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THE EFFECT OF FINASTERIDE ON THE RISK OF ACUTE URINARY RETENTION AND THE NEED FOR SURGICAL TREATMENT AMONG MEN WITH BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Background Finasteride is known to improve urinary symptoms in men with benign prostatic hyperplasia, but the extent to which the benefit is sustained and whether finasteride reduces the incidence of related events, including the need for surgery and the development of acute urinary retention, are not known.

Methods In this double-blind, randomized, placebo-controlled trial, we studied 3040 men with moderate-to-severe urinary symptoms and enlarged prostate glands who were treated daily with 5 mg of finasteride or placebo for four years. Symptom scores (on a scale of 1 to 34), urinary flow rates, and the occurrence of outcome events were assessed every four months in 3016 men. Prostate volume was measured in a subgroup of the men. Complete data on outcomes were available for 2760 men.

Results During the four-year study period, 152 of the 1503 men in the placebo group (10 percent) and 69 of the 1513 men in the finasteride group (5 percent) underwent surgery for benign prostatic hyperplasia (reduction in risk with finasteride, 55 percent; 95 percent confidence interval, 41 to 65 percent). Acute urinary retention developed in 99 men (7 percent) in the placebo group and 42 men (3 percent) in the finasteride group (reduction in risk with finasteride, 57 percent; 95 percent confidence interval, 40 to 69 percent). Among the men who completed the study, the mean decreases in the symptom score were 3.3 in the finasteride group and 1.3 in the placebo group ($P < 0.001$). Treatment with finasteride also significantly improved urinary flow rates and reduced prostate volume ($P < 0.001$).

Conclusions Among men with symptoms of urinary obstruction and prostatic enlargement, treatment with finasteride for four years reduces symptoms and prostate volume, increases the urinary flow rate, and reduces the probability of surgery and acute urinary retention. (N Engl J Med 1998;338:557-63.)

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BENIGN prostatic hyperplasia is common among older men, and its symptoms interfere with normal activities and reduce the sense of well-being.¹ It can also be progressive, with a risk of urinary retention, bladder infection, bladder calculi, and renal failure.²⁻⁴ Although many men with mild-to-moderate symptoms do well without therapy, others have gradually increasing symptoms and require medical therapy or surgery.^{4,5} Among 50-year-old men, the lifetime incidence of surgical or medical intervention for benign prostatic hyperplasia is estimated to be 35 percent,⁶ and in one three-year study 24 percent of men with moderate symptoms who were assigned to watchful waiting underwent prostate surgery, and urinary retention developed in 3 percent.⁷

Finasteride, a selective inhibitor of 5 α -reductase, decreases the conversion of testosterone to dihydrotestosterone, improves urinary symptoms, and reduces the volume of the prostate in men with benign prostatic hyperplasia and enlarged prostate glands.⁸⁻¹⁰ A persistent reduction in prostate volume due to finasteride therapy may prevent the progression of benign prostatic hyperplasia.¹¹ In the present

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study, we evaluated the long-term effects of finasteride on the symptoms of benign prostatic hyperplasia and on the incidence of important outcomes related to it, including the development of acute urinary retention and the need for surgery.

METHODS

Subjects

Between 1990 and 1992, we studied 3040 men with benign prostatic hyperplasia diagnosed on the basis of moderate-to-severe symptoms of urinary obstruction (determined by means of a validated symptom-score questionnaire¹²), decreased maximal urinary flow rates (<15 ml per second with a voided volume of 150 ml or more; measured with a Urolynx 1000 uroflowmeter, Dantec, Mahwah, N.J.), and an enlarged prostate gland on digital rectal examination. Men who were receiving α -adrenergic-antagonist drugs or antiandrogens and those with a history of chronic prostatitis, recurrent urinary tract infections, prostate or bladder cancer or surgery, or a serum prostate-specific antigen concentration of 10 ng per milliliter or more were excluded. Men with serum prostate-specific antigen concentrations of 4.0 to 9.9 ng per milliliter were required to have had negative results on a prostatic biopsy in order to be enrolled in the study.

