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Usefulness of prostate-specific antigen (PSA) rise as a marker of prostate cancer in men treated with dutasteride: lessons from the REDUCE study

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Accepted for publication 26 April 2011

Study Type – Prognostic (RCT)
Level of Evidence 1b

What's known on the subject? and What does the study add?
Previous studies used the decrease in PSA after 6 months of dutasteride treatment as a new 'baseline' PSA value from which subsequent rises may serve as a warning for prostate cancer; however, PSA tends to continue to decrease as dutasteride treatment continues. By comparing positive biopsy rates in the REDUCE study using any rise from nadir in the dutasteride arm and standard PSA decision criteria (NCCN) in the placebo arm, we demonstrated that the ability to detect prostate cancer and high grade prostate cancer is maintained with dutasteride treatment.

OBJECTIVES

- To determine if dutasteride-treated men can be monitored safely and adequately for prostate cancer based on data from the Reduction by Dutasteride in Prostate Cancer Events (REDUCE) study.
- To analyse whether the use of treatment-specific criteria for repeat biopsy maintains the usefulness of prostate-specific antigen (PSA) level for detecting high grade cancers.

PATIENTS AND METHODS

- The REDUCE study was a randomized, double-blind, placebo-controlled investigation of whether dutasteride (0.5 mg/day) reduced the risk of biopsy-detectable prostate cancer in men with a previous negative biopsy.
- The usefulness of PSA was evaluated using biopsy thresholds defined by National Comprehensive Cancer Network guidelines in the placebo group and any rise in PSA from nadir (the lowest PSA level achieved while in the study) in the dutasteride group.
- The number of cancers detected on biopsy in the absence of increased/suspicious PSA level as well as sensitivity, specificity, positive predictive value and negative predictive value for high grade prostate cancer detection were analysed by treatment group.
- Prostate cancer pathological characteristics were compared between men who did and did not meet biopsy thresholds.

RESULTS

- Of 8231 men randomized, 3305 (dutasteride) and 3424 (placebo) underwent at least one prostate biopsy during the study and were included in the analysis.
- If only men meeting biopsy thresholds underwent biopsy, 25% (47/191) of Gleason 7 and 24% (7/29) of Gleason 8–10 cancers would have been missed in the dutasteride group, and 37% (78/209) of Gleason 7 and 22% (4/18) Gleason 8–10 cancers would have been missed in the placebo group.
- In both groups, the incidence of Gleason 7 and Gleason 8–10 cancers generally increased with greater rises in PSA.
- Sensitivity of PSA kinetics was higher and specificity was lower for the detection of Gleason 7–10 cancers in men treated with dutasteride vs placebo.
- Men with Gleason 7 and Gleason 8–10 cancer meeting biopsy thresholds had greater numbers of positive cores, percent core involvement, and biopsy cancer volume vs men not meeting thresholds.

CONCLUSION

- Using treatment-specific biopsy thresholds, the present study shows that the ability of PSA kinetics to detect high grade prostate cancer is maintained with dutasteride compared with placebo in men with a previous negative biopsy.
- The sensitivity of PSA kinetics with dutasteride was similar to (Gleason 8–10) or higher than (Gleason 7–10) the placebo group; however, biopsy decisions based on a single increased PSA measurement from nadir in the dutasteride group resulted in a lower specificity compared with using a comparable biopsy threshold in the placebo group, indicating the importance of confirmation of PSA measurements.

KEYWORDS

prostate-specific antigen, dutasteride, 5α-reductase inhibitor, performance, REDUCE study

INTRODUCTION

5α-reductase inhibitors (5ARIs) have been shown to enhance the predictive value of PSA as a marker of biopsy-detectable prostate cancer [1–3]. However, their impact on PSA secretion from benign and malignant tissue, leading to a reduction in serum PSA levels, has also raised concerns about the potential of 5ARIs to obscure or hide the diagnosis of prostate cancer, especially high grade cancer [4]. The interpretation of PSA levels in men taking a 5ARI may therefore require a different approach from that used for the general population. In the present analysis, we investigate whether the use of modified criteria for repeat biopsy in men taking dutasteride maintains the usefulness of PSA for detecting high grade cancers. Specifically, we explored the use of a treatment-specific biopsy threshold defined as any rise in PSA from nadir in men taking dutasteride. This threshold was previously suggested after analysis of PSA data from the Prostate Cancer Prevention Trial (PCPT) [5].

