

SERUM PROSTATE-SPECIFIC ANTIGEN AND PROSTATE VOLUME PREDICT LONG-TERM CHANGES IN SYMPTOMS AND FLOW RATE: RESULTS OF A FOUR-YEAR, RANDOMIZED TRIAL COMPARING FINASTERIDE VERSUS PLACEBO

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ABSTRACT

Objectives. To determine whether baseline prostate-specific antigen (PSA), in addition to prostate volume, is associated with long-term changes in symptoms and urinary flow rate.

Methods. Three thousand forty men with benign prostatic hyperplasia enrolled in the PLESS trial were randomly assigned to **finasteride 5 mg or placebo for 4 years**. Symptoms and flow rate were assessed every 4 months, and data were analyzed by dividing the patients into three groups by baseline **PSA tertiles** (0 to 1.3, 1.4 to 3.2, and 3.3 ng/mL or greater) and baseline **prostate volume tertiles** (14 to 41, 42 to 57, and 58 to 150 mL).

Results. After the initial placebo effect, a **slow deterioration** in symptoms over time was observed in the placebo-treated men with a baseline **PSA 1.4 ng/mL or greater**. However, placebo-treated men in the lowest **PSA tertile (less than 1.4 ng/mL)** had sustained symptomatic improvement that was not seen in placebo-treated men in the higher tertiles ($P < 0.001$). In all finasteride-treated groups, there was initial improvement followed by maintenance or continued symptom improvement over time (**~3 to 3.5 points by the end of 4 years**). The differences in symptom score improvement between placebo and finasteride were marginal for men with baseline PSA levels less than 1.4 ng/mL ($P = 0.128$) but were highly significant for men with PSA levels 1.4 ng/mL or greater ($P < 0.001$). Urinary flow rate results were similar to those observed for symptoms. Analysis of symptom and flow rate data by prostate volume tertiles in a 10% subset of men yielded similar results, namely a deterioration of symptoms and flow rate in the two higher tertiles treated with placebo (greater than 41 mL) and a sustained improvement in all three groups of finasteride-treated patients.

Conclusions. Baseline PSA and prostate volume are good predictors of long-term symptomatic and flow rate changes. Baseline PSA levels of 1.4 ng/mL or greater and enlarged prostate glands predict the best long-term response to finasteride compared with placebo. UROLOGY 54: 662–669, 1999. © 1999, Elsevier Science Inc.

About one half of all patients with histologic evidence of benign prostatic hyperplasia (BPH) will ultimately develop symptoms suffi-

ciently severe to consider therapeutic intervention.¹ Disease severity is evaluated by administering standardized, quantitative symptom severity,

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* A complete list of the members of the PLESS Study Group is given in the Appendix.

From the University of Texas Southwestern Medical Center, Dallas, Texas; European Institute of Oncology, Milan, Italy; Tampa Bay Medical, Clearwater, Florida; Lovelace Medical Center, Albuquerque, New Mexico; South Florida Medical Research, Adventura, Florida; Piedmont Research Associates, Winston-Salem, North Carolina; Montefiore Medical Center, Bronx,

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frequency, and bother scores,² impact indices,³ and quality-of-life scores.⁴ Although less important to the patient, urinary flow rate recordings are also part of the evaluation in most cases.

In patients treated by watchful waiting, medical therapy, or surgery, progression or regression of the disease is monitored by re-administering the same quantitative symptom score and repeating the urinary flow rate recordings. In most clinical trials involving patients with lower urinary tract symptoms and BPH, quantitative symptom scores and urinary flow rate recordings are the primary efficacy end point parameters. In almost all placebo-controlled trials, an improvement from baseline is noted in both the placebo arm and the active intervention arm.⁵ Recently, this placebo effect was described as being due to a unilateral regression to the mean induced by the inclusion and exclusion criteria imposed at the beginning of the trial.⁶