Study Design

The study was approved by the institutional review committees of all 95 participating centers, and all the men gave written informed consent. This was a four-year, randomized, double-blind, placebo-controlled trial (Fig. 1). After a one-month single-blind run-in period in which all men were treated with placebo, men were randomly assigned to receive 5 mg of finasteride (Proscar, Merck, West Point, Pa.) or placebo daily according to a computer-generated schedule, without stratification according to site. They were subsequently evaluated every four months, at which time symptoms and side effects were assessed and the urinary flow rate was measured (the results were excluded from the analysis if the urine volume was less than 150 ml). Serum prostate-specific antigen was measured every four months for one year and every eight months thereafter. Physical examinations, including digital rectal examinations, and routine hematologic and serum-chemistry tests were performed yearly. Prostate biopsies were performed if clinically indicated. At the end of the study, investigators were asked to perform another biopsy in patients with base-line serum prostate-specific antigen concentrations of 4 ng per milliliter or higher. Magnetic resonance imaging of the prostate was performed yearly at 13 centers. A safety committee periodically reviewed the data on safety. Men who had serious adverse effects that were considered drug-related, those who required prostate surgery, and those in whom prostate cancer was diagnosed were withdrawn from the study. Other men discontinued the study because of side effects, lack of improvement, worsening of their disease, or other reasons or were lost to follow-up.

The primary end point, the symptom score, was measured by means of a self-administered questionnaire that contained questions about the frequency of lower urinary tract symptoms.¹² After the study was initiated, the American Urological Association (AUA) symptom score was adopted as a standard for the assessment of such symptoms.¹³ All seven components of the AUA symptom score (nocturia, impairment of size and force of stream of urine, urinary frequency, delayed, strained, or interrupted urination, and incomplete emptying of the bladder) were components of our original questionnaire. Since the number of choices for each response differed between the two scores, the responses to these seven questions on our questionnaire were adjusted to approximate the scores on the AUA symptom scale. A "quasi-AUA score" (total range, 0 to 34; 0 to 5 for each of six questions and 0 to 4 for one question), similar to the AUA score (total range, 0 to 35; 0 to 5 on each of seven questions), was constructed.^{10,14}

Surgery for benign prostatic hyperplasia and the occurrence of acute urinary retention during the four-year period were the pre-defined secondary end points. Complete data on outcomes, including four-year follow-up information for the men who discontinued treatment, were available for 92 percent of the men in both treatment groups. In the other 8 percent, complete information was available until discontinuation of the study medication (median time after randomization, 20 months) or up to the 6-month follow-up assessment after discontinuation. One site at which 24 men had been enrolled was closed prematurely because of inadequate study documentation. The results for these men were included in the safety analysis but not in the analysis of efficacy.

An end-points committee, whose members were unaware of the treatment-group assignments, reviewed all study documents for each man who underwent surgery (such as transurethral prostatectomy or open, laser, or incisional prostatectomy) for benign prostatic hyperplasia or who had acute urinary retention requiring catheterization of the bladder. Acute urinary retention was then classified as either spontaneous (if there was no precipitating factor) or precipitated (if there was a possible contributing factor to the development of retention, including preceding surgery, a medical event such as a stroke or urinary tract infection, or ingestion of an α -adrenergic drug). Data on surgical procedures or acute urinary retention in men with prostate cancer were censored at the time of the diagnosis of cancer.

All the magnetic resonance images of the prostate were read by a central radiologist who was unaware of the treatment group and the time the image was obtained (i.e., at base line or at follow-up).

Statistical Analysis

The data on surgery and acute urinary retention were analyzed with use of the log-rank test for the time to the first event and Fisher's exact test for cumulative incidence. For the analyses of symptoms, urinary flow rates, and prostate volume, all data were included (according to the intention-to-treat approach) in a pre-defined stratified analysis, the strata being the number of years the men stayed in the study (0 to <1, 1 to <2, 2 to <3, and 3 to <4 years and completion of the study).¹⁵ On the basis of the mean of the last two values for symptom scores and urinary flow rate and the last value for prostate volume, mean values for the men who completed the study and those who withdrew were calculated. The pooled means in the two groups were compared. Adverse effects and safety were assessed with Fisher's exact test. All statistical tests were two-sided.

RESULTS

Base-Line Characteristics

A total of 3040 men were enrolled in the study. The men assigned to the finasteride and placebo groups were similar in terms of age, base-line demographic characteristics, symptoms, and other variables (Table 1). The base-line characteristics of the men in whom prostate volume was measured were similar to those of the study group as a whole.

