ORIGINAL ARTICLE

# Effect of Dutasteride on the Risk of Prostate Cancer

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ABSTRACT

**BACKGROUND**

We conducted a study to determine whether dutasteride reduces the risk of incident prostate cancer, as detected on biopsy, among men who are at increased risk for the disease.

**METHODS**

In this 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, we compared dutasteride, at a dose of 0.5 mg daily, with placebo. Men were eligible for inclusion in the study if they were 50 to 75 years of age, had a prostate-specific antigen (PSA) level of 2.5 to 10.0 ng per milliliter, and had had one negative prostate biopsy (6 to 12 cores) within 6 months before enrollment. Subjects underwent a 10-core transrectal ultrasound-guided biopsy at 2 and 4 years.

**RESULTS**

Among 6729 men who underwent a biopsy or prostate surgery, cancer was detected in 659 of the 3305 men in the dutasteride group, as compared with 858 of the 3424 men in the placebo group, representing a relative risk reduction with dutasteride of 22.8% (95% confidence interval, 15.2 to 29.8) over the 4-year study period ($P<0.001$). Overall, in years 1 through 4, among the 6706 men who underwent a needle biopsy, there were 220 tumors with a Gleason score of 7 to 10 among 3299 men in the dutasteride group and 233 among 3407 men in the placebo group ($P=0.81$). During years 3 and 4, there were 12 tumors with a Gleason score of 8 to 10 in the dutasteride group, as compared with only 1 in the placebo group ($P=0.003$). Dutasteride therapy, as compared with placebo, resulted in a reduction in the rate of acute urinary retention (1.6% vs. 6.7%, a 77.3% relative reduction). The incidence of adverse events was similar to that in studies of dutasteride therapy for benign prostatic hyperplasia, except that in our study, as compared with previous studies, the relative incidence of the composite category of cardiac failure was higher in the dutasteride group than in the placebo group (0.7% [30 men] vs. 0.4% [16 men], $P=0.03$).

**CONCLUSIONS**

Over the course of the 4-year study period, dutasteride reduced the risk of incident prostate cancer detected on biopsy and improved the outcomes related to benign prostatic hyperplasia. (ClinicalTrials.gov number, NCT00056407.)

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*The principal investigators in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

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THE 5α-REDUCTASE INHIBITORS THAT ARE used to treat benign prostatic hyperplasia block the conversion of testosterone to dihydrotestosterone and may reduce the risk of prostate cancer.[1] The results of the Prostate Cancer Prevention Trial showed that finasteride, as compared with placebo, reduced the risk of prostate cancer by 25%, but among the tumors that were detected, there was a 27% increase in the number of those that had Gleason scores of 7 to 10.[2] (The Gleason score is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 being the most cytologically aggressive.) A subsequent analysis showed that the odds ratio for tumors with Gleason scores of 7 to 10 in the finasteride group decreased from 1.27 to 1.03 in a logistic model that included both baseline variables that are known to affect the risk of cancer and the post-baseline prostate volume.[3] Guidance on the use of 5α-reductase inhibitors to prevent prostate cancer has been published recently.[4]

There are two isoforms of 5α-reductase, type 1 and type 2. Expression of type 1 in the prostate is enhanced during the development of prostate cancer, whereas the expression of type 2 is decreased or unchanged.[5,6] Unlike finasteride, dutasteride inhibits both isoforms of 5α-reductase.[7] In this trial, we examined the effect of dutasteride on the incidence of prostate cancer detected on biopsy among men at increased risk for the disease.

## METHODS

### STUDY CONDUCT

Investigators at GlaxoSmithKline designed the study, in consultation with external consultants. The study protocol and analysis plan can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org. The investigators at GlaxoSmithKline had access to the data when the data were unblinded, and all the authors had access to the data approximately 2 weeks thereafter. Investigators at GlaxoSmithKline and members of the steering committee and the independent data and safety monitoring committee monitored the study and collected and analyzed the data. The steering committee was responsible for overseeing the conduct of the trial; the independent data and safety monitoring committee was responsible for ensuring patient safety and had access to unblinded data.

The first draft was written by one of the academic authors. All the coauthors, along with a consultant who was paid by GlaxoSmithKline for his help, contributed to subsequent versions, and the coauthors made the decision to submit the manuscript for publication. The first author vouches for the accuracy and completeness of the data and analyses. All authors who were not affiliated with GlaxoSmithKline signed confidentiality agreements with GlaxoSmithKline regarding the data in this trial; these agreements have remained in force pending publication of the data.