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study provides a unique setting for investigating whether dutasteride enhances or impairs prostate cancer diagnosis. Patients underwent repeat biopsies largely independently of absolute PSA level and PSA dynamics, allowing a comparatively unbiased assessment of the effect of dutasteride on the usefulness of PSA measurements for the diagnosis of prostate cancer. It has been shown that in men with a previous negative biopsy, dutasteride significantly improved the diagnostic performance of final PSA level and change from month 6 to final PSA level as tests for prostate cancer and high grade prostate cancer, compared with placebo. This analysis also found that if men underwent biopsy based on any rise in PSA from month 6, 43 Gleason 7–10 cancers would have been missed in the placebo group and 93 such cancers would have been missed in the dutasteride group [1].

This analysis of change in PSA level from month 6 provides insight into the usefulness of PSA in prostate cancer diagnosis, however, these results may not directly translate to clinical practice because most men on dutasteride have a continued decrease in PSA level after month 6. As such, the month 6 PSA does not always represent the nadir. When PSA levels of some men in the dutasteride group continued to decline beyond month 6, subsequent increases may not have been captured as a 'rising' PSA in an analysis of change in PSA from month 6. Furthermore, in men not taking 5ARIs, a rise in PSA does not always lead to a recommendation to undergo biopsy. Biopsy decisions are usually based on multiple factors, including absolute PSA level and the magnitude of PSA velocity [6]. For example, the National Comprehensive Cancer Network (NCCN) recommends a minimum PSA velocity of 0.35 or 0.75 ng/mL/year as a criterion for considering repeat prostate biopsy, depending on the baseline PSA level [7].

To better understand the usefulness of PSA as a marker of prostate cancer in clinical practice and derive a more clinically applicable approach to PSA monitoring, in the present investigation we assessed the diagnostic accuracy of using treatment-specific biopsy thresholds for PSA to predict prostate cancer using data in which men underwent protocol-mandated repeat TRUS-guided biopsy in dutasteride-treated vs placebo-treated men. We compared a threshold defined by NCCN recommendations in the placebo group with a threshold defined as any rise in PSA level from nadir in the dutasteride group. To further consider the clinical significance of these tumours, we also examined the pathological characteristics of prostate cancers in men with and without PSA changes greater than the treatment-specific biopsy thresholds.

PATIENTS AND METHODS

PARTICIPANTS

The design of the REDUCE study has been reported [8]. Eligible men included men 50–75 years old, with PSA levels of 2.5–10 ng/mL, if 50–60 years old, or 3–10 ng/mL, if >60 years old, and a single negative prostate biopsy (6–12 cores) within 6 months of enrolment and performed independently of the study.

STUDY DESIGN

REDUCE was a multicentre, double-blind, placebo-controlled study in which men were randomized to receive 0.5 mg daily dutasteride or placebo for 4 years [9]. Visits occurred every 6 months and included measurement of total serum PSA (Beckman Coulter Inc., Brea, CA, USA). PSA values were reported to investigators, and doubled PSA values (±0.1 ng/mL in half the men) were reported for men in the dutasteride group. Unscheduled PSA measurements were permitted if obtained through the central study laboratory.

Ten-core TRUS-guided biopsies were performed at 2 and 4 years (protocol-mandated) or if clinically indicated based on the clinical judgement of the study investigator. All study-mandated biopsies were processed and read at the central pathology facility. Positive biopsies were graded using the classic Gleason scoring method, and pathological data including number of positive cores and volume of cancer were collected. Clinically significant prostate cancer was defined as tumours not meeting a modified version of the original Epstein criteria [10], and included Gleason 6 cancers with >50% of any one core positive or three or more positive cores, and all Gleason 7–10 cancers.

STATISTICAL ANALYSIS

Analyses were conducted based on the group of men who had undergone at least one post-baseline biopsy (biopsied population). The usefulness of final PSA and change from month 6 to final PSA as indicators of biopsy-detectable prostate cancer in men from the REDUCE study has been reported [1]. In the present analysis, the usefulness of PSA as a marker of prostate cancer in men with a single previous negative prostate biopsy was evaluated using treatment-specific biopsy thresholds defined *post hoc*.

In the dutasteride group, the biopsy threshold was defined as any rise in PSA from nadir. Actual PSA values (vs the doubled PSA values reported to investigators during the study) were used in the analysis, and nadir PSA was defined as the lowest PSA level achieved while in the study. Final PSA was the last PSA value recorded before prostate cancer diagnosis or final cancer-assessment biopsy. PSA measurements on the date of a biopsy (or

within 42 days after) were excluded from the analysis to minimize the potential impact of prostate biopsy on PSA levels. Mean PSA values were summarized by treatment group and prostate cancer status, and the last observation carried forward approach was used to address missing values.