The 5-alpha-reductase inhibitor finasteride (Proscar, Merck, West Point, Pa) acts by inhibiting the conversion of serum testosterone to dihydrotestosterone, leading to shrinkage of the prostate gland, together with a reduction in both symptom severity and risk of acute urinary retention (AUR) and BPH-related surgery. These treatment effects have been demonstrated in 1-year,⁷ 2-year,⁸⁻¹⁰ and 4-year¹¹ studies. In addition, a recent meta-analysis of all 1-year, randomized, placebo-controlled finasteride studies demonstrated that the efficacy of finasteride in comparison with placebo is dependent on baseline prostate volume.¹² The larger the prostate at baseline, the greater the chance for significant symptom and flow rate improvement in comparison with placebo. The critical cutpoints, at which there are significant improvements in comparison to placebo, appear to be at approximately 30 to 40 mL by transrectal ultrasound or magnetic resonance imaging (MRI). The objective of the present analysis was to determine whether long-term changes in symptoms and flow rate can also be predicted by baseline serum PSA and/or prostate volume, using data from the 4-year, randomized, placebo-controlled PLESS trial.¹¹

MATERIAL AND METHODS

Three thousand forty men with clinical BPH diagnosed on the basis of moderate to severe symptoms, a decreased peak urinary flow rate (less than 15 mL/s with a voided volume of 150 mL or more; Urodyn 1000, Dantec, Mahwah, NJ), and an enlarged prostate gland by digital rectal examination were enrolled in a 4-year study comparing finasteride with placebo.¹¹ Men receiving alpha-blocking agents or antiandrogens and men with a history of chronic prostatitis, recurrent urinary tract infections, prostate or bladder cancer or surgery, or with serum PSA levels greater than 10 ng/mL were excluded. Men with serum PSA levels between 4 and 9.9 ng/mL had to have a negative prostate biopsy before enrollment.¹³

The study was approved by the Institutional Review Boards

of all 95 participating centers, and all men gave written informed consent. After a 1-month, single-blind placebo lead-in, men were randomly assigned to receive placebo or 5 mg finasteride (Proscar) daily. Symptom score (quasi-American Urological Association Symptom Score), ranging from 0 to 34 points, adverse events, and urinary flow rates were assessed every 4 months.¹¹ Serum PSA was measured at baseline, every 4 months during the first year, and every 8 months thereafter at a central laboratory (Smith Kline Laboratories, King of Prussia, Pa) using the Hybritech assay. Physical examinations and routine hematologic and serum chemistry tests were performed yearly. MRI to determine prostate volume was performed at baseline and then yearly in a subset of 10% of participants at 13 centers. More detailed information on the study design has been previously published.^{11,13}

STATISTICAL ANALYSIS

The effect of baseline prostate volume and serum PSA levels on the changes in symptoms and flow rate over time were assessed by dividing patients into three groups on the basis of tertiles of baseline prostate volume and baseline serum PSA levels. Within-group comparisons between PSA tertiles and between-treatment-group comparisons were performed using analysis of variance with factors for treatment, study site, baseline PSA tertile category, and the interaction between treatment and PSA tertile category. Because of the small number of men with prostate volume imaging, assessment of the effect of baseline prostate volume on symptoms and flow rate was performed only with descriptive statistics. Since the goal of this analysis was to look at long-term effects of therapy, the data analysis reflects the data available at each time point throughout the study. Results using the intention-to-treat approach gave similar between-group differences (data not shown).

RESULTS

Baseline characteristics were similar for both treatment groups (Table 1). The median prostate volume in the subset of men with yearly MRIs was 49 and 46 mL in the placebo and finasteride groups, respectively. Prostate volume ranged from 14 to 41 mL in the lower tertile, 41.1 to 57 mL in the middle tertile, and from 58 to 150 mL in the upper tertile (except for 1 patient randomized to placebo with a baseline prostate volume of 222 mL). Although the prostate volume was obtained in only a subset of men, baseline serum PSA measurements were available for most patients. The breakpoint between the first and second PSA tertiles was 1.4 ng/mL and between the second and third tertiles was 3.3 ng/mL. The highest recorded baseline PSA was 12.0 (although patients had to have a screening PSA of 10 ng/mL or less, all baseline values for the study were obtained after the placebo run-in period, at the time of randomization, which occurred approximately 1 month after screening).

