The Effect of Dutasteride on the Usefulness of Prostate Specific Antigen for the Diagnosis of High Grade and Clinically Relevant Prostate Cancer in Men With a Previous Negative Biopsy: Results From the REDUCE Study

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Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor
AUC = area under the curve
NPV = negative predictive value
PPV = positive predictive value
PSA = prostate specific antigen
REDUCE = REduction by DUtasteride of prostate Cancer Events
ROC = receiver operating characteristic

Purpose: We assessed whether dutasteride enhances the usefulness of total prostate specific antigen for diagnosing clinically significant prostate cancer. 

Materials and Methods: The 4-year REDUCE study evaluated the efficacy and safety of 0.5 mg dutasteride daily for prostate cancer risk reduction in men with a prostate specific antigen of 2.5 to 10.0 ng/ml and a negative prostate biopsy. Specificity, sensitivity, and positive and negative predictive values of prostate specific antigen for the diagnosis of prostate cancer were assessed.

Results: Final prostate specific antigen before biopsy and change from month 6 to final prostate specific antigen performed better for the diagnosis of Gleason score 7–10 tumors in men who received dutasteride vs placebo as assessed by the area under the ROC curves (0.700 vs 0.650, p = 0.0491; and 0.699 vs 0.593, p = 0.0001, respectively). Increases in prostate specific antigen were associated with a higher likelihood of biopsy detectable, Gleason score 7–10 and clinically significant (modified Epstein criteria) prostate cancer. Percentage decreases in prostate specific antigen from baseline to month 6 in the dutasteride arm did not predict prostate cancer overall or Gleason score 7–10 cancer.

Conclusions: In men with a previously negative prostate biopsy, prostate specific antigen performed better during the 4-year study as a marker of prostate cancer in men who received dutasteride vs placebo. The degree of prostate specific antigen increase after 6 months was a better indicator of clinically significant cancer in the dutasteride arm than in the placebo arm. Conversely, the initial decrease in prostate specific antigen in men taking dutasteride did not predict the likelihood of prostate cancer.

Key Words: prostatic neoplasms, dutasteride, prostate-specific antigen, sensitivity and specificity
Serum PSA remains the most widely validated marker of prostate cancer risk.1 Widespread implementation of PSA screening has led to the diagnosis of many low volume, low grade cancers that are less likely to cause harm had they not been diagnosed.2 The primary observation of the REDUCE study was that treatment with the dual 5ARI dutasteride resulted in a 23% relative risk reduction in biopsy detectable prostate cancer in men with an increased PSA (2.5 ng/ml or greater) and negative prostate biopsy before study entry.3 In the REDUCE study PSA driven unscheduled (for-cause) biopsies were uncommon, allowing for an unbiased assessment of the usefulness of serum PSA measurements for the diagnosis of prostate cancer. Dutasteride may enhance the usefulness of PSA for the diagnosis of clinically significant prostate cancer by suppressing PSA synthesis from benign prostate tissue and cancer in which growth is controlled by dutasteride, allowing subsequent PSA changes to better reflect the biology of dutasteride resistant cancer. Conversely, it has been argued that 5ARIs may mask the diagnosis of prostate cancer by suppressing PSA synthesis.4 These analyses from the REDUCE study were designed to address both hypotheses.

MATERIALS AND METHODS

Study Population

The design of the REDUCE study has been reported.5 Eligible men were 50 to 75 years old with a serum PSA of 2.5 to 10 ng/ml if 50 to 60 years old, or 3 to 10 ng/ml if older than 60 years, and a single, negative prostate biopsy (6 to 12 cores) within 6 months before enrollment (independent of the study).

Study Design

The REDUCE study was a 4-year, multicenter, double-blind, placebo controlled study.5 Eligible subjects were randomized to 0.5 mg dutasteride daily or placebo. Visits occurred every 6 months. Total serum PSA (Beckman Coulter Inc.) was assessed every 6 months, with doubled PSA values (±0.1 ng/ml in half of the subjects) reported to investigators for men receiving dutasteride.5 Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Subjects underwent 10-core transrectal ultrasound guided biopsy at 2 and 4 years (protocol dependent biopsies), and unscheduled biopsies were performed if clinically indicated (protocol independent biopsies). For cause biopsies obtained during months 19 to 24 and 43 to 48 replaced those scheduled for years 2 and 4, and were included in the definition of protocol dependent biopsies.