The biopsy threshold in men from the placebo group was defined by current NCCN guidelines for men with a previous negative biopsy, who were not taking a 5ARI. While a recent investigation found that incorporating PSA velocity into biopsy decisions offered limited improvement in the predictive accuracy for prostate cancer diagnosis compared with PSA level alone, the analysis was based on a population of men with low baseline PSA levels (≤3.0 ng/mL) who may or may not have had a previous negative biopsy [11], and these results may not be applicable to the REDUCE study population. The NCCN guidelines were used to evaluate PSA levels in the placebo group because they provided explicit recommendations on the management of patients with a previous negative biopsy. The NCCN recommends repeat biopsy based on an increase in PSA of ≥0.75 ng/mL/year for men with a PSA >4.0 ng/mL, and based on an increase of ≥0.35 ng/mL/year in men with a PSA of 2.5–4 ng/mL [7]. The guidelines further specify that measurement should be made on at least three consecutive measurements drawn over a minimum of an 18–24 month period. For the present analysis, PSA velocity was calculated as (final PSA – month 6 PSA)/(days between two measurements/365.25). Month 6 was chosen as the baseline in the placebo group because an unknown number of the PSA measurements at the beginning of the study (month 0) were obtained too soon after the pre-study biopsy to exclude the possibility that the measurements were elevated secondary to the biopsy procedure. The threshold PSA velocity was based on month 6 PSA (>4.0 ng/mL or 2.5–4.0 ng/mL).

Using the biopsy criteria specified, PSA usefulness was evaluated by examining the numbers of men with cancer who met or did not meet the thresholds. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of prostate cancer and high grade prostate cancer were analysed by treatment group. Associated Clopper-Pearson 95% CIs were computed, conditional on the denominators. Pathological characteristics of Gleason 7 and Gleason 8–10 cancers were summarized by treatment group and whether men met biopsy thresholds. Among men who met biopsy thresholds, pathological characteristics were compared between treatment groups using the Wilcoxon rank sum test.

TABLE 1 Study population

	Dutasteride	Placebo
Study populations [1,9]		
Randomized men	4105	4126
Efficacy population	4049	4073
Biopsied population*	3305	3424
Scheduled biopsies	3208	3291
Prostate cancer diagnosed in biopsied population*		
All Gleason scores	657	850
Gleason 5	1	4
Gleason 6	436	613
Gleason 7	191	214
Gleason 3+4	146	176
Gleason 4+3	45	38
Gleason 8–10	29	19

**All men with at least one post-baseline needle biopsy.*

TABLE 2 Baseline characteristics of the biopsied population

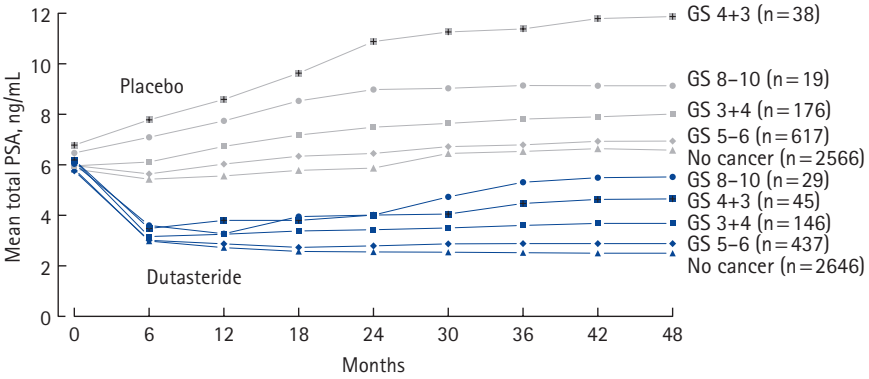
	Dutasteride, $N = 3305$	Placebo, $N = 3424$
Age, years		
Mean (SD)	62.8 (5.96)	62.7 (6.04)
Range	49–76	49–77
Race, *n* (%)		
Caucasian	3028 (92)	3129 (91)
Non-Caucasian	277 (8)	295 (9)
Positive family history of prostate cancer, *n* (%)	448 (14)	437 (13)
Prostate volume, mean mL (SD)	45.7 (17.24)	45.5 (17.61)
PSA, mean ng/mL (SD)	5.9 (1.91)	5.9 (1.93)
PSA density, mean ng/mL/cc (SD)	0.15 (0.084)	0.15 (0.095)
No. of cores in pre-study negative biopsy mean (SD)	8.8 (2.47)	8.7 (2.41)

