and combination-therapy groups than in the terazosin and placebo groups. The maximal reductions in prostatic volume in the finasteride and combination-therapy groups occurred at 26 weeks. The prostatic volume did not change significantly in the terazosin and placebo groups. The difference between groups in mean prostatic volume was statistically significant for the following pairs: the combination-therapy group and the terazosin group, the finasteride group and the terazosin group, the combination-therapy group and the placebo group, and the finasteride

group and the placebo group ($P < 0.001$ for all comparisons).

The base-line serum concentration of prostate-specific antigen was 2.4 ng per milliliter in the placebo group, 2.2 ng per milliliter in the finasteride group, 2.2 ng per milliliter in the terazosin group, and 2.3 ng per milliliter in the combination-therapy group. The mean changes from base line at 52 weeks were a decrease of 0.1 ng per milliliter in the placebo group, an increase of 0.9 ng per milliliter in the finasteride group, a decrease of 0.4 ng per milliliter in the terazosin group, and an increase of 0.9 ng per milliliter in the combination-therapy group. The difference between groups in the mean serum concentration of prostate-specific antigen was statistically significant for the following pairs: the combination-therapy group and the terazosin group, the finasteride group and the terazosin group, the combination-therapy group and the placebo group, and the finasteride group and the placebo group ($P < 0.001$ for all comparisons).

DISCUSSION

This study was designed to compare the efficacy and safety of finasteride, terazosin, and the combi-

nation of the two drugs in men with symptomatic benign prostatic hyperplasia. The study was conducted, monitored, and analyzed independently of its pharmaceutical sponsors by the Veterans Affairs Cooperative Studies Program Coordinating Center. The proportion of black men studied approached that of the U.S. population, enhancing the generalizability of the study. Eighty-two percent of the men completed one-year of follow-up during which they continued to receive their assigned treatments (with no significant differences among the three active-treatment groups), and compliance approached 100 percent.

The use of α -adrenergic blockade to treat men with symptomatic benign prostatic hyperplasia is based on the hypotheses that the disorder arises from bladder-outlet obstruction and that 40 percent of the cellular volume of the hyperplastic prostate is made up of smooth muscle,²⁰ whose tension is mediated by α_1 -adrenoceptors.²¹ Therapy with α_1 -adrenergic-antagonist drugs (such as terazosin, doxazosin, and tamsulosin) has been found to be safe and effective in men with benign prostatic hyperplasia,⁸⁻¹³ a finding that our study confirmed. There was a decrease of 6.1 points in American Urological Association symptom scores and an increase of 2.7 ml per second in peak urinary-flow rates after one year of terazosin therapy, changes nearly identical to those observed in an earlier clinical trial of terazosin at the same dose.⁸

The rationale for 5 α -reductase inhibition in the treatment of benign prostatic hyperplasia is that the development of the condition is an androgen-dependent event. Castration during childhood or puberty prevents it from developing, and the suppression of androgens in adult men promotes its regression.²² Finasteride was previously reported to be safe and effective for the treatment of benign prostatic hyperplasia.⁵⁻⁷ Its effects on the primary outcome measures (symptom scores and peak urinary-flow rates) in the principal North American⁵ study of the drug were not in agreement with those in our study. In that study the difference in outcomes between finasteride and placebo was small but statistically significant. There are differences between the two studies that may explain the different outcomes. Two different indexes of symptoms were used, although the items in both are very similar. The mean prostatic volume at base line in the study of finasteride was approximately 50 percent greater than in the present study and other clinical trials,^{7,8,23,24} reflecting the enrollment of men with larger prostate glands. This suggests that it may be effective only in men with very large prostate glands.

In this comparative study, the differences between terazosin and finasteride were statistically significant in favor of terazosin with regard to both primary outcome measures — symptom scores and urinary-flow

rate — and the combination of terazosin and finasteride was no more effective than terazosin alone.

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APPENDIX

The following persons participated in the Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group: R. Frontera, Allen Park, Mich.; G.J. Faerber, Ann Arbor, Mich.; M. Naslund, Baltimore; P.P. Hudson, Bay Pines, Fla.; D. Urban, Birmingham, Ala.; A. Crowley, Brooklyn, N.Y.; J.B. Graham, Chicago; P. O'Donnell, Cincinnati; S. Weinstein, Columbia, Mo.; E.D. Crawford, Denver; P. Gilhooly, East Orange, N.J.; C.P. Steidel, Fort Wayne, Ind.; H.B. Epstein, Gainesville, Fla.; J.S. Wheeler, Jr., Hines, Ill.; D. Kadmon, Houston; R.S. Foster, Indianapolis; T. Moon, Madison, Wis.; A.L. Patterson, Memphis, Tenn.; N. Block, Miami; D. Dewire, Milwaukee; P.K. Reddy, Minneapolis; R. Thomas and O.J. Dean, Jr., New Orleans; D. Culkin, Oklahoma City; K. Van Arsdalen, Philadelphia; A. Acosta-Otero, San Juan, P.R.; E. Tanagho, San Francisco; D. Venable, Shreveport, La.; H. Foster, West Haven, Conn.; W. Aronson, West Los Angeles; and S.N. Rous, White River Junction, Vt.

