Efficacy and Safety of Dutasteride on Prostate Cancer Risk Reduction in Asian Men: The Results from the REDUCE Study

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Objective: A post hoc analysis of Asian men in the REDUCE study was conducted to investigate whether the outcomes were in line with those of the overall population.

Methods: REDUCE was a 4-year international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Inclusion criteria were men between 50 and 75 years of age, a serum prostate-specific antigen level of 2.5–10.0 ng/ml (50–60 years) or 3.0–10.0 ng/ml (>60 years), and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment. The primary endpoint was biopsy-detectable prostate cancer. This post hoc analysis included subjects who were recorded as Asian.

Results: A total of 134 Asians, including 57 Japanese, were randomized to the study treatment. During the study period, the incidence of prostate cancer in the placebo and dutasteride groups was 19.6% (11/56) and 9.3% (5/54), respectively (relative risk reduction, 54%; 95% confidence intervals, 22 to 83%, P = 0.12), in the Asian subpopulation. Fewer tumors with the Gleason scores of 7–10 and 8–10 were detected among dutasteride-treated men. Although the incidences of drug-related sexual adverse events were higher in the dutasteride group, only in rare occasions did they lead to drug discontinuation.

Conclusions: The incidence of prostate cancer in the dutasteride group was lower than that in the placebo group, although the difference was not significant. These results paralleled those for the overall population and support the value of dutasteride for prostate cancer risk reduction in Asian men with an increased risk of prostate cancer.

Key words: prostate cancer – REDUCE – dutasteride – Asian – Japanese

INTRODUCTION

Prostate cancer is the second most common cancer in men and the third most common cause of male cancer death worldwide (1). It is well known that the incidence of prostate cancer varies worldwide, with higher rates found in North America and Europe, whereas lower rates are observed in Asia (1). African-Americans have the highest incidence, which is ~2.6 times higher than that of Asian Americans (2). Lower prostate cancer rates in Asian countries and among Asian races may be associated not only with genetic susceptibility but also with the lifestyle and environmental factors. Recently, in Asian countries, a trend toward an increased incidence and mortality of prostate cancer has been observed because of globalization of lifestyle, dietary and environmental factors (3).

Because of its high incidence, high mortality and long latency period from histological lesions to clinical disease,
strategies to reduce the risk of prostate cancer represent a reasonable and promising approach (4,5). To date, only 5-alpha-reductase (5AR) inhibitors have shown a significant prostate cancer risk reduction in appropriately powered and prospective randomized clinical trials. The Prostate Cancer Prevention Trial (PCPT) showed that finasteride, a type-2 5AR inhibitor, reduced the risk of prostate cancer by 24.8%, but with a significantly higher incidence of high-grade tumor in the finasteride group compared with the placebo group (6). Several factors have been suggested as possible explanations for the increase in high-grade tumors observed in the finasteride group, such as a decreased prostate volume (7–9), an increased prostate-specific antigen (PSA) sensitivity for cancer detection (10) and a selective inhibition of low-grade tumors (11). It is now generally accepted that finasteride does not cause high-grade disease or histopathological changes mimicking high-grade disease (11), and American Urological Association/American Society of Clinical Oncology guidelines concluded that 5AR inhibitors may be beneficial mainly based on the PCPT results (12).

Dutasteride inhibits both type-1 and type-2 isofoms of 5AR and almost completely suppresses intraprostatic dihydrotestosterone (13). Type-1 5AR is overexpressed in human prostate cancer tissue compared with benign prostatic tissue, and its expression is greater in more aggressive cancer (14). In Phase III benign prostatic hyperplasia (BPH) trials, the incidence of prostate cancer reported as an adverse event (AE) was reduced by ~50% in the dutasteride group versus the placebo group at 27 months (1.2 and 2.5%, P = 0.002) (15). On the basis of these findings, the REduction by DUtasteride of prostate Cancer Events (REDUCE) study was initiated and demonstrated that dutasteride significantly reduced the risk of biopsy-detectable prostate cancer by ~23%, without a significant increase in tumors with the Gleason scores of 7–10 or 8–10 (16). Because both the PCPT and the REDUCE studies included a predominantly Caucasian population, similarly as for many other randomized clinical trials, lack of published data on Asian populations still remains an issue. Considering the recent increasing incidence and mortality of prostate cancer observed in Asian countries (1), evaluating the effect of dutasteride on prostate cancer risk reduction therapies among Asian men is of relevance. The aim of this post hoc analysis was to determine whether the results of Asian subjects were in line with those of the overall REDUCE study population.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