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS

Of the 8231 randomized men (4105 dutasteride, 4126 placebo), 3305 (81.6%) men in the dutasteride group and 3424 (84.1%) men in the placebo group underwent at least one prostate biopsy during the study and were included in the biopsied population (Table 1) [1,9]. The majority of biopsies were conducted as protocol-mandated biopsies and were therefore assessed independently of PSA level. Similar percentages of men in each treatment group refused biopsies at year 2 (placebo 2.9%, dutasteride 3.3%) and year 4 (placebo 5.0%, dutasteride 4.5%). Baseline characteristics of the biopsied population were similar to the overall REDUCE study population [9] and similar between the treatment groups (Table 2). Baseline characteristics were also similar between men in the biopsied population and those who did not undergo prostate biopsies

FIG. 1. Trends in changes in PSA levels over time for groups defined by their final prostate cancer status. Data points represent mean values by treatment group and ultimate prostate cancer diagnosis (no cancer or Gleason scores: 5–6, 3+4, 4+3, 8–10) in the biopsied population. Last observation carried forward.



during the study [1]. Over 4 years, prostate cancer was diagnosed via needle biopsy in 657 men in the dutasteride group and 850 men in the placebo group within the biopsied population.

PSA CHANGE AND INCIDENCE OF PROSTATE CANCER

In the placebo group, mean PSA levels increased in all categories of prostate cancer, including in men without prostate cancer (Fig. 1). In the dutasteride group following 6 months of treatment, mean PSA decreased by approximately 46%, regardless of eventual prostate cancer status [1]. The percentage of men in the dutasteride arm reaching nadir by any given timepoint was 13% at month 6, 30% at month 12, 51% at month 18, 56% at month 24, 68% at month 30, 81% at month 36, 97% at month 42, and 100% at month 48.

In both treatment groups, the likelihood of Gleason 6 prostate cancer was not greater for men having an increase in PSA from nadir compared with those who did not have such an increase (Table 3). In the dutasteride group there was no difference in the percent of men with Gleason 6 cancers as a function of whether or not they had a rise in PSA from nadir (13.0% with any increase vs 13.6% with no increase, $P = 0.67$). Paradoxically, in the placebo group there was a higher percentage of men with Gleason 6 cancer among those who did not have a rise in PSA from nadir (24.4% vs 17.2% in men with a rise in PSA, $P < 0.002$). For men with increases, the incidence of Gleason 7 and Gleason 8–10 prostate cancer generally increased with greater rises in PSA from nadir.

DETECTION OF PROSTATE CANCER USING TREATMENT-SPECIFIC THRESHOLDS FOR BIOPSY

In the dutasteride group, 2150 men had an increase in PSA from nadir (Table 4). If only these men were biopsied, it follows that 47/191 (25%) of Gleason 7 cancers that were ultimately found in the whole cohort would not have been identified based on a rising PSA from nadir, and 7/29 (24%) of Gleason 8–10 cancers would have been missed. Using NCCN biopsy thresholds in the placebo group, 1369 men would have received a recommendation for biopsy. If only these men were biopsied, 78/209 (37%) Gleason 7 cancers and 4/18 (22%) Gleason 8–10 cancers would have been missed.

Based on treatment-specific criteria, the sensitivity, specificity, PPV, and NPV were calculated by treatment group and by Gleason score (Table 5). These criteria for biopsy provided a higher sensitivity for Gleason 7–10 cancers in the dutasteride group compared with placebo, and a lower specificity. In both groups, the NPV of these cut-offs is high and the PPV is low because of the low frequency of high grade cancers.

PATHOLOGICAL CHARACTERISTICS OF CANCERS WITH AND WITHOUT AN ASSOCIATED CHANGE IN PSA

Pathological characteristics of prostate cancer that did or did not meet treatment-specific thresholds for biopsy were compared (Table 6). In both treatment groups for both Gleason 7 and Gleason 8–10 cancers, men who met the biopsy threshold had a numerically higher mean number of positive cores, greater percent of core involvement, and greater mean volume of cancer on biopsy compared with those who did not meet biopsy thresholds.

DISCUSSION

SUMMARY OF RESULTS

Dutasteride treatment maintained the ability of PSA kinetics to detect overall prostate cancer and high grade prostate cancer when using treatment-specific thresholds for biopsy. Of the Gleason 7 cancers ultimately found in the whole cohort, based on treatment-specific PSA kinetics, 25% would have been missed in the dutasteride group compared with 37% in the placebo group. For the Gleason 8–10 cancers, 24% and 22% would have been missed in the dutasteride and placebo groups, respectively.