The differences in symptom score improvement between placebo and finasteride were marginal for men with PSA levels less than 1.4 ng/mL ($P = 0.128$) but were highly significant for men with PSA levels 1.4 ng/mL or greater ($P < 0.001$; Fig. 1A). Considerably fewer patients were available to assess symptom score response on the basis of

TABLE I. Baseline characteristics of men in the finasteride and placebo groups

| Parameter* | Placebo (n) | Finasteride (n) |
|--------------------------------------|------------------|------------------|
| Age (yr) | 64 ± 7 (1503) | 64 ± 6 (1513) |
| Quasi-AUA Symptom Score [†] | 15 ± 6 (1503) | 15 ± 6 (1513) |
| Peak flow rate (mL/s) | 11 ± 4 (1196) | 11 ± 4 (1208) |
| Prostate volume (mL) [‡] | 55 ± 26 (155) | 54 ± 25 (157) |
| First tertile (14–41) | 32.5 ± 6.3 (45) | 32.6 ± 6.0 (59) |
| Second tertile (42–57) | 48.9 ± 4.9 (60) | 47.8 ± 4.5 (44) |
| Third tertile (58–150) [§] | 81.4 ± 28.9 (50) | 82.3 ± 21.6 (54) |
| Serum PSA (ng/mL) | 2.8 ± 2.1 (1498) | 2.8 ± 2.1 (1512) |
| First tertile (0.2–1.3) | 0.86 ± 0.3 (511) | 0.83 ± 0.3 (472) |
| Second tertile (1.4–3.2) | 2.24 ± 0.6 (514) | 2.21 ± 0.6 (536) |
| Third tertile (3.3–12.0) | 5.36 ± 1.7 (473) | 5.39 ± 1.7 (504) |

KEY: AUA = American Urological Association; PSA = prostate-specific antigen.

Data are mean ± SD.

* None of the differences were significant.

[†] The Quasi-AUA symptom score is based on an adaptation of the American Urological Association symptom score.¹¹

[‡] Prostate volume was measured in approximately 10% of patients at 13 of the participating centers.

[§] One additional patient in the placebo group had a baseline prostate volume of 222 mL.

baseline prostate volume. However, the symptom score improvement broken down by prostate volume tertiles was similar to that obtained by PSA tertiles, with the greatest between-group differences seen in men in the upper tertiles (Fig. 1B).

Both treatment groups experienced an initial mean improvement in symptoms during the first year (Fig. 2A). The placebo response at 1 year was a decrease from baseline of approximately 1.5 to 2 points on the 0 to 34-point symptom score scale in all three PSA tertiles. However, the symptoms of placebo-treated men in the lowest PSA tertile (PSA less than 1.4 ng/mL) did not deteriorate during the next 3 years but showed maintenance of their initial improvement. These placebo-treated patients, with baseline PSA less than 1.4 ng/mL, had a significantly better long-term symptomatic improvement than placebo-treated men in the higher tertiles ($P < 0.001$). In placebo-treated patients in the highest two tertiles (with baseline PSA 1.4 ng/mL or greater), symptom scores deteriorated after the first year in both tertiles. There was no significant difference between responses in the highest two PSA tertiles of placebo-treated men ($P = 0.649$).

In all three tertiles of finasteride-treated patients, there was an initial improvement from baseline in symptom score of 2 to 2.5 points during the first year, with continued improvement over time, so that by the end of the 4-year study, the symptom score improvement, relative to placebo, was approximately 3 to 3.5 points (Fig. 2A). There were no significant differences in the mean symptom score improvement among finasteride-treated patients in the three PSA tertiles at the end of the study.