### PARTICIPANTS

The design of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study has been described previously.[8] We enrolled men who were considered to be at high risk for prostate cancer, on the basis of their age, an elevated prostate-specific antigen (PSA) level, and a previous suspicion of prostate cancer that led to a prostate biopsy. Men were eligible for the study if they were 50 to 75 years of age; had a serum PSA level of 2.5 to 10.0 ng per milliliter, in the case of men 50 to 60 years of age, or 3.0 to 10.0 ng per milliliter, in the case of men older than 60 years of age; and had undergone a single prostate biopsy (6 to 12 cores) within 6 months before enrollment. Men were excluded if they had undergone more than one biopsy; had prostate cancer of any grade, high-grade intraepithelial neoplasia, atypical small acinar proliferation, a history of prostate cancer, or a prostate volume greater than 80 ml; had undergone previous prostate surgery; or had an International Prostate Symptom Score of 25 or higher, or 20 or higher in the case of men taking alpha-blockers. The International Prostate Symptom Score assesses symptoms related to benign prostatic hyperplasia on a scale of 0 to 35, with 0 to 7 indicating mild symptoms; 8 to 20, moderate symptoms; and 21 to 35, severe symptoms. The protocol was approved by the institutional review board at each research site, and all participants provided written informed consent.

### STUDY DESIGN

We conducted a 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. After a 4-week placebo-based run-in period, eligible subjects were randomly assigned to re-



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ceive dutasteride at a dose of 0.5 mg daily or placebo; randomization was stratified according to center. Visits were scheduled every 6 months; the International Prostate Symptom Score and free and total serum PSA levels were measured at each visit. To maintain the blinded nature of the study, the PSA levels in the dutasteride-treated men were doubled, since dutasteride reduces PSA levels by a mean of about 50%, and then were randomly adjusted by 0.1 ng per milliliter so that the final reported values were equally even and odd.[8] Prostate volume was measured by ultrasonography at the time of randomization and 2 and 4 years later. Ten-core transrectal, ultrasound-guided biopsies were performed as part of the protocol at 2 and 4 years; biopsies were performed independently of the protocol when they were clinically indicated.

#### ASSESSMENT OF PROSTATE BIOPSIES

Baseline biopsies had been performed before the start of the study (and independently of the study) and were reread centrally (Bostwick Laboratories) to confirm that the results were negative. Biopsies that were performed as part of the study were also read centrally. The central pathology laboratory had no access to the randomization codes. Biopsies that were performed independently of the study protocol were processed and read locally, and representative slides were read centrally. All positive biopsies were reviewed by the author affiliated with Bostwick Laboratories, who remained unaware of the treatment assignments; the diagnosis and Gleason score that he recorded were the ones that were used in the study. During the first 2 years, a randomly chosen set of 200 biopsies (100 showing cancer and 100 showing no cancer) were reread by an outside expert pathologist; a predefined rate of disagreement on cancer diagnosis of less than 3% was considered to be acceptable. There were two cases (1%) in which the outside pathologist disagreed with the recorded diagnosis of cancer.

#### END POINTS

The primary end point was prostate cancer detected on biopsy after 2 or 4 years of treatment. A participant with prostate cancer detected on biopsy at 2 years was withdrawn from the study medication. Biopsies that were performed because of a clinical indication between months 19 and 24 and between months 43 and 48 were classified as per-protocol biopsies and replaced the protocol-mandated biopsies at years 2 and 4, respectively. Those that were performed between months 1 and 18 (360 biopsies) and between months 25 and 42 (450 biopsies) were classified as protocol-independent biopsies. Other end points related to the detection of prostate cancer on biopsy included the Gleason score, the tumor volume, the percent of the biopsy cores that were positive for prostate cancer, the percent of core involvement with cancer, and the presence of high-grade intraepithelial neoplasia or atypical small acinar proliferation (which are lesions that are associated with a higher incidence of cancer on repeat biopsy). End points related to benign prostatic hyperplasia included the International Prostate Symptom Score, the change in total prostate volume from baseline, and the proportions of men who received alpha-blocker therapy, had acute urinary retention, underwent surgery related to benign prostatic hyperplasia, or had a urinary tract infection.

#### STATISTICAL ANALYSIS

For the primary end point, two-sided P values of 0.01 or less were considered to indicate statistical significance in the assessment of the superiority of dutasteride over placebo. We estimated that with 8000 subjects, the study would have approximately 90% power to show a 20% reduction with dutasteride in the incidence of prostate cancer detected on biopsy (i.e., an estimated rate of 19.0% in the placebo group and 15.2% in the dutasteride group), at a two-sided alpha level of 0.01.

The efficacy population included all randomly assigned subjects who had a baseline prostate biopsy that was considered to be negative on central review and who received at least one dose of the assigned study medication. The safety population included all subjects who underwent randomization. Calculation of three rates of prostate cancer was planned: a restricted crude rate, which included men who had at least one biopsy after baseline; a crude rate, which included all men in the efficacy population; and a modified crude rate, which included men who had a positive result on biopsy and men who underwent the biopsy at the end of the study. All three rates are reported for the primary end point; for other end points, the restricted crude rate is reported. The statistical