Discontinuation of the Study Drug

During the four-year study, 524 men in the finasteride group (34 percent) discontinued treatment, as compared with 633 men in the placebo group (42 percent, $P < 0.001$). The most common reasons were adverse drug effects or treatment failures (Fig. 1). More men in the placebo group discontinued treatment because of lack of improvement or worsening of disease or to receive medical or surgical therapy.

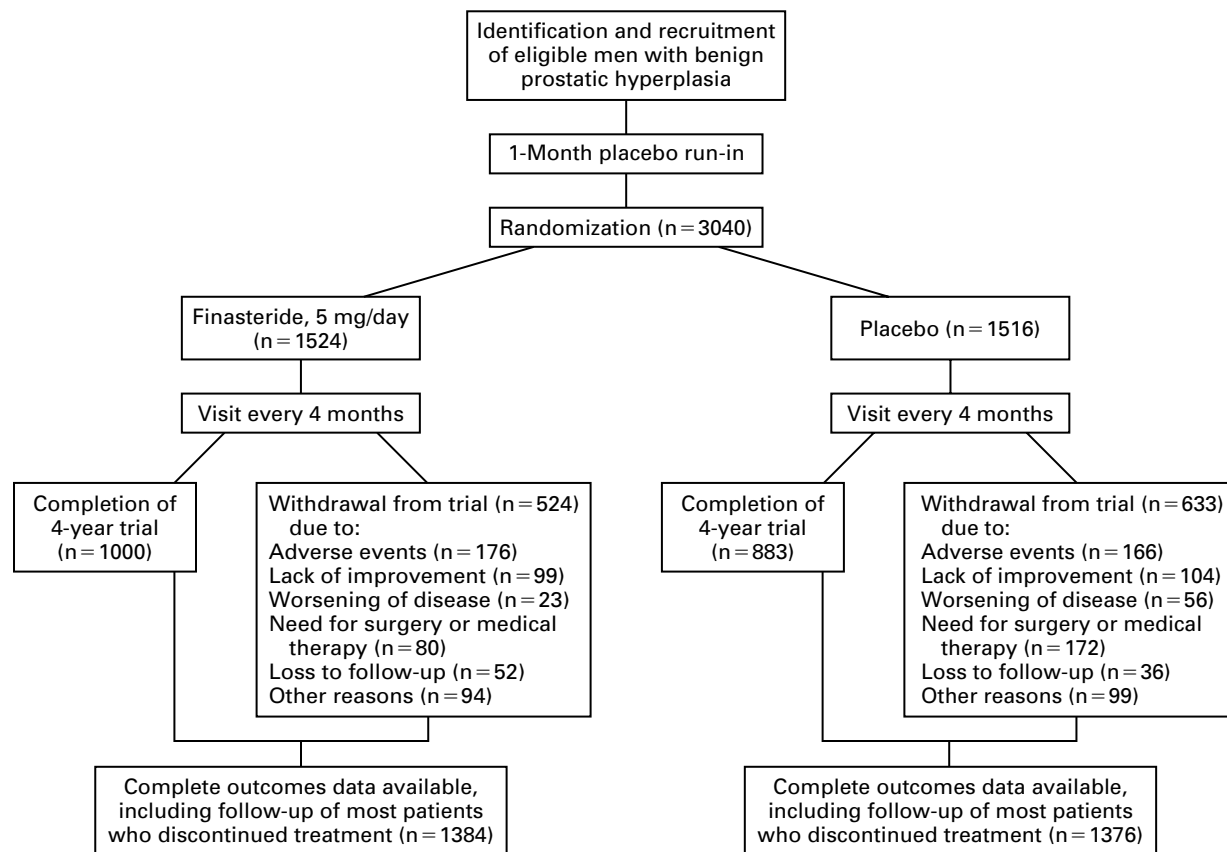


Figure 1. Diagram of the Trial, Showing the Numbers of Men Who Entered and Completed the Study and the Numbers Who Discontinued Treatment.

Surgery for Benign Prostatic Hyperplasia and Occurrence of Acute Urinary Retention

Two hundred ninety-nine men either had surgery or required catheterization for acute urinary retention during the study: 199 in the placebo group (13 percent) and 100 in the finasteride group (7 percent; reduction in risk with finasteride, 51 percent; $P < 0.001$) (Table 2). Differences in the rates of surgery and acute urinary retention were evident within four months, with continued divergence throughout the four-year period (Fig. 2).