The study design and population of the REDUCE study have previously been reported (17). This study was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with 42 participating countries including Japan. Men considered to be at high risk of prostate cancer were enrolled. Inclusion criteria were men between 50 and 75 years of age, a serum PSA level of 2.5–10.0 ng/ml (50–60 years) or 3.0–10.0 ng/ml (>60 years), and a single, negative prostate biopsy (6–12 cores) within 6 months before enrollment. Men with more than one prostate biopsy, the presence of high-grade prostate intraepithelial neoplasia (HG-PIN) or atypical small acinar proliferation (ASAP) in the baseline biopsy, history of prostate cancer, prostate volume >80 ml; or International Prostate Symptom Score of 25 or higher, or 20 or higher in the case of men taking α-blockers were excluded from the study. The REDUCE protocol was approved by Institutional Review Boards at each study site. The study was conducted in accordance with the Helsinki Declaration, and all participants signed informed consent forms.

After a 4-week placebo-based run-in period, eligible subjects were randomized to receive dutasteride 0.5 mg or placebo once daily for 4 years. Ten-core transrectal ultrasound-guided ‘protocol-dependent’ biopsies were conducted at 2 and 4 years. The investigator was allowed to perform ‘protocol-independent’ (for-cause) biopsies whenever clinically necessary. Baseline biopsies before enrollment (obtained independently of the study), protocol-mandated biopsies and for-cause biopsies were reviewed centrally (Bostwick Laboratories, Richmond, VA, USA). All positive biopsies were also reviewed centrally to confirm the diagnosis and the Gleason score.

STUDY ENDPOINTS

The primary endpoint was biopsy-detectable prostate cancer at years 2 and 4. For-cause biopsies conducted between months 19 and 24 and between months 43 and 48 were used. For-cause biopsies conducted between months 1 and 18 were used. Biopsies between months 19 and 24 and between months 43 and 48 counted as protocol-mandated biopsies at years 2 and 4, respectively. Biopsies between months 1 and 18 and between months 25 and 42 were considered ‘protocol-independent’ biopsies. Key secondary endpoints included the Gleason score, amount of cancer and occurrence of HG-PIN and ASAP.

STATISTICAL ANALYSIS

The efficacy population consisted of subjects who received the study medication at least once and had had a negative biopsy before the study. The safety population included all randomized subjects. The results of these post hoc analyses included subjects who were recorded as Asian by self-report. Statistical analysis for the primary endpoint was performed using the Mantel-Cox test stratified by the time period. The Mantel-Haenszel estimate of the relative risk and associated confidence intervals (CIs) were calculated. In this post hoc analysis, a restricted crude rate approach (men with at least one post-baseline biopsy) was used. For the secondary
endpoints and safety variables, summary statistics were calculated.

RESULTS

SUBJECT DEMOGRAPHICS AND DISPOSITION

Subject demographics and disposition are shown in Table 1 and Fig. 1. A total of 134 Asian men enrolled in Argentina, Australia, Brazil, Canada, Germany, Japan, Mexico, the Netherlands, New Zealand, Slovenia, South Africa, the UK and the USA were randomized into a double-blind phase. Of these, 57 were Japanese men enrolled at the sites in Japan. The efficacy population consisted of 133 (99%) Asian subjects, of which 56 (98%) were Japanese. A total of 110 (83%) Asians including 52 (93%) Japanese men underwent at least one biopsy during the double-blind phase.