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**Table 1. Baseline Characteristics of the Study Participants.***

| Characteristic | Total (N=8231) | Dutasteride (N=4105) | Placebo (N=4126) |
|---|---|---|---|
| Age — yr | | | |
| Mean | 62.8±6.06 | 62.8±6.04 | 62.7±6.08 |
| Range | 48–77 | 49–76 | 48–77 |
| Race or ethnic group — no. (%)† | | | |
| White | 7491 (91.0) | 3744 (91.2) | 3747 (90.8) |
| Black | 190 (2.3) | 91 (2.2) | 99 (2.4) |
| Asian | 134 (1.6) | 67 (1.6) | 67 (1.6) |
| American Hispanic | 333 (4.0) | 160 (3.9) | 173 (4.2) |
| Other | 82 (1.0) | 43 (1.0) | 39 (0.9) |
| Body-mass index‡ | 27.4±4.05 | 27.4±3.89 | 27.4±4.20 |
| Geographic region — no. (%) | | | |
| Europe | 4972 (60.4) | 2471 (60.2) | 2501 (60.6) |
| Canada, United States, and Puerto Rico | 2136 (26.0) | 1076 (26.2) | 1060 (25.7) |
| Other | 1123 (13.6) | 558 (13.6) | 565 (13.7) |
| Family history of prostate cancer — no. (%) | 1066 (13.0) | 546 (13.3) | 520 (12.6) |
| Prostate-specific antigen | | | |
| Total — ng/ml | 5.9±1.98 | 5.9±1.97 | 5.9±2.00 |
| Free — % | 16.7±6.21 | 16.7±6.32 | 16.7±6.11 |
| Prostate volume — ml | 45.7±18.49 | 45.7±18.20 | 45.7±18.78 |
| PSA density§ | 0.15±0.092 | 0.15±0.084 | 0.15±0.098 |
| Cores at baseline biopsy — no. | 8.8±2.46 | 8.8±2.48 | 8.8±2.44 |
| International Prostate Symptom Score¶ | 8.7±5.66 | 8.7±5.70 | 8.6±5.62 |

* Plus–minus values are means ±SD. Data are for the safety population (i.e., all subjects who underwent randomization).
† Race or ethnic group was self-reported. A total of 8% of the patients in the United States were black.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The prostate-specific antigen (PSA) density is the serum PSA level (in nanograms per milliliter) divided by the prostate volume (in milliliters).
¶ The International Prostate Symptom Score assesses symptoms related to benign prostatic hyperplasia on a scale of 0 to 35, with 0 to 7 indicating mild symptoms; 8 to 20, moderate symptoms; and 21 to 35, severe symptoms.

analysis of the primary end point was performed with the use of the Mantel–Cox test, stratified according to time period and predefined clusters of study sites.[9] The Mantel–Haenszel estimate of the relative risk of prostate cancer with dutasteride as compared with placebo for years 1 through 4 was calculated on the basis of the results from years 1 and 2 and from years 3 and 4. For all end points, statistical analyses were performed for years 1 and 2 and for years 1 through 4.

Prespecified subgroup analyses of prostate-cancer rates were performed according to baseline age (<65 or ≥65 years), body-mass index (grouped in thirds), self-reported race or ethnic group, family history of prostate cancer (negative or positive), International Prostate Symptom Score (<8 or ≥8), prostate volume (grouped in thirds), and PSA level (grouped in thirds). For each subgroup, analyses of the incidence of prostate cancer (with the use of the restricted crude rate) were planned, with relative risks and associated confidence intervals calculated for each subgroup with the use of Mantel–Haenszel estimates. P values for the frequencies of any biopsy (assessed in the efficacy population) and of adverse events (assessed in the safety population) were calculated with the use of Fisher's exact test. For the end points related to benign prostatic hyperplasia, log-rank tests of the time to the first episode of acute urinary retention, surgery related to be-