One-hundred fifty-two of the men in the placebo group (10 percent) and 69 of the men in the finasteride group (5 percent) underwent surgery (reduction in risk with finasteride, 55 percent; $P < 0.001$) (Table 2 and Fig. 2). The probability of undergoing the most commonly performed procedure, transurethral prostatectomy, was 49 percent lower among the finasteride-treated men (Table 2).

Acute urinary retention developed in 99 men in the placebo group (7 percent) and 42 men in the finasteride group (3 percent) during the study (reduc-

TABLE 1. BASE-LINE CHARACTERISTICS OF MEN WITH BENIGN PROSTATIC HYPERPLASIA IN THE PLACEBO AND FINASTERIDE GROUPS.*

CHARACTERISTIC	PLACEBO (N = 1516)	FINASTERIDE (N = 1524)
Age (yr)	64±7	64±6
Race (%)		
White	95.5	94.9
Black	3.0	3.0
Other	1.5	2.1
Quasi-AUA symptom score†	15±6	15±6
Maximal urinary flow rate (ml/sec)	11±4	11±4
Prostate volume (ml)‡	55±26	54±25
Serum PSA (ng/ml)	2.8±2.1	2.8±2.1

*Plus-minus values are means ±SD. There were no significant differences in base-line characteristics between the treatment groups. PSA denotes prostate-specific antigen.

†The quasi-AUA symptom score is the symptom score based on an adaptation of the American Urologic Association symptom scale, as described in the Methods section.

‡Prostate volume was measured in 312 men, 155 in the placebo group and 157 in the finasteride group.

TABLE 2. FOUR-YEAR INCIDENCE OF ACUTE URINARY RETENTION OR SURGERY FOR BENIGN PROSTATIC HYPERPLASIA AMONG MEN IN THE PLACEBO AND FINASTERIDE GROUPS.*

OUTCOME	PLACEBO (N=1503)	FINASTERIDE (N=1513)	RISK REDUCTION (95% CI)
	no. (%)		%
Surgery or acute urinary retention	199 (13)	100 (7)	51 (38–61)
Surgery	152 (10)	69 (5)	55 (41–65)
Transurethral prostatectomy	125 (8)	64 (4)	49 (33–62)
Acute urinary retention†	99 (7)	42 (3)	57 (40–69)
Spontaneous	56 (4)	20 (1)	62 (40–76)
Precipitated	48 (3)	23 (2)	52 (23–70)

*Twenty-four men from one center were excluded from the analysis (see the Methods section). Risk reduction has been calculated with the log-rank test for the time to a first event. CI denotes confidence interval.

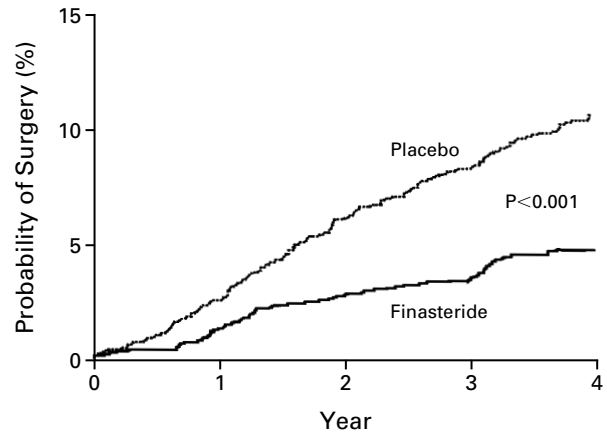
†Acute urinary retention was classified as spontaneous when there was no evidence of precipitating factors other than benign prostatic hyperplasia and as precipitated when there was evidence of precipitating factors in addition to benign prostatic hyperplasia, such as preceding surgery, predisposing medications, or urinary tract infection. A single patient may have had an episode of both spontaneous and precipitated acute urinary retention at different times, but each man was only counted once in the total.

tion in risk with finasteride, 57 percent; $P<0.001$) (Fig. 2 and Table 2). Finasteride decreased the risk of both spontaneous and precipitated acute urinary retention ($P<0.001$ for both comparisons with placebo) (Table 2). Many men with spontaneous acute urinary retention ultimately underwent surgery (72 percent in the placebo group and 33 percent in the finasteride group). Fewer men who had precipitated urinary retention (24 percent in the placebo group and 10 percent in the finasteride group) ultimately underwent surgery.