These results support the idea that PSA kinetics accurately reflect the biology of prostate cancers in men taking dutasteride. By suppressing PSA from benign prostatic tissue and indolent cancers, subsequent rises in PSA levels after nadir may reflect growth that is not controlled by dutasteride. This may suggest that in men taking dutasteride, even high grade cancers without a rising PSA are behaving indolently. This is reflected by the pathological characteristics of tumours in men who did and did not meet biopsy thresholds (Table 6); in both treatment groups, cancers not meeting biopsy thresholds tended to be smaller than those with a rising PSA that met biopsy thresholds. However, as long-term outcome data are not currently available, we cannot firmly conclude that these tumours are of a more indolent nature, although the tumour volumes on biopsy would suggest so. By contrast, the individual high-volume cancers that were not identifiable based on PSA changes may be a subset of cancers that did not produce PSA.

While the sensitivity of PSA kinetics with dutasteride for detecting high grade cancer was similar to (Gleason 8–10) or higher than (Gleason 7–10) the placebo group, the

TABLE 3 Incidence of prostate cancer by change in PSA from nadir

	Proportion of men with PCa meeting PSA criteria* and cancer volume							
	Change in PSA from nadir to final PSA (ng/mL)							
	No increase	Any increase	Increase of >0.0–≤0.5	Increase of >0.5–≤1.0	Increase of >1.0–≤2.0	Increase of >2.0		
Dutasteride, *N* = 3305								
Overall incidence of prostate cancer (%)	210/1149 (18.3)	447/2150 (20.8)	181/1088 (16.6)	112/461 (24.3)	73/330 (22.1)	81/271 (29.9)		
Incidence of GS 6 (%)	156/1149 (13.6)	280/2150 (13.0)	137/1088 (12.6)	66/461 (14.3)	44/330 (13.3)	33/271 (12.2)		
Clinically significant** (%)	68/1149 (5.9)	198/2149 (9.2)	61/1087 (5.6)	53/461 (11.5)	30/330 (9.1)	54/271 (19.9)		
Incidence of GS 7 (%)	47/1149 (4.1)	144/2150 (6.7)	42/1088 (3.9)	42/461 (9.1)	23/330 (7.0)	37/271 (13.7)		
3+4 (%)	38/1149 (3.3)	108/2150 (5.0)	31/1088 (2.8)	35/461 (7.6)	18/330 (5.5)	24/271 (8.9)		
4+3 (%)	9/1149 (0.8)	36/2150 (1.7)	11/1088 (1.0)	7/461 (1.5)	5/330 (1.5)	13/271 (4.8)		
Incidence of GS 8–10 (%)	7/1149 (0.6)	22/2150 (1.0)	2/1088 (0.2)	4/461 (0.9)	5/330 (1.5)	11/271 (4.1)		
Volume GS 7, mL $\times 10^{-3}$ (SD)	3.7 (5.53)	4.3 (4.40)	3.4 (2.74)	4.8 (4.95)	3.9 (4.30)	5.1 (5.21)		
Volume GS 8–10, mL $\times 10^{-3}$ (SD)	1.4 (1.34)	6.5 (4.73)	3.1 (3.33)	7.4 (3.07)	5.5 (1.86)	7.4 (6.14)		
	No increase	Any increase	Increase of >0.0–≤0.5	Increase of >0.5–≤1.0	Increase of >1.0–≤2.0	Increase of >2.0	Increase of >2.0–≤4.0	Increase of >4.0
Placebo, *N* = 3424								
Overall incidence of prostate cancer (%)	104/356 (29.2)	745/3050 (24.4)	87/407 (21.4)	92/446 (20.6)	207/826 (25.1)	359/1371 (26.2)	230/856 (26.9)	129/515 (25.0)
Incidence of GS 6 (%)	86/356 (24.2)	526/3050 (17.2)	72/407 (17.7)	70/446 (15.7)	158/826 (19.1)	226/1371 (16.5)	145/856 (16.9)	81/515 (15.7)
Clinically significant cancers** (%)	30/356 (8.4)	299/3049 (9.8)	28/407 (6.9)	33/446 (7.4)	71/825 (8.6)	167/1371 (12.2)	107/856 (12.5)	60/515 (11.7)
Incidence of GS 7 (%)	13/356 (3.7)	201/3050 (6.6)	14/407 (3.4)	21/446 (4.7)	43/826 (5.2)	123/1371 (9.0)	80/856 (9.3)	43/515 (8.3)
3+4 (%)	13/356 (3.7)	163/3050 (5.3)	11/407 (2.7)	19/446 (4.3)	40/826 (4.8)	93/1371 (6.8)	67/856 (7.8)	26/515 (5.0)
4+3 (%)	0/356 (0.0)	38/3050 (1.2)	3/407 (0.7)	2/446 (0.4)	3/826 (0.4)	30/1371 (2.2)	13/856 (1.5)	17/515 (3.3)
Incidence of GS 8–10 (%)	4/356 (1.1)	15/3050 (0.5)	0/407 (0)	1/446 (0.2)	5/826 (0.6)	9/1371 (0.7)	4/856 (0.5)	5/515 (1.0)
Volume GS 7, mL $\times 10^{-3}$ (SD)	3.6 (2.49)	5.0 (6.91)	2.8 (2.45)	3.0 (4.85)	4.1 (4.93)	5.9 (7.93)	5.4 (6.32)	6.8 (10.32)
Volume GS 8–10, mL $\times 10^{-3}$ (SD)	4.6 (5.33)	4.6 (7.32)	NA	3.1	1.5 (1.55)	6.6 (9.05)	4.4 (3.68)	8.3 (12.05)