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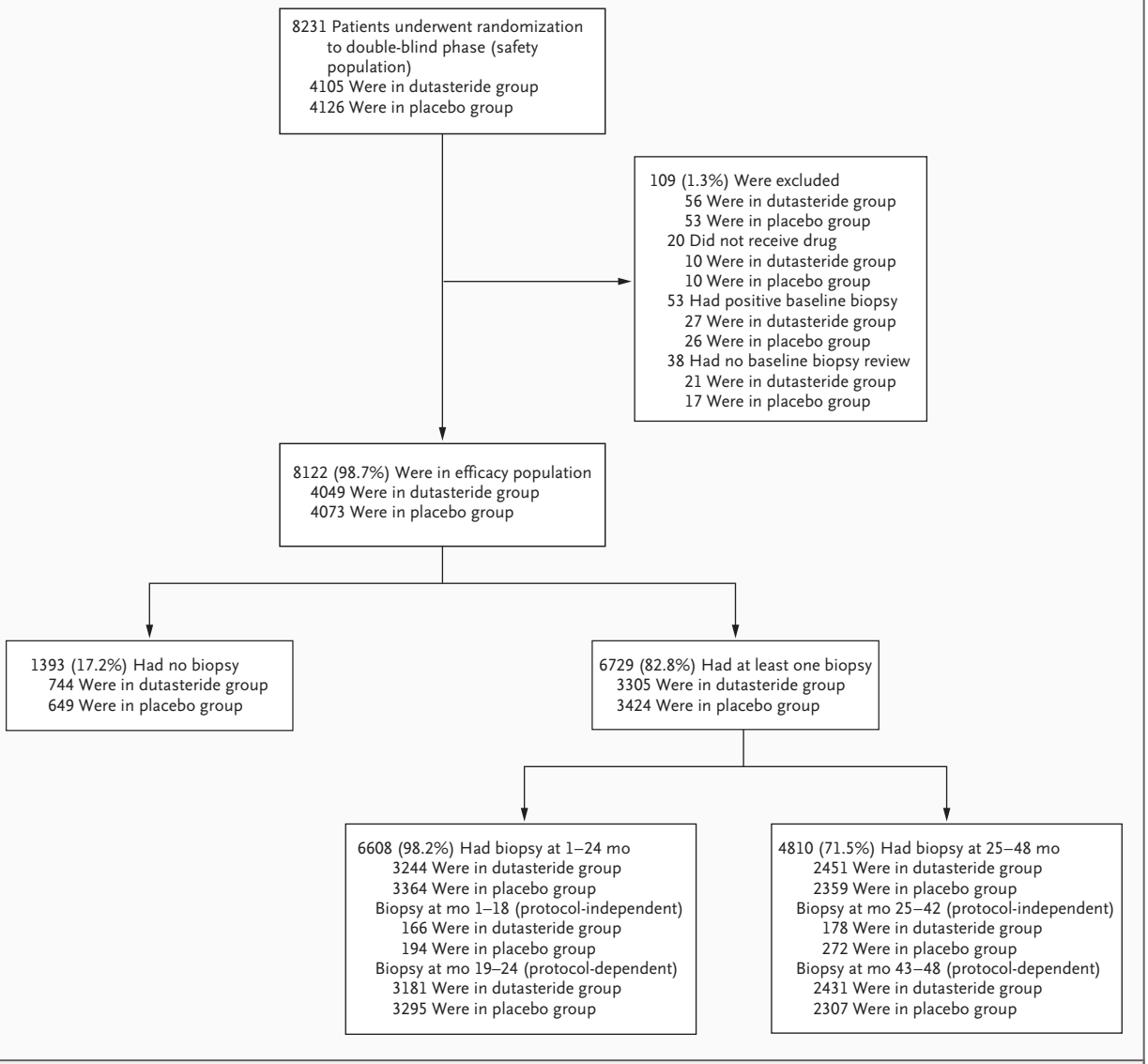


**Figure 1. Randomization and Numbers of Study Participants Who Underwent Biopsy.**
Participants could undergo a biopsy independently of the protocol, if it was clinically indicated, and subsequently undergo a per-protocol biopsy.

nign prostatic hyperplasia, and urinary tract infection were performed. The survival end point was analyzed with the use of the log-rank test.

To determine the effect of covariates on the primary end point, logistic models were fitted to the data relating the incidence of prostate cancer detected on biopsy (all tumors and tumors with Gleason scores of 7 to 10) to baseline covariates, and to baseline covariates with the addition of post-baseline prostate volume at the time of biopsy (see the Supplementary Appendix).

## RESULTS

### PARTICIPANTS

Table 1 provides a summary of the baseline characteristics of the participants. Of the 8231 men who underwent randomization (safety population), 109 (1.3%) did not undergo a baseline biopsy, had a positive or suspicious result on the baseline biopsy, or did not receive the study medication (Fig. 1). Of the remaining 8122 men, 81.6% of the men in the dutasteride group and 84.1% of



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the men in the placebo group underwent at least one post-baseline study biopsy (P=0.004); 96.9% of the biopsies were needle biopsies.

### PRIMARY END POINT

*Overall Population*

During the 4 years of the study, 659 of the 3305 men in the dutasteride group (19.9%) and 858 of the 3424 men in the placebo group (25.1%) received a diagnosis of prostate cancer, representing an absolute risk reduction with dutasteride of 5.1 percentage points. For the restricted crude rate of prostate cancer detected on biopsy, dutasteride was associated with a relative risk reduction of 22.8% (95% confidence interval [CI], 15.2 to 29.8; P<0.001). The risk reduction in years 1 and 2 was similar to that in years 3 and 4 (22.4% and 23.7%, respectively) (Fig. 2). For the crude rate and the modified crude rate of prostate cancer detected on biopsy over the 4-year study period, the risk reductions were 23.3% (95% CI, 15.6 to 30.3) and 23.1% (95% CI, 15.5 to 30.0), respectively (P<0.001 for both comparisons). Of the protocol-independent biopsies, 16.6% in the dutasteride group and 16.7% in the placebo group showed tumors, of which 7.1% of the tumors in the dutasteride group and 5.6% of those in the placebo group had a Gleason score of 7 to 10.

*Prespecified Subgroups*

The risks of prostate cancer detected on biopsy were significantly lower with dutasteride across all prespecified major subgroups, including subgroups according to age (<65 or ≥65 years), family history of prostate cancer (negative or positive), baseline PSA in thirds (<4.9, 4.9 to <6.8, or ≥6.8 ng per milliliter), baseline prostate volume in thirds (<36.6, 36.6 to <51.8, or ≥51.8 ml), baseline International Prostate Symptom Score (<8 or ≥8), and body-mass index (the weight in kilograms divided by the square of the height in meters) in thirds (<25.5, 25.5 to <28.4, or ≥28.4) (Table 2).