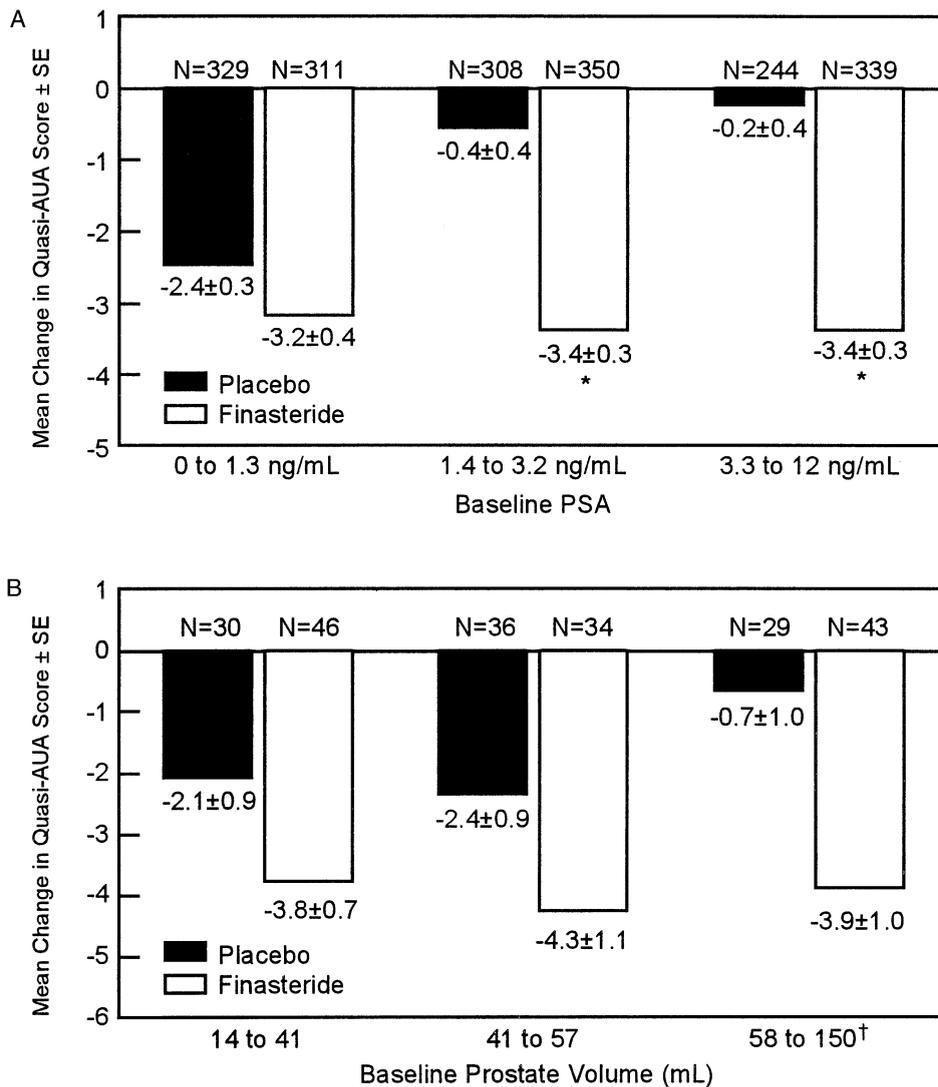
The difference between finasteride and placebo in the first PSA tertile was significantly less than

that seen in men in the second ($P = 0.004$) and third ($P = 0.001$) PSA tertiles because of the deterioration of symptoms in placebo-treated patients in the top two tertiles (PSA 1.4 ng/mL or greater). There were no significant differences in symptomatic response (finasteride versus placebo-treated patients) between the second and third PSA tertiles.

Because data were available on fewer patients with prostate volume assessments, tertile analyses and inferential statistical assessments of the tertiles could not be performed. Therefore, the results for symptom scores stratified by prostate volume are presented descriptively. The symptom score changes stratified by prostate volume tertiles were very similar to those seen in the PSA tertile analysis (Fig. 2B). The initial placebo response, depending on prostate volume, ranged from -1 to -3 points. During the course of 4 years, placebo-treated patients in the highest prostate volume tertile experienced a return to baseline of their symptoms; placebo-treated men with baseline prostate volumes in the lowest tertile maintained their symptomatic improvement over time. In contrast, the mean symptom scores for each of the finasteride-treated prostate volume tertiles demonstrated maintenance or continued improvement after the first year of the study and were similar across tertiles (Fig. 2B).

Overall, the flow rate response of placebo and finasteride-treated patients was somewhat more variable than that observed for symptom score (Fig. 3). Even so, at the end of the 4 years, the comparative flow rate responses were shown to be significantly different ($P < 0.001$) in both the upper two PSA tertiles in favor of finasteride.

In placebo-treated men with baseline PSA 1.4



* $p < 0.001$ versus placebo.

[†] One patient had a prostate volume of 222 mL.