**Number of men with prostate cancer meeting PSA criteria/total number of men meeting PSA criteria (%).*

***Clinically significant cancers were defined as those not meeting a modified version of the original Epstein criteria [10], and included all Gleason 7–10 cancers and Gleason 6 cancers with >50% of any one core positive or ≥3 positive cores. GS, Gleason score; NA, not applicable.*

specificity for dutasteride was lower (Table 5). This lower specificity with dutasteride results from using any rise in PSA as a reason for biopsy, rather than attempting to confirm the nadir value and any subsequent rise. If a higher threshold for biopsy were used for patients on dutasteride, the specificity would increase, but with a decrease in sensitivity. As seen in Table 3, using any increase in PSA from nadir, 22 of 29 Gleason 8–10 cancers within the dutasteride group would be identified. If the threshold were raised, fewer cancers would be identified; 20 of 29 Gleason 8–10 cancers would have been identified if using any increase ≥0.5 ng/mL, and 16 of 29 would have been identified if using any increase ≥1.0 ng/mL.

METHODOLOGICAL LIMITATIONS

This evaluation of PSA changes from nadir presents a few limitations. When change from actual nadir was initially assessed, it became apparent that the chance of a spurious PSA value defining a nadir was increased if the lowest of all nine potential PSA values (baseline and every 6 months determination for 4 years) was used for a given man. To minimize the possible impact of prostate biopsy on PSA levels, data from some men were excluded because PSA measurements were made within 42 days after a biopsy. In addition, a small percentage of PSA measurements obtained in the REDUCE trial were erroneous; ≈0.5% did not belong to the patients to whom they were assigned [12]. Therefore, relying on a single PSA value as defining a nadir or rise from nadir runs the risk of increasing random 'noise' in this evaluation. In the placebo group, the risk of noise was lower, because not just any rise would prompt a biopsy, but only rises above the NCCN thresholds. This risk highlights the importance of repeating any PSA test that indicates a rise from nadir in order to confirm the result. A further consideration regarding PSA measurements in 5ARI studies is the potential influence of treatment compliance. Our investigation assumes that men were compliant with study treatment, however, misclassification could occur in the dutasteride group if a man was non-compliant.

In the present analysis we used a biopsy threshold based on NCCN criteria for the placebo group. These guidelines provided specific recommendations for biopsy decisions in men with a previous negative biopsy. A recent analysis of PSA data from the placebo group of the PCPT found that PSA velocity was no better than absolute level of PSA as a standard predictor of prostate cancer, because of the strong correlation of these measurements before biopsy [11]. It should, however, be noted that the PCPT data is from a population of men with low baseline

*TABLE 4 Detection of Gleason 7 and Gleason 8–10 cancers using treatment-specific biopsy thresholds**

	Dutasteride, *N* = 3305	Placebo, *N* = 3424
Total number of men meeting PSA criteria	2150	1369
Men without cancer	1703	936
	Proportion of cancers meeting criteria**	
Gleason 5–6	281/437 (64)	287/607 (47)
Gleason 7	144/191 (75)	131/209 (63)
3+4	108/146 (74)	103/172 (60)
4+3	36/45 (80)	28/37 (76)
Gleason 8–10	22/29 (76)	14/18 (78)

*Biopsy thresholds defined by NCCN guidelines [7] for the placebo group and any increase in PSA from nadir for the dutasteride group.
**Number of cancers meeting criteria/total number of cancers (%)