### PATHOLOGICAL END POINTS

*Gleason Scores*

Table 3 shows the numbers and proportions of men with prostate cancer according to Gleason score, treatment period, and study group. Over the 4 years of the study, there were 437 tumors with Gleason scores of 5 to 6 in the dutasteride group and 617 in the placebo group (P<0.001), and such tumors accounted for 70% of the total

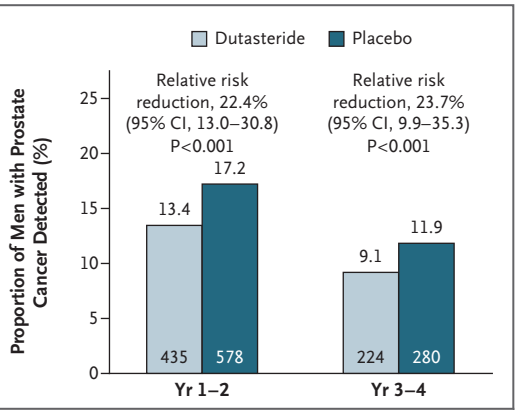


**Figure 2. Proportions of Men with a Positive Biopsy for Prostate Cancer, According to Treatment Period and Group.**

Data are shown for the efficacy population (i.e., all randomly assigned subjects with a baseline prostate biopsy that had been reviewed centrally and determined to be negative and who received at least one dose of study medication). Restricted crude rates of prostate cancer are shown (i.e., from analysis that included men who underwent at least one biopsy after baseline). The P value is for the comparison of dutasteride with placebo, with the use of the Mantel–Cox test. The numbers in the bars are numbers of men.

number of cancers. The number of tumors with Gleason scores of 7 to 10 did not differ significantly between the dutasteride group and the placebo group (220 and 233, respectively; P=0.81). There were 29 tumors with Gleason scores of 8 to 10 in the dutasteride group and 19 in the placebo group (P=0.15). Although the numbers of tumors with Gleason scores of 8 to 10 were similar in the two groups during years 1 and 2 (17 and 18 in the dutasteride and placebo groups, respectively), during years 3 and 4, there were 12 tumors with Gleason scores of 8 to 10 in the dutasteride group, as compared with only 1 in the placebo group (P=0.003).

*Biopsy Results*

Among the subjects with biopsy specimens that showed cancer, the two study groups were similar with respect to the mean number of positive cores (1.8 in the dutasteride group and 1.9 in the placebo group), percentage of cores with cancer (12.2% and 13.4%, respectively), and tumor volume (0.0022 ml and 0.0024 ml, respectively). These features were also similar between the two groups for tumors with Gleason scores of 7 to 10 (number of positive cores, 2.5 in both groups;



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**Table 2. Incidence of Prostate Cancer and Relative Risk Reduction over the Course of the 4-Year Study Period, According to Baseline Subgroups.***

| Baseline Subgroup | Incidence of Prostate Cancer | | Relative Risk Reduction with Dutasteride† |
|---|---|---|---|
| | Dutasteride | Placebo | |
| | *no./total no. (%)* | | *% (95% CI)* |
| Age | | | |
| <65 yr | 342/1953 (17.5) | 462/2053 (22.5) | 24.1 (13.5–33.4) |
| ≥65 yr | 317/1352 (23.4) | 396/1371 (28.9) | 22.1 (10.8–32.0) |
| Family history of prostate cancer | | | |
| Yes | 105/448 (23.4) | 141/437 (32.3) | 31.4 (12.3–46.2) |
| No | 554/2853 (19.4) | 717/2987 (24.0) | 21.7 (13.2–29.4) |
| International Prostate Symptom Score‡ | | | |
| <8 | 328/1586 (20.7) | 429/1666 (25.8) | 21.1 (9.7–30.9) |
| ≥8 | 306/1643 (18.6) | 407/1688 (24.1) | 26.1 (15.0–35.6) |
| Prostate volume | | | |
| <36.6 ml | 268/1065 (25.2) | 350/1121 (31.2) | 20.5 (8.0–31.2) |
| 36.6 to <51.8 ml | 214/1093 (19.6) | 250/1133 (22.1) | 16.1 (0.4–29.3) |
| ≥51.8 ml | 169/1097 (15.4) | 244/1112 (21.9) | 32.0 (18.1–43.5) |
| PSA level | | | |
| <4.9 ng/ml | 194/1095 (17.7) | 259/1173 (22.1) | 22.7 (7.7–35.2) |
| 4.9 to <6.8 ng/ml | 239/1121 (21.3) | 308/1138 (27.1) | 23.5 (10.7–34.6) |
| ≥6.8 ng/ml | 225/1086 (20.7) | 290/1105 (26.2) | 23.2 (9.8–34.6) |
| Body-mass index | | | |
| <25.5 | 218/1097 (19.9) | 297/1153 (25.8) | 24.3 (11.0–35.6) |
| 25.5 to <28.4 | 215/1077 (20.0) | 278/1102 (25.2) | 23.7 (10.0–35.4) |
| ≥28.4 | 215/1082 (19.9) | 267/1119 (23.9) | 18.9 (4.1–31.5) |

* Data are shown for the efficacy population (i.e., all randomly assigned subjects who had a baseline prostate biopsy that had been reviewed centrally and determined to be negative and who had received at least one dose of study medication). The rates of prostate cancer are restricted crude rates, which include men who underwent at least one biopsy after baseline. PSA denotes prostate-specific antigen.