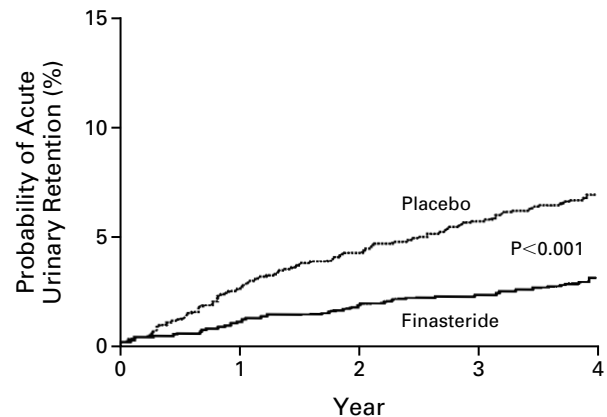
Symptoms, Prostate Volume, and Urinary Flow Rate

Symptom scores decreased in both groups during the first eight months, with further improvement over time in the finasteride group but not the placebo group (Fig. 3). The mean decreases in symptom scores (including those in the men who discontinued treatment) were 2.6 in the finasteride group and 1.0 in the placebo group (mean difference between groups, 1.6; 95 percent confidence interval, 2.5 to 0.7; $P<0.001$). Among the men who completed the study, the mean symptom score decreased by 3.3 points in the finasteride group and 1.3 points in the placebo group (mean difference, 2.1; 95 percent confidence interval, 2.6 to 1.6; $P<0.001$).

The mean prostate volume decreased during the first year in the finasteride group, with no further increase thereafter (Fig. 3). In contrast, prostate volume increased continuously in the placebo group. Among men who completed the study, the overall mean decrease in prostate volume was 18 percent in



PLACEBO GROUP				
No. of events	37	52	32	31
No. at risk	1503	1454	1374	1314
FINASTERIDE GROUP				
No. of events	18	22	9	20
No. at risk	1513	1483	1438	1410



PLACEBO GROUP				
No. of events	36	25	20	18
No. at risk	1503	1454	1398	1347
FINASTERIDE GROUP				
No. of events	14	11	7	10
No. at risk	1513	1487	1449	1421

Figure 2. Probability of Undergoing Surgery for Benign Prostatic Hyperplasia or the Development of Acute Urinary Retention during the Four-Year Study Period in the Placebo and Finasteride Groups.

The figure shows life-table analyses of the proportion of men with each outcome. The numbers of events shown below the graphs are those that occurred during each one-year interval. The numbers of men at risk are those at the beginning of the respective one-year intervals. Data on men who died, were given a diagnosis of prostate cancer, or were lost to follow-up were censored at the time of death, diagnosis of prostate cancer, or discontinuation of therapy.

Figure 3. The Effect of Finasteride or Placebo on Symptom Scores (on the Quasi-AUA Symptom Scale), Prostate Volume, and Maximal Urinary Flow Rate over Time.

Values are mean (\pm SE) changes from base line. The numbers below the panels show the numbers of patients with valid data who remained in the study.

the finasteride group, as compared with an overall increase of 14 percent in the placebo group (mean difference between groups, 32 percent; 95 percent confidence interval, 28 to 36 percent; $P < 0.001$).

There was a clear separation between the treatment groups in the maximal urinary flow rate within the first four months of the study (Fig. 3). Among men who completed the study, the mean increase in the maximal flow rate was 1.9 ml per second in the finasteride group and 0.2 ml per second in the placebo group (mean difference between groups, 1.7 ml per second; 95 percent confidence interval, 1.3 to 2.1; $P < 0.001$).

Safety

There were no significant differences between the groups in the incidence of serious adverse effects. The only drug-related adverse effects that occurred in 1 percent or more of the men for which the rates differed significantly between the groups were symptoms of sexual dysfunction, breast enlargement or tenderness, and rashes (Table 3). Decreased libido and impotence were more frequent in the finasteride group only during the first year. There were no cases of breast cancer in the finasteride group, but two were reported in the placebo group; neither man had a history of gynecomastia.