TABLE 5 Sensitivity and specificity of treatment-specific biopsy thresholds as a predictor of prostate cancer

Treatment Group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	False-positives	Undetected cancers/ False-negatives, *n* (%)*
All						
Placebo	0.518 (0.483, 0.552)	0.629 (0.610, 0.648)	0.318 (0.293, 0.343)	0.796 (0.778, 0.814)	936	406 (48%)
Dutasteride	0.680 (0.643, 0.715)	0.356 (0.337, 0.374)	0.208 (0.191, 0.226)	0.817 (0.793, 0.839)	1704	211 (32%)
Gleason 7–10						
Placebo	0.639 (0.573, 0.701)	0.608 (0.591, 0.626)	0.106 (0.090, 0.123)	0.959 (0.949, 0.967)	1224	82 (36%)
Dutasteride	0.755 (0.692, 0.810)	0.356 (0.339, 0.373)	0.077 (0.066, 0.089)	0.953 (0.939, 0.965)	1984	54 (25%)
Gleason 8–10						
Placebo	0.778 (0.524, 0.936)	0.594 (0.577, 0.610)	0.010 (0.006, 0.017)	0.998 (0.995, 0.999)	1355	4 (22%)
Dutasteride	0.759 (0.565, 0.897)	0.349 (0.333, 0.366)	0.010 (0.006, 0.015)	0.994 (0.987, 0.998)	2128	7 (24%)

*Undetected cancers defined as cancers detected on biopsy in the absence of increased/suspicious PSA and represent false-negatives. Percentage calculated as: number of undetected cancers (false-negatives)/total number of cancers. Values calculated using biopsy thresholds defined by NCCN guidelines [7] for the placebo group and any increase in PSA from nadir for the dutasteride group. Clopper-Pearson 95% CIs were computed conditional on the denominators.

TABLE 6 Pathological characteristics of prostate cancer by Gleason score and PSA changes: comparison of cancers that did or did not meet biopsy thresholds in each treatment group*

	Gleason 7, mean (SD; *n*)		Gleason 8–10, mean (SD; *n*)	
	Below biopsy threshold	Meeting biopsy threshold	Below biopsy threshold	Meeting biopsy threshold
Mean no. of positive cores				
Dutasteride	2.2 (1.63; 47)	2.5 (1.66; 144)	1.4 (0.53; 7)	3.2 (1.85; 22)
Placebo	2.2 (1.30; 78)	2.8 (1.89; 131)	1.5 (1.00; 4)	1.8 (1.42; 14)
P (placebo vs dutasteride) for cases meeting biopsy threshold**		>0.05		0.0055
Percent of cores affected by tumour				
Dutasteride	17.1 (16.52; 47)	20.9 (16.76; 144)	9.9 (5.53; 7)	29.6 (19.45; 22)
Placebo	19.4 (16.93; 78)	24.1 (19.60; 130)	20.8 (23.68; 4)	28.1 (22.86; 14)
P (placebo vs dutasteride) for cases meeting biopsy threshold**		>0.05		>0.05
Mean volume of cancer on biopsy (cc $\times 10^{-3}$)				
Dutasteride	3.7 (5.53; 46)	4.3 (4.40; 144)	1.4 (1.34; 6)	6.5 (4.73; 22)
Placebo	3.2 (3.67; 78)	5.9 (7.90; 131)	3.0 (4.06; 4)	4.8 (7.58; 14)
P (placebo vs dutasteride) for cases meeting biopsy threshold**		>0.05		0.0193

**Biopsy thresholds defined by NCCN guidelines [7] for the placebo group and any increase in PSA from nadir for the dutasteride group. **P values calculated for placebo vs dutasteride based on Wilcoxon rank sum test.*

PSA levels (<3.0 ng/mL) who may or may not have had a previous negative biopsy.

We believe that the treatment-specific biopsy thresholds allow a better assessment of PSA monitoring in a clinical setting, however, the use of different biopsy thresholds may lead to a bias when comparing results between treatment groups. The biopsy threshold for the dutasteride group does not include an element of time; in contrast, the biopsy threshold in the placebo group is calculated as a velocity (ng/mL/year). Therefore, the treatment-specific biopsy thresholds could be assessed over different time periods, which may introduce bias in our assessment, although it is difficult to predict the potential impact of this bias.