† The relative risk reduction was calculated with the use of Mantel–Haenszel estimates.

‡ The International Prostate Symptom Score assesses symptoms related to benign prostatic hyperplasia on a scale of 0 to 35, with 0 to 7 indicating mild symptoms; 8 to 20, moderate symptoms; and 21 to 35, severe symptoms.

percentage of cores with cancer, 20.6% in the dutasteride group and 22.7% in the placebo group), and tumor volume (0.0043 and 0.0049 ml, respectively).

### *High-Grade Intraepithelial Neoplasia and Atypical Small Acinar Proliferation*

The men in the dutasteride group had lower rates of high-grade intraepithelial neoplasia (without atypical small acinar proliferation or prostate cancer) than did the men in the placebo group (3.7% vs. 6.0%; relative risk reduction with dutasteride, 39.2%; 95% CI, 24.2 to 51.1; P<0.001); they also had lower rates of atypical small acinar proliferation (without prostate cancer and with or without high-grade intraepithelial neoplasia) than did the men in the placebo group (3.8% vs. 4.9%; relative risk reduction, 21.2%; 95% CI, 1.3 to 37.1; P=0.04).

## END POINTS RELATED TO BENIGN PROSTATIC HYPERPLASIA

In the placebo group, the mean (±SE) prostate volume increased from 45.8±0.30 ml at baseline to 52.3±0.40 ml at year 2 (a mean increase of 13.0%) and to 56.2±0.44 ml at year 4 (a mean



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**Table 3. Detection of Prostate Cancer on Biopsy, According to Gleason Score, Treatment Period, and Treatment Group.***

| Gleason Grade and Score | Years 1 and 2 | | | Years 3 and 4 | | | Years 1 through 4 | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dutasteride (N=3239) | Placebo (N=3346) | P Value† | Dutasteride (N=2447) | Placebo (N=2343) | P Value† | Dutasteride (N=3299) | Placebo (N=3407) | P Value† |
| | *no. (%)* | | | *no. (%)* | | | *no. (%)* | | |
| All tumors | 434 (13.4) | 576 (17.2) | | 223 (9.1) | 274 (11.7) | | 657 (19.9) | 850 (24.9) | |
| Grade 5 or 6 | 290 (9.0) | 401 (12.0) | <0.001 | 147 (6.0) | 216 (9.2) | <0.001 | 437 (13.2) | 617 (18.1) | <0.001 |
| 5 | 1 (<0.1) | 3 (0.1) | | 0 | 1 (<0.1) | | 1 (<0.1) | 4 (0.1) | |
| 6 | 289 (8.9) | 398 (11.9) | | 147 (6.0) | 215 (9.2) | | 436 (13.2) | 613 (18.0) | |
| Grades 7–10 | 144 (4.4) | 175 (5.2) | 0.15 | 76 (3.1) | 58 (2.5) | 0.19 | 220 (6.7) | 233 (6.8) | 0.81 |
| 7‡ | 127 (3.9) | 157 (4.7) | | 64 (2.6) | 57 (2.4) | | 191 (5.8) | 214 (6.3) | |
| 3+4 | 99 (3.1) | 125 (3.7) | | 47 (1.9) | 51 (2.2) | | 146 (4.4) | 176 (5.2) | |
| 4+3 | 28 (0.9) | 32 (1.0) | | 17 (0.7) | 6 (0.3) | | 45 (1.4) | 38 (1.1) | |
| 8–10 | 17 (0.5) | 18 (0.5) | 1.00 | 12 (0.5) | 1 (<0.1) | 0.003 | 29 (0.9) | 19 (0.6) | 0.15 |
| 8 | 7 (0.2) | 11 (0.3) | | 5 (0.2) | 0 | | 12 (0.4) | 11 (0.3) | |
| 9 | 10 (0.3) | 7 (0.2) | | 6 (0.2) | 1 (<0.1) | | 16 (0.5) | 8 (0.2) | |
| 10 | 0 | 0 | | 1 (<0.1) | 0 | | 1 (<0.1) | 0 | |

* The Gleason score is the sum of the two most common histologic patterns or grades in a prostate tumor, each of which is graded on a scale of 1 to 5, with 5 being the most cytologically aggressive.
† P values were calculated with the use of Fisher's exact test (unstratified analysis).
‡ Prostate cancers that comprise both Gleason pattern 3 and Gleason pattern 4 are classified as 3+4 if pattern 3 predominates and 4+3 if pattern 4 predominates.