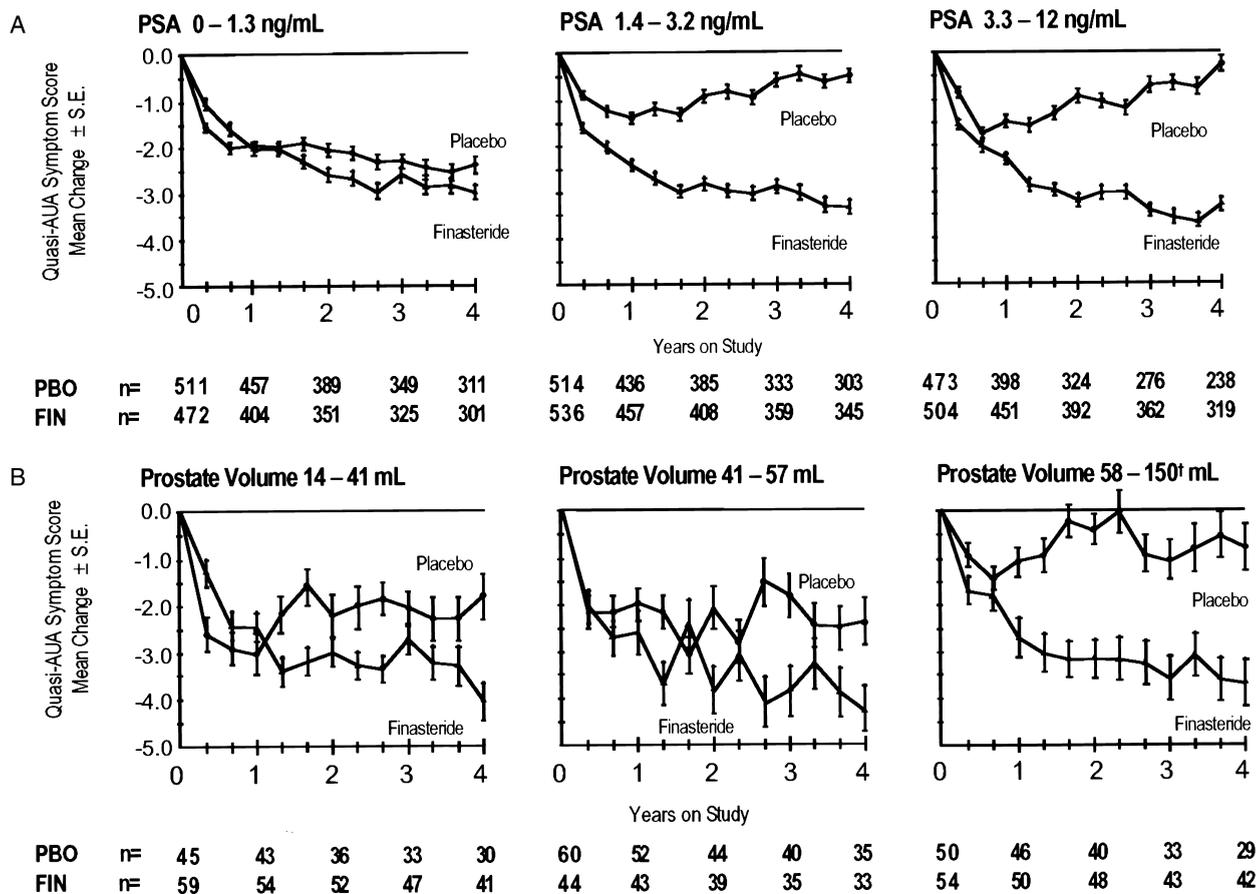
FIGURE 1. Symptom score responses at year 4 stratified by (A) baseline serum PSA and (B) baseline prostate volume tertiles in men who completed the study.

ng/mL or greater, there was an absence of improvement (upper two tertiles) and subsequent deterioration (upper tertile) of peak urinary flow rates (Fig. 3A). In contrast, the lowest PSA tertile placebo group had sustained improvement in maximum urinary flow rate throughout the 4-year study. At the end of 4 years, the flow rate response in placebo-treated men in the lowest PSA tertile was significantly different from that seen in placebo-treated men in the middle ($P = 0.01$) and highest ($P < 0.001$) tertiles.

In contrast, the peak urinary flow rate in finasteride-treated patients increased from approximately 1 to 1.3 mL/s at 1 year and continued to improve to a mean increase of +1.5 to +2.0 mL/s by the end of the study (Fig. 3A). Although finas-

teride-treated patients in the highest PSA tertile maintained the greatest improvement in peak urinary flow rate from baseline in comparison with placebo-treated patients throughout the study, there were no significant differences in flow rate response among the three finasteride-treated PSA tertiles.

Mean peak urinary flow rates stratified by prostate volume tertiles in placebo-treated patients exhibited a similar pattern to that seen with PSA tertiles (Fig. 3B), although there was considerable variability because of the small sample size. Initially, the placebo-treated patients in the lowest and middle tertiles demonstrated a peak flow rate improvement from 0.7 to 1.2 mL/s, which was maintained during the 4 years in the lowest volume



†One patient had a prostate volume of 222 mL

FIGURE 2. Symptom scores (mean \pm 95% confidence interval) stratified by (A) baseline serum PSA and (B) baseline prostate volume tertiles for patients randomized to placebo (PBO) and finasteride (FIN).