COMPARISON WITH OTHER STUDIES

Data from the PCPT show increased sensitivity for PSA in detecting prostate cancer and high grade prostate cancer in men taking finasteride vs placebo [2]. Similarly, previous investigations from the REDUCE study found that dutasteride improved the diagnostic performance of PSA as a test for prostate cancer and high grade prostate cancer based on final PSA values and the change from month 6 to final PSA [1]. Additional investigations from the PCPT found that a rising PSA, based on a PSA velocity (log ng/mL/year) >0 increased the risk of prostate cancer from 7.5% to 24.8%, and of high grade disease from 1.7% to 11.3% [5]. Consistent with the present analysis, these investigators concluded that a rising PSA in men taking finasteride increased the likelihood of prostate cancer. In contrast to this investigation from the PCPT, which defined PSA velocity retrospectively from the time of biopsy, the present analysis defined the PSA biopsy thresholds from a prospective perspective of measurements after nadir (dutasteride) or baseline (defined as month 6; placebo) and therefore may be more applicable to a clinical setting.

CLINICAL IMPLICATIONS

The present analysis approximates the use of PSA in a clinical setting and shows that the use of any rise in PSA from nadir as a threshold for biopsy in men taking dutasteride maintains the sensitivity of PSA as a marker of prostate cancer. Guidelines recommend examination of PSA values over time and confirmation of abnormal values [6,7]. Thus, in clinical practice, any rise in PSA in men taking dutasteride necessitates confirmation and further evaluation, as well as a check on drug compliance [13] or any external factors that may affect PSA values [6].

Clinical judgement is needed in the interpretation of PSA kinetics. A small rise that does not progress over time might not be meaningful, and one needs to approach a single nadir value with the same scepticism as a single (unconfirmed) rise from a supposed nadir. Very small (0.1–0.2 ng/mL) rises in PSA may be particularly difficult to interpret, as such changes could reflect variations in PSA assays and 'background noise' within the test [6,14]. Thus, some previous studies have recommended a PSA rise of 0.3 ng/mL as a threshold for biopsy in men taking a 5ARI [15].

In conclusion, using data from the REDUCE study, we analysed the detection of prostate cancer using treatment-specific biopsy thresholds for PSA to assess the usefulness of PSA in a clinical practice setting. A similar percentage of cases of Gleason 7 (25% dutasteride, 37% placebo) and Gleason 8–10 (24% dutasteride, 22%

placebo) prostate cancer would have been missed in each group using treatment-specific biopsy thresholds to guide biopsy decisions. These data show that the use of dutasteride does not impair detection of prostate cancer and high grade prostate cancer; however, biopsy decisions based only on a single increased PSA measurement also resulted in a higher false-positive rate and lower specificity in the dutasteride group compared with the placebo group. In clinical practice, PSA should be monitored regularly in men taking dutasteride and any increase from nadir warrants confirmation and further investigation.

ACKNOWLEDGEMENTS

Editorial support in the form of assistance with the preparation of the first draft, collation of author comments, preparation of the tables and figure was provided by Meredith Kalish, MD, and Brigitte Teissedre, PhD, at Choice Pharma and funded by GlaxoSmithKline. Mark Emberton receives research support from the UK's National Institute of Health Research, through the UCLH/UCL Comprehensive Biomedical Research Centre, London, UK. Responsibility for opinions, conclusions and interpretation of data lies with the authors.

CONFLICT OF INTEREST

Michael Marberger is a Paid Consultant to GSK, MSD and GP Pharm. Stephen J. Freedland receives research finding from, and is a Paid Consultant to GSK. Gerald L. Andriole is a Paid Consultant to Amgen, Augmenix, Bayer, Cambridge Endo, Caris, France Foundation, GenProbe, GlaxoSmithKline, Myriad Genetics, Steba Biotech and Ortho-Clinical Diagnostics, is also a Study Investigator Funded by Ferring Pharmaceuticals, and is an investor with Envisioneering Medical and Viking Medical. Mark Emberton is a Paid Consultant to, and a Study Investigator funded by GSK, and a member of GSK's European Advisory Board. Curtis Pettaway is a GSK REDUCE trial steering committee member and on Ferring Pharmaceuticals Data and safety monitoring committee. Francesco Montorsi is a speaker for GSK. Claudio Teloken is a GSK REDUCE trial steering committee member. Roger S. Rittmaster, Matthew C. Somerville and Ramiro Castro are Employees of GSK.

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Abbreviations: **REDUCE**, Reduction by Dutasteride in Prostate Cancer Events; **5ARI**, 5α-reductase inhibitor; **PCPT**, Prostate Cancer Prevention Trial; **NCCN**, National Comprehensive Cancer Network; **PPV**, positive predictive value; **NPV**, negative predictive value.