overall increase of 19.7%). In the dutasteride group, the mean prostate volume decreased from 45.7±0.28 ml at baseline to 38.6±0.31 ml at year 2 (a mean decrease of 17.4%) and to 39.0±0.32 ml at year 4 (a mean overall decrease of 17.5%). The difference in the prostate volume between the groups was significant at each time point (P<0.001). Dutasteride significantly reduced the risk of acute urinary retention, the need for surgery related to benign prostatic hyperplasia, and urinary tract infection (Fig. 3). The men in the dutasteride group who had moderate or severe baseline symptoms of benign prostatic hyperplasia, as indicated by an International Prostate Symptom Score of 12 or higher, had a greater mean reduction in the score than did the men with similar symptoms in the placebo group (reduction of 3.9 points vs. 1.3 points), despite the fact that more men in the placebo group than in the dutasteride group were receiving an alpha-blocker (18.9% vs. 12.7%, P<0.001).

### OVERALL SURVIVAL

A total of 70 men in the dutasteride group (1.7%) and 77 men in the placebo group (1.9%) died during the course of the study (P=0.65). No deaths were attributed to prostate cancer (see the Supplementary Appendix).

### SAFETY AND SIDE EFFECTS

Table 4 provides a summary of adverse events, as reported by the investigators. The nature and frequency of common adverse events with dutasteride were similar to those reported in previous studies of dutasteride therapy for men with benign prostatic hyperplasia. A drug-related decrease in libido was reported by 3.3% of the men in the dutasteride group, as compared with 1.6% of the men in the placebo group (P<0.001), and a loss of libido was reported by 1.9% of the men in the dutasteride group, as compared with 1.3% of the men in the placebo group (P=0.03). A drug-related decrease in or loss of erectile function was reported in 9.0% of the men in the dutasteride group and in 5.7% of the men in the placebo group (P<0.001). There was an unexpected imbalance in a composite event termed "cardiac failure," which included conditions such as congestive heart failure, cardiac failure, acute cardiac failure, ventricular failure, cardiopulmonary failure, and congestive cardiomyopathy. Although there was no significant difference between the



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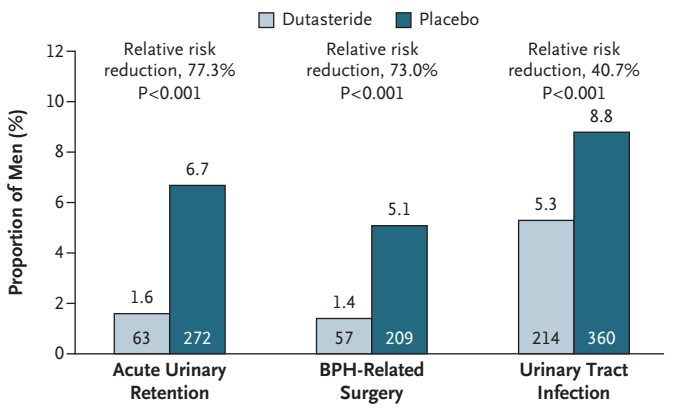


**Figure 3. Proportions of Men Who Had an Episode of Acute Urinary Retention, Who Underwent Surgery Related to Benign Prostatic Hyperplasia (BPH), or Who Had a Urinary Tract Infection over the Course of the 4-Year Study Period.**
The P values are for the comparison of dutasteride with placebo, with the use of the log-rank test. The numbers in the bars are numbers of men.

**Table 4. Incidence of Adverse Events.***

| Event | Dutasteride (N=4105) | Placebo (N=4126) | P Value† |
|---|---|---|---|
| | *no. (%)* | | |
| Any adverse event | 3017 (73.5) | 2966 (71.9) | 0.10 |
| Any serious adverse event | 748 (18.2) | 837 (20.3) | 0.02 |
| Drug-related adverse event | | | |
| Any | 904 (22.0) | 604 (14.6) | <0.001 |
| Leading to permanent discontinuation of treatment | 176 (4.3) | 83 (2.0) | <0.001 |
| Occurring in ≥1% of subjects in either study group | | | |
| Decreased libido | 137 (3.3) | 65 (1.6) | <0.001 |
| Loss of libido | 79 (1.9) | 54 (1.3) | 0.03 |
| Erectile dysfunction | 369 (9.0) | 237 (5.7) | <0.001 |
| Decreased semen volume‡ | 56 (1.4) | 9 (0.2) | <0.001 |
| Gynecomastia | 76 (1.9) | 43 (1.0) | 0.002 |
| Death§ | 70 (1.7) | 77 (1.9) | 0.65 |

* Data are shown for the safety population (i.e., all subjects who underwent randomization).
† P values are for the comparison of dutasteride with placebo, with the use of Fisher's exact test.
‡ Decreased semen volume was self-reported.
§ The analysis of deaths was performed with the use of the log-rank test.

two groups in the overall incidence of cardiovascular events or deaths from cardiovascular events, there was a higher incidence of the composite event of cardiac failure in the dutasteride group than in the placebo group (0.7% [30 of 4105 men] vs. 0.4% [16 of 4126 men], P=0.03; relative risk estimate, 1.91; 95% CI, 1.04 to 3.50).