The baseline characteristics were consistent with those of a population considered to be at an increased risk of prostate cancer based on an elevated PSA. Asian and Japanese baseline characteristics—age, family history of prostate cancer and PSA—were generally similar to those of the overall REDUCE study population, but their prostate volume was slightly lower.

PRIMARY ENDPOINT

Over the 4-year study period, the incidence of biopsy-detectable prostate cancer in the placebo and dutasteride groups was 19.6% (11/56) and 9.3% (5/54), respectively (relative risk reduction, 54%; 95% CI, 227 to 83%, P = 0.12), in the Asian subpopulation. Among Japanese, the incidence was 21.4% (6/28) in the placebo group and 8.3% (2/24) in the dutasteride group (relative risk reduction, 62%; 95% CI, 275 to 92%, P = 0.20). Similar risk reduction was observed in years 1–2 and years 3–4 in both Asian and Japanese men (Fig. 2). Only 1 out of the 16 biopsy-detected prostate cancers was diagnosed in a protocol-independent biopsy.

PATHOLOGIC ENDPOINTS

GLEASON SCORES

The Gleason score distributions are shown in Table 2. In the Asian subpopulation, there were seven (12.5%) and three (5.6%) tumors with the Gleason scores of 5–6 in the placebo and dutasteride groups, respectively. The number of tumors with the Gleason scores of 5–6 was two (7.1%) in the placebo group and one (4.2%) in the dutasteride group in Japanese subjects. Compared with the placebo group, a numerically smaller number of tumors with the Gleason scores of 7–10 were observed in the dutasteride group. Regarding the Gleason score 8–10 tumors, one case in the placebo group was identified (Gleason score 8), whereas no case was observed in the dutasteride group.

BIOSY CANCER MEASUREMENTS

In the Asian subpopulation, the mean number of positive cores, percentage of cores with cancer and tumor volume for the placebo and dutasteride groups, respectively, were 1.8 and 1.6, 17.2 and 16.4%, and 0.00222 and 0.00287 ml. In the Japanese subjects, these were 2.2 and 1.5, 11.6 and 10.0%, and 0.00221 and 0.00216 ml, respectively.

HIGH-GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA AND ATYPICAL SMALL ACINAR PROLIFERATION

In the Asian subpopulation, the rates of HG-PIN (without ASAP or prostate cancer) and ASAP (without prostate cancer) were 16.5% and 8.5%, respectively. In the Japanese subjects, these were 13.9% and 8.5%, respectively.

Table 1. Baseline demographics and patient characteristics (safety population)

<table>
<thead>
<tr>
<th></th>
<th>Total population (n = 8231)</th>
<th>Asian (n = 134)</th>
<th>Japanese (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8 ± 6.06</td>
<td>62.6 ± 6.73</td>
<td>64.3 ± 5.91</td>
</tr>
<tr>
<td>Range</td>
<td>48–77</td>
<td>50–75</td>
<td>51–74</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 ± 4.05</td>
<td>25.3 ± 3.24</td>
<td>25.3 ± 3.19</td>
</tr>
<tr>
<td>Family history of prostate cancer, no. (%)</td>
<td>1066 (13)</td>
<td>6 (9)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Total PSA (ng/ml)</td>
<td>5.9 ± 1.98</td>
<td>5.8 ± 2.06</td>
<td>5.6 ± 1.97</td>
</tr>
<tr>
<td>Free PSA (%)</td>
<td>16.7 ± 6.21</td>
<td>16.5 ± 5.03</td>
<td>16.3 ± 4.94</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>45.7 ± 18.49</td>
<td>38.5 ± 13.76</td>
<td>35.4 ± 11.53</td>
</tr>
<tr>
<td>PSA density (ng/ml/ml)</td>
<td>0.15 ± 0.092</td>
<td>0.16 ± 0.076</td>
<td>0.17 ± 0.083</td>
</tr>
<tr>
<td>Cores at baseline biopsy (no.)</td>
<td>8.8 ± 2.46</td>
<td>9.0 ± 2.20</td>
<td>8.6 ± 2.25</td>
</tr>
<tr>
<td>International Prostate Symptom Score</td>
<td>8.7 ± 5.66</td>
<td>9.9 ± 5.84</td>
<td>9.3 ± 5.88</td>
</tr>
</tbody>
</table>