The men were carefully monitored for prostate cancer with serial digital rectal examinations and measurements of serum prostate-specific antigen. Prostate biopsies were performed during the study in 325 men in the finasteride group and 320 in the placebo group. The overall incidence of prostate cancer was 5 percent in each group.

DISCUSSION

The most important finding of this study is that finasteride, as compared with placebo, decreased the need for prostate surgery and the risk of acute urinary retention. The differences were evident within four months after the start of the study and continued throughout the four-year study period. On the basis of these results, 15 men (95 percent confidence interval, 1 to 23) would need to be treated for four years to prevent one event (either surgery or acute urinary retention). Although α -adrenergic-antagonist drugs also provide symptomatic relief, a reduced requirement for surgery has not been demonstrated with such treatment.¹⁶ Clearly, a decrease in the need

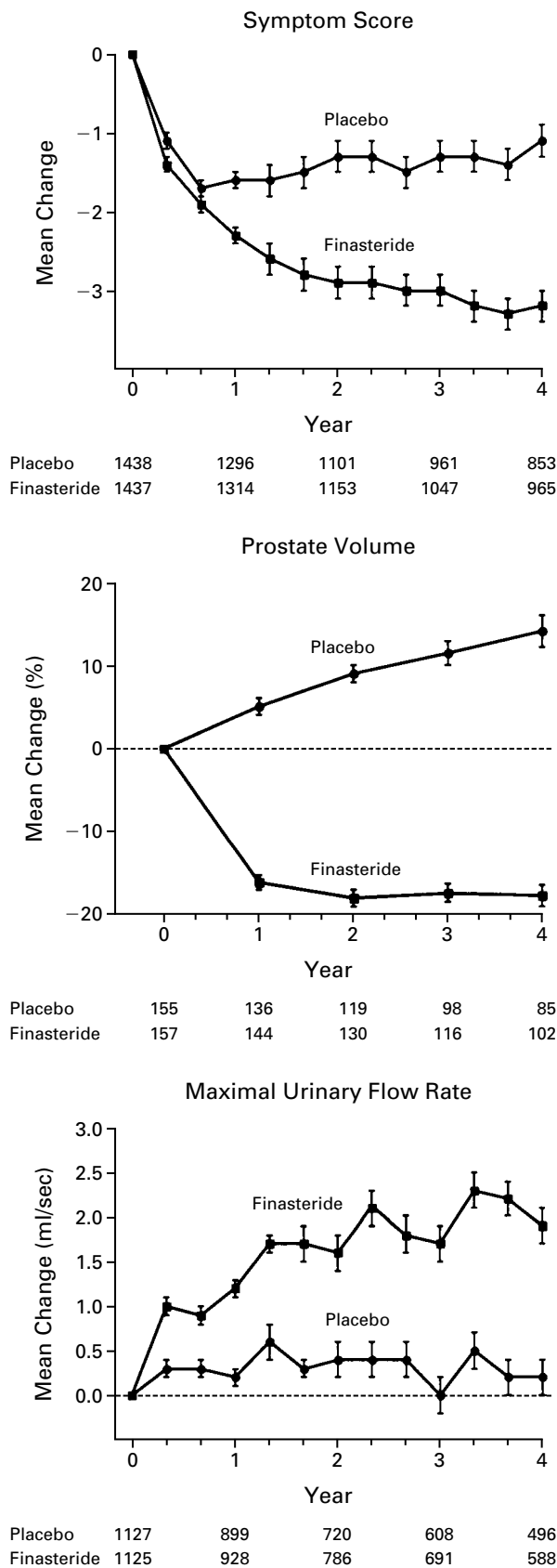


TABLE 3. DRUG-RELATED ADVERSE EVENTS THAT OCCURRED IN 1 PERCENT OR MORE OF MEN IN YEAR 1 AND YEARS 2 THROUGH 4 OF THE STUDY AND WHOSE INCIDENCE DIFFERED SIGNIFICANTLY BETWEEN GROUPS.