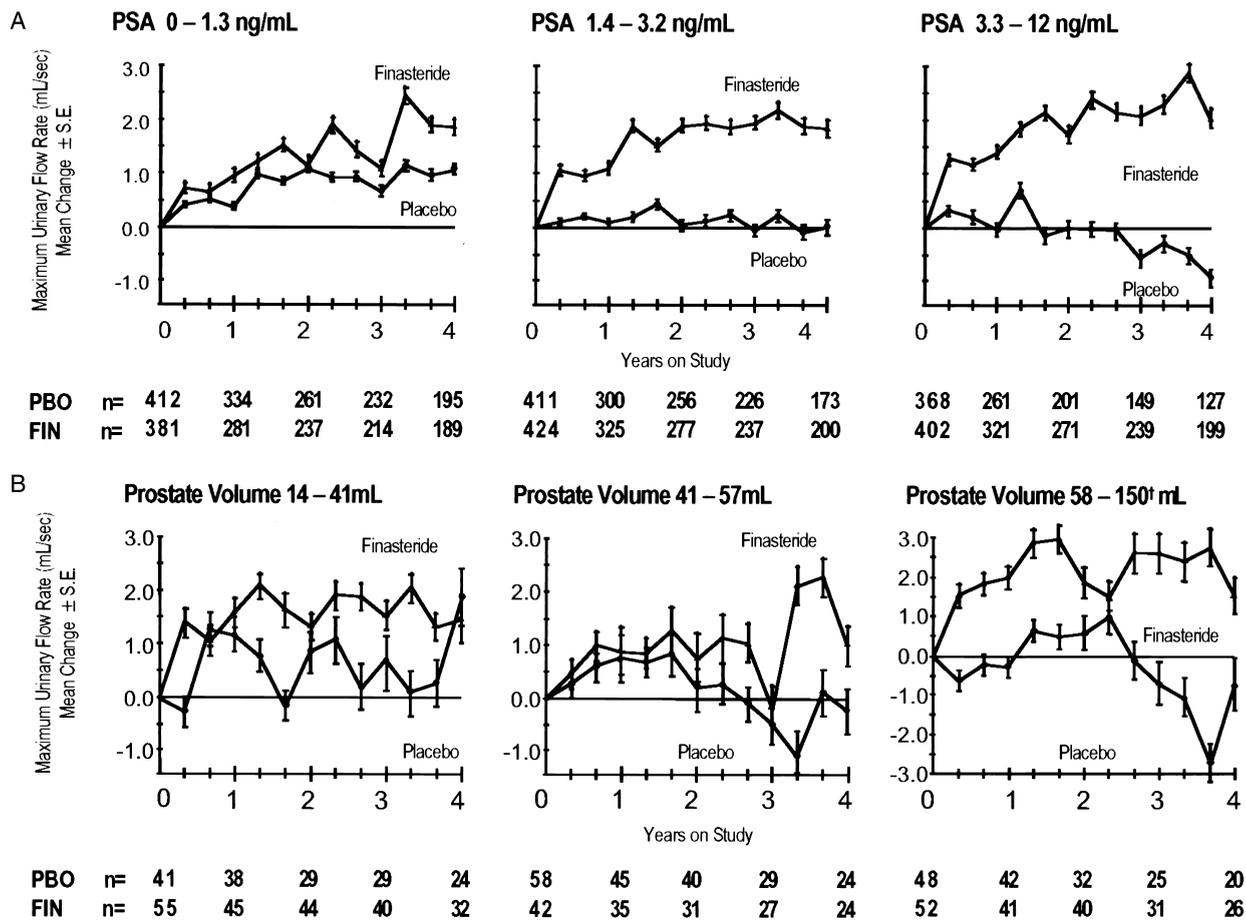
tertile. The mid-tertile placebo-treated patients experienced some deterioration, with quite a bit of variability toward the end of the study. Placebo-treated patients in the highest prostate volume tertile also experienced an overall decrease in peak urinary flow rate toward the end of the study. Among finasteride-treated patients, the most consistent improvement in maximum urinary flow rate occurred in men in the largest prostate volume tertile.