## DISCUSSION

We found that the dual 5α-reductase inhibitor dutasteride reduced the incidence of prostate cancer detected on biopsy among men who had an increased risk of prostate cancer. This reduction in the incidence of prostate cancer was observed mainly among men who had tumors with Gleason scores of 5 to 6.

It is likely that most tumors that were diagnosed during the trial were present at the time of randomization but had not been detected in the baseline biopsy, performed before the study. Modeling data from the Prostate Cancer Prevention Trial[10] and an analysis of prostate-biopsy specimens from men treated with dutasteride for 4 months before surgery[11] support the hypothesis that the major effect of dutasteride is the shrinkage of prostate tumors or inhibition of their growth.

During the first 2 years of the trial, there were 141 more tumors with a Gleason score of 5 to 7 in the placebo group than in the dutasteride group (558 among 3346 participants vs. 417 among 3239 participants); the number of tumors with a Gleason score of 8 to 10 was similar in the two groups (18 and 17, respectively). During years 3 and 4, however, only 1 tumor with a Gleason score of 8 to 10 was detected among the 2343 men in the placebo group, whereas 12 such cancers were found among the 2447 men in the dutasteride group (P=0.003). We speculate that if the men in the placebo group who had the 141 excess tumors with a Gleason score of 5 to 7 detected during years 1 and 2 had remained in the study (i.e., if they had not been withdrawn as the trial required), a proportion of the cancers might have been upgraded on biopsy during years 3 and 4 to higher-grade tumors, thus narrowing the difference between the two groups in the number of tumors with a Gleason score of 8 to 10 in years 3 and 4. Supporting this speculation is a study involving 105 men who had prostate tumors with Gleason scores of 7 or lower and who were being followed without treatment ("active surveillance"); a repeat biopsy after a median follow-up period of 22 months showed that in 8 of the men (7.6%) the tumor was upgraded to a Gleason



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score of 8 to 10.[12] An alternative explanation, which is also consistent with our data, is that the difference in the number of cancers with a Gleason score of 8 to 10 was due in part to dutasteride therapy.

The detection of prostate cancer in a biopsy specimen is a function of tumor volume, prostate volume, and the number of cores in the sample.[10] Serfling et al. predicted an 11 to 17% increase in biopsy-detected cancer among men treated with dutasteride, as compared with men receiving placebo, assuming that dutasteride did not reduce tumor volume and reduced prostate volume by 25%.[10] In our study, the between-group difference in the mean percent change from baseline in prostate volume was 30.4±0.79% at year 2 and 37.1±0.93% at year 4 ($P<0.001$). The reduction in prostate volume with dutasteride, along with the increase in prostate volume with placebo, could have caused an increase in the number of biopsy-detected prostate cancers among men in the dutasteride group, but the actual result was a 23% relative reduction in prostate cancer, a finding that supports a mechanism of tumor shrinkage with dutasteride. Other biases may enhance the detection of prostate cancer among men who are being treated with 5$\alpha$-reductase inhibitors, including an improvement in the sensitivity of PSA tests and of digital rectal examination.[13,14] By requiring a baseline biopsy and biopsies after 2 and 4 years, the design of the REDUCE trial minimized the proportion of study participants who underwent protocol-independent biopsies (≤7%) and minimized biases that could have caused between-group differences in the rate of protocol-independent biopsies.

Biases could explain the relative risk of 1.27 (95% CI, 1.07 to 1.50) for tumors with Gleason scores of 7 to 10 in the finasteride group of the Prostate Cancer Prevention Trial,[2,13,14] and models that account for volume and PSA-driven biases have suggested that there may be reductions of 12 to 27% in the incidence of tumors with Gleason scores of 7 to 10 with finasteride.[2,15-18] In our trial, there was no significant increase in the dutasteride group, as compared with the placebo group, in the incidence of tumors with Gleason scores of 7 to 10 over the 4 years of the trial, both before and after adjustment for possible confounding variables (Table 3, and the Supplementary Appendix).

In addition to a reduction in the risk of prostate cancer, the risk of the progression of benign prostatic hyperplasia was reduced with dutasteride. The risks of acute urinary retention and of benign prostatic hyperplasia requiring surgery were reduced with dutasteride therapy by 77.3% and 73.0%, respectively, and the risk of urinary tract infection was reduced by 40.7%. These effects should be balanced against adverse events related to sexual function that were observed in a minority of men receiving dutasteride, typically in the early months of therapy, with such events decreasing in the longer term.[19] There was also an increased incidence of cardiac failure in men treated with dutasteride. The rate of discontinuation of the study drug owing to drug-related adverse events was less than 5%.

In conclusion, among men at increased risk for prostate cancer and for benign prostatic hyperplasia, dutasteride reduced the risk of prostate cancers and precursor lesions and improved many outcomes related to benign prostatic hyperplasia. Dutasteride may be considered as a treatment option for men who are at increased risk for prostate cancer.

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