ADVERSE EVENT AND STUDY GROUP	YR 1	YR 2-4	P VALUE*
	% of patients		
Decreased libido			0.002
Placebo	3.4†	2.6	
Finasteride	6.4	2.6	
Impotence			<0.001
Placebo	3.7†	5.1	
Finasteride	8.1	5.1	
Decreased ejaculate volume			<0.001
Placebo	0.8†	0.5‡	
Finasteride	3.7	1.5	
Ejaculation disorder			0.002
Placebo	0.1‡	0.1	
Finasteride	0.8	0.2	
Breast enlargement			0.03
Placebo	0.1§	1.1	
Finasteride	0.5	1.8	
Breast tenderness			0.03
Placebo	0.1	0.3	
Finasteride	0.4	0.7	
Rash			0.04
Placebo	0.2	0.1	
Finasteride	0.5	0.5	

*P values are for the comparison of the overall (four-year) incidence of each event between the groups.

†P<0.001 for the comparison with the finasteride group.

‡P=0.003 for the comparison with the finasteride group.

§P=0.04 for the comparison with the finasteride group.

for surgery has important public health and economic implications, since transurethral prostatectomy is the second most common operation in older men.¹⁷

Although many factors enter into a decision to operate on a man with benign prostatic hyperplasia, including the preferences of both the physician and the patient, the placebo-controlled design of this study precluded any bias in the choice of surgical therapy. Although this study was performed in the United States, the rate of surgery in the placebo group was similar to that in several worldwide placebo-controlled trials.¹¹ In addition, in a controlled trial of medical therapy, there may be a tendency to encourage patients to stay in the study. Therefore, rates of surgery in this study might be lower than the actual rates among similar patients in clinical practice. In fact, in a recent four-year cohort study of men with benign prostatic hyperplasia who were treated at five North American urology practices, 24 percent of patients with moderate symptoms and 39 percent of those with severe symptoms underwent surgery.⁴

Acute urinary retention is often considered the

most serious outcome of benign prostatic hyperplasia.¹⁸ In this study, 4 percent of the men in the placebo group had a spontaneous episode of acute urinary retention — a rate similar to the incidence in other U.S. and worldwide trials.^{7,11,19} The rate was 1 percent in the finasteride group. No other therapies have been reported to decrease the incidence of acute urinary retention in long-term studies. In a six-month placebo-controlled study of the α -adrenergic-antagonist drug alfuzosin in 518 men, 7 men in the placebo group and 1 in the alfuzosin group had acute urinary retention.²⁰ However, 31 percent of enrolled men who discontinued therapy prematurely were lost to follow-up. In a one-year study of 2084 men given terazosin, another α -adrenergic-antagonist drug, or placebo, the incidence of acute urinary retention was 1.3 percent in both groups.¹⁹

The reduction in the risk of spontaneous acute urinary retention is important in terms of reducing morbidity and also in terms of decreasing the number of men who need surgery. Acute urinary retention is a painful condition and may increase the morbidity of transurethral prostatectomy.²¹⁻²³

In several one- and two-year placebo-controlled trials, the administration of finasteride resulted in symptomatic improvement in men with prostatic enlargement and moderate-to-severe symptoms.^{8,10,14,24-26} Men with little or no enlargement of the prostate gland were less likely to have improvement.^{10,27} The present study confirms and extends these observations by demonstrating statistically significant and clinically meaningful improvements in symptom scores among men with enlarged prostate glands.

Our study could be criticized for the high rate of discontinuation of the study drugs. However, in the one-year study comparing terazosin with placebo, 38 percent of the men in the terazosin group and 46 percent of those in the placebo group discontinued therapy prematurely.¹⁶ In addition, in the four-year cohort study of men followed by North American urologists, complete data were not available for 26 percent of men.⁴ When viewed in this context, the discontinuation rate in the present four-year study is not surprising. Moreover, the intention-to-treat analysis included all events during the four-year period, including those that occurred in men who had stopped taking the study drug, with complete information available on outcomes for 92 percent of the men.

Another important caveat is that the enrollment criteria were moderate-to-severe symptoms and an enlarged prostate on digital rectal examination. Although some men with symptoms have enlargement of the prostate gland, many others have similar urinary symptoms but no such enlargement.²⁸ The decreased rates of surgery and acute urinary retention may not be generalizable to the men without prostatic enlargement.

In summary, among men with symptoms of urinary obstruction and prostatic enlargement, treatment with finasteride reduced the four-year risk of requiring surgery and of acute urinary retention. The benefit of finasteride was evident within four months after the initiation of treatment, and it continued throughout the four-year study period.

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APPENDIX

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