Statistical Analyses

Analyses were conducted of men who had undergone at least 1 biopsy (biopsied population). To compare various PSA constructs to predict prostate cancer, AUC values from ROC curves were calculated for baseline PSA, final PSA and change in PSA from month 6 to final PSA (by treatment group). Final PSA was defined as the last PSA value recorded before prostate cancer diagnosis and for men without prostate cancer it was the last PSA value before the final cancer assessment biopsy. PSA measurements made on the same date as the biopsy (or up to 42 days afterward) were excluded from analysis. Actual PSA values for dutasteride and placebo were used in this analysis.

The value of PSA and PSA dynamics during the first 2 years were examined. However, 68.6% (4,044 of 5,899) of month 24 PSA measurements were done on the day or after the date of biopsy and, thus, were excluded from study. Month 6 PSA was defined as the nadir for the purposes of these analyses. Differences between AUC values were examined using the z-test. Sensitivity, specificity, PPV and NPV for prostate cancer detection were analyzed by treatment group, by threshold values for PSA and baseline PSA constructs to predict prostate cancer, AUC values for dutasteride and placebo were used in this analysis.

RESULTS

Study Population and Baseline Characteristics

Demographics of the biopsied population in this study are similar to those of the overall REDUCE study population.6 Of 8,122 men in the efficacy population 3,305 (81.6%) in the dutasteride group and 3,424 (84.1%) in the placebo group underwent at least 1 prostate biopsy during the study (p = 0.004).

For the biopsied population prostate cancer was detected in 659 men (19.9%) in the dutasteride group and 858 (25.1%) in the placebo group (p < 0.0001). Gleason 7–10 cancer was detected in 220 men (6.7%) in the dutasteride group and 233 (6.8%) in the placebo group (p = 0.81). Most prostate cancer was diagnosed from protocol dependent biopsies, with 41
of 659 (6.2%) in the dutasteride group and 57 of 858 (6.6%) in the placebo group diagnosed from protocol independent biopsies. All AUC analyses were repeated with the protocol independent biopsies removed and there were no meaningful differences in the results.

Changes in PSA from Baseline by Prostate Cancer Status
After 6 months of dutasteride treatment PSA was reduced by a mean of 46.9% in men ultimately found to have no cancer, 45.4% in men with Gleason score 5–6 cancer and 46.3% in men found to have Gleason score 7–10 cancer. Reductions were similar for median values and at the extremes of PSA suppression. Thereafter, in both treatment arms mean PSA was highest in men eventually diagnosed with Gleason score 7–10 (high grade) cancer, and similar in men eventually found to have low grade or no cancer (see figure).

AUC Comparisons
Baseline PSA was a poor predictor of the future diagnosis of any prostate cancer (AUC 0.530 for placebo vs 0.514 for dutasteride, \( p = 0.42 \)) or Gleason score 7–10 prostate cancer (AUC 0.543 for placebo vs 0.552 for dutasteride, \( p = 0.79 \), table 1). Final PSA was also a relatively poor predictor of cancer of any Gleason score and a better predictor of Gleason score 7–10 cancer in both treatment arms, with significantly higher AUC values in the dutasteride vs placebo group (any Gleason score, \( p = 0.0020 \); Gleason score 7–10, \( p = 0.0491 \)).

In men on placebo the change in PSA from month 6 to final PSA was a relatively poor predictor of cancers of any Gleason score and Gleason score 7–10, and was a worse predictor than the final PSA. The AUCs for the change in PSA from month 6 in men treated with dutasteride were significantly greater than those for men on placebo (any Gleason score, \( p < 0.0001 \); Gleason score 7–10, \( p = 0.0001 \)), and of a magnitude similar to those for final PSA (table 1). AUCs during the first 2 years of study were also calculated. However, of the 24-month PSAs 68.5% (2,032 of 2,967) in the placebo group and 68.6% (2,012 of 2,932) in the dutasteride group were done on the same day or after the year 2 biopsy and, thus, the final PSA for most year 2 biopsies was the month 18 PSA. AUCs for final PSA during years 1 to 2 were similar in the placebo and dutasteride groups for overall prostate cancer (AUC 0.615 vs 0.614, \( p = 0.94 \)) and Gleason score 7–10 prostate cancer (AUC 0.696 vs 0.704, \( p = 0.79 \)), respectively. AUCs for the change in PSA from month 6 to final PSA during years 1 to 2 were also similar between the placebo and dutasteride groups for overall prostate cancer (0.581 vs 0.612, \( p = 0.12 \)) and Gleason score 7–10 prostate cancer (0.654 vs 0.675, \( p = 0.53 \)), respectively.