COMMENT

Symptom score improvements and to a lesser degree flow rate changes are paramount in the minds of physicians when initiating therapy for men with BPH. The present study clearly demonstrated that during 4 years, in a placebo-controlled setting, PSA, as well as prostate volume, were very strong predictors of long-term symptomatic and flow rate improvement with finasteride relative to placebo. Furthermore, this study also showed that among men without active treatment, only those in the higher prostate volume (prostate volume approxi-

mately greater than 40 mL) and PSA (PSA 1.4 ng/mL or greater) categories had progressive BPH, with slow deterioration (after an initial placebo response) of their symptoms and flow rates toward baseline or beyond during 4 years. The symptoms and flow rates of men with PSA levels less than 1.4 ng/mL and/or a small prostate gland did not deteriorate during 4 years and, in fact, had a sustained "placebo" response in terms of symptoms and flow rate.

Using the most commonly employed symptom severity scale, the American Urological Association Symptom Score, improvements of up to 6 points or more from baseline have been demonstrated in patients treated with long-acting α_1 -adrenergic receptor blockers in comparison to an approximately 3-point placebo response.^{14,15} Thus, the net improvement between alpha-blocker and placebo in many alpha-blocker trials is approximately 3 points on the 0 to 35-point scale. Barry *et al.*¹⁶ have demonstrated that such an improvement is consistent with the subjective perception of improvement by the patient response. In an evaluation of



†One patient had a prostate volume of 222 mL

FIGURE 3. Peak urinary flow rates (mean \pm 95% confidence interval) stratified by (A) baseline serum PSA and (B) baseline prostate volume tertiles for patients randomized to placebo (PBO) and finasteride (FIN).

all 1-year placebo-controlled finasteride data, the average improvement in symptom score for finasteride-treated patients was approximately 3 points compared with an improvement of approximately 1 point for placebo.¹¹ However, recently a great deal has been learned regarding “the right patient” for finasteride (ie, one with an enlarged prostate gland¹² or higher PSA level^{17,18}). It is now clear that only patients with a PSA of 1.4 ng/mL or greater (two-thirds of all patients in the PLESS study), which corresponds to an average prostate volume of approximately 40 mL¹⁹ in 70-year-old men with BPH, have the best long-term response to finasteride in comparison with placebo. In the present trial, patients with PSA 1.4 ng/mL or greater had a durable 3-point improvement in symptom score with long-term therapy. The difference between finasteride and placebo in these patients, with baseline PSA 1.4 ng/mL or greater, becomes more pronounced over time, as placebo-treated patients tend to lose the initial placebo effect and their symptom score deteriorates back to the baseline score.

At 1 year of follow-up in the present study, there

was similar symptom score improvement in the placebo and finasteride-treated patients in the lowest PSA tertile (0 to 1.3 ng/mL), who were likely to have small prostate glands. During the next 3 years, these same patients showed only minor differences in favor of finasteride. Thus, it is not surprising that 1-year trials enrolling a large number of patients with small prostate glands (and lower PSA levels) would be unlikely to show a benefit with finasteride compared with placebo.¹⁵ Similarly, the symptom score difference between placebo and finasteride in the second and third PSA tertiles (all men with PSA 1.4 ng/mL or greater) at 1 year was approximately 0.8 to 1 point. Following up these same patients for longer periods in the placebo-controlled setting, it is evident that after 2 years, the difference between placebo and finasteride increased even further and was statistically and clinically significant. These observations put into perspective the results of prior shorter trials in men with smaller prostate glands.¹⁵

On the basis of the findings of the present study, it is evident that with increasing PSA (and presumably prostate volume) and increasing time, the im-

provement with finasteride relative to placebo becomes greater, and the symptoms and flow rates of placebo-treated patients, particularly those with PSA levels 1.4 ng/mL or greater, deteriorate over time after the initial placebo effect. These data show that one of finasteride's greatest effects on symptoms is in arresting the progression of BPH in men with enlarged prostates and/or PSA 1.4 ng/mL or greater. Men with PSA levels less than 1.4 ng/mL do not have clinically progressive BPH and are unlikely to benefit from finasteride relative to placebo.