Plus–minus values are means ± standard deviation. PSA, prostate-specific antigen.
cancer; with or without HG-PIN) were numerically lower in the dutasteride group compared with the placebo group (9 and 7%, and 7 and 2%, respectively). Among the Japanese subjects, these rates were 4 and 0%, and 7 and 4%.

**Prostate Cancer Stage and Overall Survival**

The majority of biopsy-detected prostate cancers were T1 or T2. One T3a case was reported in the placebo group. There were no cases of metastatic disease. No deaths were reported in the Asian subjects.

**Safety and Tolerability**

A summary of AEs is presented in Table 3. Overall, slightly higher rates of AEs, drug-related AEs and serious AEs were observed with dutasteride among the Asian and Japanese subjects; however, the majority of AEs were mild or

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**Figure 1.** Subject disposition in the Asian subpopulation. Subjects were allowed to undergo a protocol-independent biopsy and have a subsequent protocol-dependent biopsy. The numbers of Asian and Japanese subjects are shown on the left and right, respectively, e.g. 'Randomized: n = 134 (n = 57)' means the number of Asian subjects was 134, and of those, 57 were Japanese.

**Figure 2.** Proportions of men with a biopsy-detectable prostate cancer by the treatment period and the treatment group in the efficacy population. The occurrence of biopsy-detectable prostate cancer was calculated by using a restricted crude rate approach (men with at least one post-baseline biopsy). The numbers in and under the bars are the numbers of subjects. CI, confidence interval; NE, not estimable.

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| Figure 1. | Figure 2. |
among the Asian subpopulation. Among the 134 Asian subjects and the overall population. Similar PSA numbers and proportions of men with prostate cancer by the Gleason score and treatment in the biopsied population.

<table>
<thead>
<tr>
<th>Gleason grade and score</th>
<th>Asian (years 1–4)</th>
<th>Japanese (years 1–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 56)</td>
<td>Dutasteride (n = 54)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 28)</td>
<td>Dutasteride (n = 24)</td>
</tr>
<tr>
<td>All tumors</td>
<td>11 (19.6%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>7 (12.5%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>5–6</td>
<td>7 (12.5%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>7</td>
<td>3 (5.4%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>7: 3 + 4</td>
<td>3 (5.4%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>7: 4 + 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1 (1.8%)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7–10</td>
<td>4 (7.1%)</td>
<td>2 (3.7%)</td>
</tr>
<tr>
<td>8–10</td>
<td>1 (1.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

The Gleason score is the sum of the two most common histological patterns or grades (each graded 1–5, with 5 being the most cytologically aggressive) in a prostate cancer.

moderate in intensity and on rare occasions led to drug discontinuation. Sexual AEs (erectile dysfunction and loss of libido) were the most common drug-related AEs in both treatment groups, with higher rates observed in the dutasteride group.

**DISCUSSION**

We report here the results of the Asian subjects participating in the REDUCE trial. In the overall REDUCE study population, dutasteride reduced the risk of prostate cancer by 23% over the 4-year study period ($P < 0.001$) (16). The relative risk reduction with dutasteride was consistent across the predefined subgroups, such as baseline age, PSA, prostate volume and family history. Similar trends in prostate cancer risk reduction were observed with less prostate cancer detected in dutasteride-treated men compared with placebo-treated men in the Asian subgroup. Among the 134 Asian men, 57 (43%) subjects were residents of Japan, and the remaining 77 (57%) subjects were residents of non-Asian countries. The incidence of prostate cancer in the dutasteride group was also lower than that in the placebo group among Japanese subjects. In the overall REDUCE study population, $\approx 70\%$ of the prostate cancers detected were tumors with the Gleason scores of 5–6, and dutasteride significantly reduced the risk of low-grade cancer, with no significant increase in tumors with the Gleason scores of 7–10 or 8–10 ($P = 0.81$ and 0.15, respectively) (16). Among the Asian subpopulation, tumors with the Gleason scores of 5–6 accounted for the majority of tumors, and less prostate cancers were detected in the dutasteride group across all the Gleason score categories. Although fewer tumors with the Gleason scores of 7–10 or 8–10 were seen in the dutasteride group in the post hoc analysis, the number of tumors in the Asian subpopulation was too small to draw any conclusions regarding the difference in high-grade tumors between Asians and the overall REDUCE population.