Analysis of Sensitivity, Specificity, PPV and NPV
The optimal balance (highest combined values) of sensitivity and specificity for final PSA for Gleason score 7–10 tumors was 2.0 to 3.0 ng/ml in the dutasteride group and 6.0 to 7.0 ng/ml in the placebo group (table 2). For the change in PSA from month 6 to final PSA in men treated with dutasteride the lowest increase of 0.1 ng/ml resulted in the optimal balance. In men treated with placebo the optimal balance was seen at an increase of approximately 1.0 ng/ml. Although sensitivity at this cutoff was greater than that in men treated with dutasteride, the specificity was substantially lower. In addition, PPV and NPV were lower at the optimal placebo cutoff compared with the optimal cutoff value for dutasteride.

Tumor Incidence and Characteristics by Change in PSA in Dutasteride Group
PSA increased from month 6 to final PSA in 72% (2,433 of 3,377) of men on placebo and only 29% (938 of 3,268) of those receiving dutasteride. Compared with no increase in PSA from month 6 to final PSA in men who received dutasteride, an increase in PSA was associated with a higher likelihood of biopsy detectable prostate cancer (any grade and Gleason score 7–10) and greater likelihood of a clinically significant tumor (modified Epstein criteria, table 3). Furthermore, greater increases in PSA were associ-

![Mean PSA by prostate cancer (PCa) status (no cancer, Gleason score 5–6 cancer and Gleason score 7–10 cancer) for dutasteride and placebo groups during course of study (biopsied population).](image)

<table>
<thead>
<tr>
<th>Table 1. AUCs of PSA parameters for prostate cancer diagnosis</th>
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<tr>
<td></td>
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<tr>
<td>PCa diagnosis any grade:</td>
</tr>
<tr>
<td>Dutasteride</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>PCa diagnosis Gleason score 7–10:</td>
</tr>
<tr>
<td>Dutasteride</td>
</tr>
<tr>
<td>Placebo</td>
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ated with greater increases in those indices of cancer significance. In contrast, PSA increase in the placebo group was less predictive of cancer overall, high grade cancer or other indices of clinically significant cancer.

**Ability of Increasing PSA to Detect Gleason Score 8–10 Tumors in Dutasteride Group**

During years 1 to 2, 16 Gleason score 8–10 tumors were identified in the dutasteride arm in men with at least 3 post-baseline PSA measurements. Of these tumors 10 occurred in men with an increase in PSA from nadir. Mean tumor volume on biopsy of these 10 tumors was $5.26 \pm 2.99$ vs $1.38 \pm 1.34 \mu l$ in the 6 Gleason score 8–10 tumors without a PSA increase (volume determined by the linear extent of the tumor multiplied by the biopsy cross-sectional area). Similarly during years 3 to 4 there were 12 Gleason score 8–10 tumors in the dutasteride arm, all associated with an increase in PSA from nadir, with a mean tumor volume of $7.62 \pm 5.71 \mu l$.

**DISCUSSION**

There has been considerable debate about how PSA should be used in men taking 5ARIs. Based on their approximately 50% median reduction in PSA, the doubling rule was established, whereby PSA in men taking 5ARIs was doubled to preserve the usefulness for the diagnosis of prostate cancer.\(^7,8\) However, this approach ignores the consid-

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**Table 2. Sensitivity, specificity, PPV and NPV of final PSA and change in PSA for Gleason score 7–10 prostate cancer detection by threshold value**