Serum PSA at baseline not only predicts deterioration of symptoms in untreated patients but also predicts improvement (relative to placebo) of symptoms and flow rate in finasteride-treated patients. Moreover, PSA has also been shown to be a powerful predictor of future prostate growth.²⁰ When patients in the PLESS study were stratified by PSA tertiles, there was little prostate growth observed during 4 years in men with PSA levels less than 1.4 ng/mL; in those with PSA 1.4 ng/mL or greater, there was progressive enlargement of the prostate gland over time (approximately 20% at 4 years).²⁰ It has also been recently demonstrated that PSA is a very good predictor of the future risk of developing AUR or the need for BPH-related surgery.¹⁸

The present data, combined with data on prostate growth,²⁰ illustrate that in men with higher PSA levels (1.4 ng/mL or greater), who presumably have larger prostate glands, there is a worsening of symptoms after an initial placebo effect, deterioration of peak flow rate, and progressive prostate enlargement that is distinctly different from the pattern observed in men with low (less than 1.4 ng/mL) PSA levels and presumably small prostate glands. Indeed, it appears that the cutpoint of PSA at 1.4 ng/mL in patients enrolled in the PLESS trial distinguishes between two different clinical entities: men with progressive growth of the prostate along with deteriorating symptoms, and men with bothersome but stable lower urinary tract symptoms and little prostate growth over time. The significance of this distinction in clinical entities becomes even more relevant when one considers that PSA also predicts the risk of developing AUR and the need for BPH-related surgery.¹⁸ Thus, that population of men with more "progressive" BPH (ie, those with rapidly growing prostate glands and worsening urinary symptoms and flow) is also the population at higher risk of developing AUR and needing surgery.

We recognize several limitations of the present trial, including that only 10% of the patients underwent accurate prostate size measurement by MRI. However, as prior analyses of large data sets have shown, average serum PSA is highly correlated with average prostate volume in men with

BPH.¹⁹ Thus, it was not surprising that, despite the smaller sample size of men stratified by prostate volume, the trends appear to be similar to those observed with the PSA-stratified data. Another important limitation of the study was that men were selected at entry based on the presence of BPH symptoms and an enlarged prostate by digital rectal examination. Thus, these data may not be directly applicable to other groups of men without symptoms or enlarged glands.

The present data set is unique in many respects. It analyzed symptoms and flow rate data in the largest and longest medical treatment study ever conducted in BPH. Furthermore, it allowed stratification of patients by baseline parameters that proved to be highly predictive of changes in both symptom severity and peak urinary flow rate. These data have importance for the clinical practice of urology. Data from the present study confirm that serum PSA may help predict future symptom severity and peak urinary flow rates, as well as prostate growth and the risk of developing AUR or needing surgery during a 4-year period in men with moderate to severe symptoms of BPH. Physicians should take comfort in the fact that patients with a PSA of less than 1.4 ng/mL are likely to have a relatively small prostate, have little chance of experiencing significant deterioration in symptoms and flow rate, and have a low risk of developing serious BPH-related outcomes, such as AUR or BPH-related surgery. In these patients, one might consider watchful waiting as a viable treatment option. However, patients with a PSA of 1.4 ng/mL or greater are more likely to have a larger prostate with progressive BPH (ie, increased prostate growth potential), increased risk of AUR and future surgery, and deteriorating symptoms and urinary flow rate over time. Thus, in these patients, one might consider counseling treatment. Although the initial symptomatic benefit can be achieved quickly with alpha-receptor blockade, long-term data show that therapy with finasteride is equally capable of improving symptoms and peak urinary flow rates. At the present time, only long-term therapy with finasteride has been shown to reduce the risk of developing AUR and the need for BPH-related surgery. A 7-year National Institutes of Health study (Medical Therapy of Prostatic Symptoms or MTOPS) using alpha-blockers, finasteride, and the combination of both is currently underway and likely to shed further light on the predictors of BPH progression and the long-term effects of treatment.

CONCLUSIONS

Long-term 4-year data from the placebo-controlled PLESS trial demonstrate that baseline PSA,

as well as prostate volume, is a good predictor of long-term symptomatic and flow rate changes. The symptoms and flow rates of placebo-treated men with baseline PSA levels less than 1.4 ng/mL and a small prostate gland are unlikely to deteriorate over time. However, among placebo-treated patients with baseline PSA levels of 1.4 ng/mL or greater, after an initial placebo response, symptoms slowly deteriorate over time. Men with a baseline PSA 1.4 ng/mL or greater have the best response to finasteride in comparison with placebo, with durable improvement that is maintained or continues to improve during 4 years.

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APPENDIX

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