No new safety issue with dutasteride treatment was identified during the 4-year treatment period among Asian men, and the safety and tolerability results of these subpopulations were consistent with those of the overall population. Most common dutasteride-related AEs were of sexual nature, such as erectile dysfunction and loss of libido; however, on rare occasions they led to drug discontinuation. In the overall population, an unexpected imbalance in a composite term of cardiac failure was observed (16); however, no cardiac failure events were reported in the Asian subpopulation. The safety and tolerability profile of dutasteride in this Asian population at an increased risk of prostate cancer was also consistent with that observed in Asian BPH populations (18,19).

Although this study was not designed to compare the differences between the Asian subpopulation and the overall population, baseline characteristics of the Asian subjects were generally similar to those observed in the overall REDUCE study populations, except for a slightly lower prostate volume in Asian men. This observation is consistent with previous reports that compared prostate volume between Caucasian and Japanese men (20–22). On the other hand, baseline PSA was similar between the Asian subjects and the overall population. Similar PSA
levels with lower prostate volume have been reported in Asian men compared with Caucasians (23,24), including a recent Asian subanalysis of the CombAT BPH study (18). The prostate cancer incidence in the placebo-treated men during the 4-year period in the Asian and Japanese subjects (19.6 and 21.4%, respectively) approached that of the overall population (25.1%), although slightly lower rates of biopsy-detectable prostate cancer were observed in both Asian and Japanese men. This observation may be caused by study population because we enrolled subjects who had an elevated PSA in the study. This is consistent with the previous report, suggesting that the risk of developing prostate cancer is generally similar between Japanese men and European men who had the same baseline PSA levels (25).

This post hoc analysis has several limitations. First, the REDUCE study was not designed for treatment comparisons among the Asian subpopulations, and second, the treatment outcomes are based on a limited number of Asian participants. However, risk reduction with dutasteride among Asian men was consistent with the trends observed for the overall population.

In the USA, most men diagnosed with prostate cancer having low-risk features will receive aggressive treatment (26–28). Although in Japan, primary androgen deprivation therapy is the most commonly provided treatment for men with low-stage prostate cancer, similar trends of potential overtreatment have also been reported (29). Thus, reducing the number of indolent prostate cancer diagnoses, and as a consequence reducing the number of cancer interventions, is an important strategy for the Asian region as well.

Risk reduction by dutasteride could be considered as a treatment option for Asian men at an increased risk of prostate cancer.

In conclusion, in the REDUCE study, the results of the Asian subpopulations were in line with those of the overall population. In Asian subjects, the incidence of prostate cancer in dutasteride-treated men was lower than that of placebo-treated men. Fewer high-grade tumors were diagnosed in the dutasteride group among Asian subjects. Dutasteride safety and tolerability profile in Asian subjects was consistent with that seen in the overall REDUCE study population and in previous dutasteride studies in Asian BPH populations. No new safety issue emerged throughout the 4-year treatment. These results support the value of dutasteride for prostate cancer risk reduction in Asian men at an increased risk of prostate cancer.

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Conflict of interest statement

Hideyuki Akaza received consulting or advisory fees from GlaxoSmithKline. Taiji Tsukamoto, Naoya Masumori and Hideki Sakai received lecture fees from GlaxoSmithKline. Yukihiro Endo and Takayoshi Yamanouchi are employees of GlaxoSmithKline.

References