<table>
<thead>
<tr>
<th>PSA Cutoff (ng/ml)</th>
<th>Dutasteride</th>
<th></th>
<th></th>
<th>Placebo</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PPV</td>
<td>NPV</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>Final PSA:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>0.092</td>
<td>0.969</td>
<td>0.805</td>
<td>0.434</td>
<td>0.071</td>
<td>0.993</td>
</tr>
<tr>
<td>3.0</td>
<td>0.130</td>
<td>0.961</td>
<td>0.600</td>
<td>0.713</td>
<td>0.073</td>
<td>0.983</td>
</tr>
<tr>
<td>4.0</td>
<td>0.163</td>
<td>0.951</td>
<td>0.382</td>
<td>0.860</td>
<td>0.077</td>
<td>0.970</td>
</tr>
<tr>
<td>6.0</td>
<td>0.242</td>
<td>0.943</td>
<td>0.195</td>
<td>0.956</td>
<td>0.097</td>
<td>0.964</td>
</tr>
<tr>
<td>7.0</td>
<td>0.246</td>
<td>0.940</td>
<td>0.127</td>
<td>0.972</td>
<td>0.103</td>
<td>0.955</td>
</tr>
<tr>
<td>8.0</td>
<td>0.311</td>
<td>0.939</td>
<td>0.086</td>
<td>0.966</td>
<td>0.109</td>
<td>0.949</td>
</tr>
<tr>
<td>10.0</td>
<td>0.333</td>
<td>0.935</td>
<td>0.036</td>
<td>0.955</td>
<td>0.124</td>
<td>0.941</td>
</tr>
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| Change in PSA from mo 6–final PSA: |  |  |  |  |  |  |
|-----------------------------------|---|---|---|---|---|
| 0.1                               | 0.132 | 0.960 | 0.571 | 0.734 | 0.077 | 0.954 | 0.812 | 0.285 |
| 0.5                               | 0.163 | 0.966 | 0.456 | 0.833 | 0.081 | 0.953 | 0.738 | 0.385 |
| 1.0                               | 0.174 | 0.948 | 0.309 | 0.895 | 0.087 | 0.951 | 0.646 | 0.506 |
| 2.0                               | 0.205 | 0.943 | 0.190 | 0.945 | 0.098 | 0.946 | 0.454 | 0.695 |
| 4.0                               | 0.277 | 0.938 | 0.083 | 0.985 | 0.109 | 0.938 | 0.162 | 0.692 |
| 6.0                               | 0.294 | 0.935 | 0.023 | 0.996 | 0.132 | 0.935 | 0.092 | 0.956 |
| 8.0                               | 0.250 | 0.934 | 0.009 | 0.998 | 0.135 | 0.933 | 0.044 | 0.980 |

**Table 3. Prostate cancer characteristics according to changes in PSA**

<table>
<thead>
<tr>
<th>% Change in Mo 6–Final PSA (No./total No.)</th>
<th>No Increase</th>
<th>Increase of 0.1–1.0</th>
<th>Increase of 1.1–2.0</th>
<th>Increase of Greater Than 2.0</th>
<th>Any Increase</th>
</tr>
</thead>
</table>

**Dutasteride group:**

- Overall PCa incidence: 15.6 (363/2,330)
- Gleason 7–10 PCa: 4.0 (93/2,328)
- Gleason 7–10 PCa greater than 3 + 4: 26
- Significant Ca using modified Epstein criteria: 32.4 (117/361)

**Placebo group:**

- Overall PCa incidence: 23.5 (222/944)
- Gleason 7–10 PCa: 4.6 (43/938)
- Gleason 7–10 PCa greater than 3 + 4: 21
- Significant Ca using modified Epstein criteria: 31.8 (70/220)

*\(^p < 0.0001\) for comparison between no increase and any increase in PSA.
† For determination of nonsignificance modified Epstein criteria include no core with more than 50% involvement of cancer, Gleason scores less than 7, fewer than 3 cores involved, PSA density ≤0.15 (using PSA within 7 days of diagnosis). Definition of Epstein criteria was modified to exclude PSA density as it was not available with prostate volume missing for some subjects.
‡\(^p < 0.01\) for comparison between no increase and any increase in PSA.
§\(^p < 0.05\) for comparison between no increase and any increase in PSA.
erable variability of PSA suppression among individuals and subsequent changes in PSA over time.

In the REDUCE study the proportion of study participants who underwent protocol independent biopsies (7% or less) was minimized by requiring 2 and 4-year biopsies. The rate of cancer detection in protocol independent biopsies was similar between treatment groups. Furthermore, most men without a prostate cancer diagnosis at the end of the 4-year REDUCE study had 3 negative biopsies. Such men have a low likelihood of being diagnosed with cancer, especially high grade cancer, on subsequent biopsies.