Cooperative Studies Program Coordinating Center, Veterans Affairs Medical Center, Perry Point, Md. — J.F. Collins, chief; K. Jones and G. Kirk, statistical programmers; E. Spence, computer programmer; M. Rhoads, P. Grubb, and B. Calvert, computer assistants; and B.A. McMullen, administrative officer.

Cooperative Studies Program Clinical Research Pharmacy Coordinating Center — M.R. Sather, chief; L.A. Guidarelli, study coordinator; L.L. Vasquez, computer assistant; L. Montano, L.V. Richards, J.D. Recio, and S. Martinez, production controllers; and C.A. Sanchez and G.E. Archuleta, research assistants.

Data Monitoring Board — B.A. Barton, Maryland Medical Research Institute, Baltimore; I.M. Thompson, Jr., Brooke Army Medical Center, Fort Sam Houston, Tex.; J.W. Basler, Jewish Hospital, St. Louis; J.A. Smith, Jr., Vanderbilt University School of Medicine, Nashville; and R.J. Krane, Boston University School of Medicine, Boston.

Human Rights Committee — S. Jones, chairman; J.P. Libonati, R. Weiss, E. Perez, T.E. Hobbins, D. Highfield, and M.M. Arthur.

Department of Veterans Affairs Central Office — D. Deykin, chief; J. Gold, administrative officer; and P.C. Huang, staff assistant.

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IMAGES IN CLINICAL MEDICINE

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CORRECTION

Terazosin, Finasteride, or Both in Benign Prostatic Hyperplasia

To the Editor: The study by Lepor et al. (Aug. 22 issue)¹ confirms the efficacy of α_1 -adrenergic antagonists in the management of benign prostatic hyperplasia. It also underscores the importance of focusing on the patients' symptoms, rather than relying on proxy physiologic measurements that correlate variably with the symptoms.^{2,3} However, although the American Urological Association Symptom Index includes both "irritative" symptoms (frequency, urgency, and nocturia) and "obstructive" symptoms (weak stream and hesitancy), only the total scores were reported.¹ It would be useful to know the score for each category of symptoms, because the degree of relief of the two types of symptoms may differ.³ For example, irritative symptoms may not improve to the same degree as obstructive symptoms after prostatectomy. This observation is of even greater concern in elderly men, who are more likely to be bothered by irritative symptoms than are younger men.³

In addition, low doses of α_1 -adrenergic antagonists may relieve irritative symptoms in many elderly men. In an earlier study of terazosin by the same group, relief of obstructive symptoms occurred only at the highest dose (10 mg), whereas irritative symptoms were relieved at lower doses (5 mg and possibly 2 mg).⁴ Although the new study was not designed to address this question, an analysis comparing the degree of relief of irritative and obstructive symptoms according to age would be of interest.^{1,4}

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To the Editor: Treatment with α_1 -adrenergic antagonists such as terazosin is known to cause orthostatic hypotension, the ultimate consequence of which is syncope. Lepor et al. excluded patients who had taken "any antihypertensive drug except a diuretic or an angiotensin-converting-enzyme inhibitor within two weeks before the lead-in period." Does this statement mean that only these two types of antihypertensive drug were used during the study?

It is unfortunate that the authors do not provide data on blood pressure measured in the supine and upright positions, especially in view of the fact that the frequency of dizziness, asthenia, and postural hypotension was significantly increased in the terazosin and combination-therapy groups. Although the number of men with syncope was similar in the four groups, the degree of the fall in blood pressure and the severity of symptoms may have varied. We think the discussion of the side effects in this well-designed study is a little too brief.

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Dr. Lepor replies:

To the Editor: Kuchel et al. ask about the effects of the different treatments on the symptoms of benign prostatic hyperplasia. Using the American Urological Association Symptom Index, which assesses seven symptoms characteristic of the disease, we found that terazosin and combination therapy resulted in a statistically significant and clinically important improvement in symptoms, but an analysis of individual symptoms was not done.

Thien and Lenders request clarification of an exclusion criterion. One of the many exclusion criteria was therapy with any antihypertensive drug other than a diuretic or an angiotensin-converting-enzyme inhibitor within two weeks before the beginning of the lead-in period. With respect to the relation between blood pressure and adverse events, orthostatic hypotension was defined as a fall of more than 20 mm Hg in the systolic blood pressure when the patient changed from the supine to the upright position. The percentages of men who had at least one episode of orthostatic hypotension during the study in the placebo, finasteride, terazosin, and combination groups were 30, 26, 45, and 39 percent, respectively, and syncopal episodes occurred in only 0, 1.0, 1.0, and 2.3 percent of the men.

In the article, in the right-hand column of page 537, the mean changes from base line in the serum prostate-specific antigen concentration at 52 weeks are stated incorrectly. The correct values are as follows: an increase of 0.1 ng per milliliter in the placebo group, a decrease of 0.9 ng per milliliter in the finasteride group, an increase of 0.4 ng per

milliliter in the terazosin group, and a decrease of 0.9 ng per milliliter in the combination-therapy group.

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