One insight from the REDUCE study is that the initial decrease in PSA with dutasteride does not predict the diagnosis of prostate cancer. This is likely because dutasteride reduces PSA secretion from benign and malignant prostate tissue, at least in men in whom a larger, more aggressive cancer was ruled out by an initial negative biopsy.

In addition, among men with a decreasing or constant PSA the NPV for Gleason score 7–10 prostate cancer is 95% to 96% on subsequent biopsy, regardless of treatment arm. However, this low risk group includes 71% of men treated with dutasteride but only 28% of those on placebo. This could translate into a lower number of biopsies in those men treated with dutasteride due to a lower number of false-positive PSA signals.

Finally, any increase from month 6 to final PSA was more indicative of high grade tumors in the dutasteride group vs the placebo group, a finding similar to that seen with finasteride in the Prostate Cancer Prevention Trial. This finding makes sense given that PSA tends to increase over time in men receiving placebo, whether PSA is arising from benign or malignant tissue. In contrast, PSA tended to decrease or remain stable over time with dutasteride in men who had low grade tumors or no tumor.

The ideal test for prostate cancer would maximize the early detection of clinically meaningful cancer, while minimizing false-positive signals arising from PSA produced by benign prostatic tissue and indolent cancer. We hypothesized that an increasing PSA in men receiving dutasteride would serve as a biomarker for aggressive cancer. The results of this study support this hypothesis. Compared with men with a stable or decreasing PSA, men with an increasing PSA on dutasteride had a higher likelihood of prostate cancer, a greater proportion of cancer diagnosed as high grade (Gleason score 7–10), a numerically greater proportion of Gleason score 7–10 cancer being Gleason score 4 + 3 or higher, and a greater percentage of cancer being clinically significant using the modified Epstein criteria. An increasing PSA in men treated with dutasteride can be viewed as a risk factor for prostate cancer, with greater increases correlated with a higher incidence of clinically significant disease.

The ability of dutasteride to improve PSA performance results in more Gleason score 7–10 cancer being undiagnosed. If only men with an increasing PSA in the REDUCE study underwent biopsy, 43 of 229 (19%) of Gleason score 7–10 cancers would be missed in the placebo group and 93 of 217 (43%) such cancers would be missed in the dutasteride group (table 3). In the placebo and dutasteride groups 21% and 26% of those cancers would be Gleason score 4 + 3 or higher, respectively. The lack of PSA increase in some Gleason score 7–10 tumors could be due to their relatively small volume. In addition, part of the apparent higher proportion of such tumors in the dutasteride arm could be accounted for by the higher accuracy of Gleason scoring on biopsy in smaller prostates treated with 5ARIs. To diagnose all Gleason score 7–10 cancers all men would need to undergo biopsy regardless of PSA dynamics. The result would be that many more low grade, low volume cancers would also be diagnosed.

Does the strategy of only biopsying men receiving dutasteride who have an increasing PSA miss clinically important cancers? Of the Gleason score 8–10 cancers in the REDUCE study 10 of 16 cancers during years 1 and 2, and all 12 cancers during years 3 and 4, demonstrated an increasing PSA from nadir. Cancers that would have been missed due to a lack of PSA increase had a lower mean volume on biopsy, demonstrating the difficulty of detecting small cancers using PSA, even if high grade.

A limitation to this analysis is that erroneous PSA values obtained through handling or laboratory error were not eliminated in this study. Month 6 PSA was chosen as the nadir to minimize the likelihood of misinterpreting erroneous PSA values as a nadir. Also, this analysis pertains to men with a previously negative biopsy. Although the general principles may apply to men who have never had a biopsy, the degree to which large, undiagnosed cancers might alter PSA usefulness is unknown.

CONCLUSIONS

The REDUCE study demonstrates that dutasteride enhances the usefulness of PSA for diagnosing high Gleason grade prostate cancer and clinically relevant disease during 4 years. Although the initial decrease in PSA with dutasteride does not predict the diagnosis of prostate cancer, a subsequent increase in PSA better identifies a population at increased risk for high grade or clinically relevant tumors vs placebo. Dutasteride has the benefit of decreasing the overall number of false-positive PSA signals, reducing the risk of...
diagnosis of low grade cancers that are less likely to cause harm if left untreated, and enhancing the diagnosis of high grade cancers or those cancers not responding to dutasteride therapy that may benefit from early diagnosis and treatment.

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REFERENCES


