

## Prostate Specific Antigen Density Velocity (PSADV) on Dutasteride Helps Predict Negative Prostate Biopsy: Analysis of the REDUCE Trial

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### ABSTRACT

**AIM:** Prostate specific antigen (PSA) is a widely utilized screening marker for prostate cancer. Its performance in detecting prostate cancer is enhanced with the 5 $\alpha$ -reductase inhibitor (5 $\alpha$ RI) dutasteride. We evaluated if PSA density velocity (PSADV) further improved the ability to predict prostate cancer risk on repeat biopsy utilizing the REDUCE trial data in order to avoid unnecessary biopsies.

**MATERIALS AND METHODS:** The REDUCE study randomized 8 231 men aged 50 to 75 years with a PSA between 2.5 and 10 ng/mL and a previously benign prostate biopsy. Prostate volume, PSA and biopsy results at 24 months were available for 1 074 subjects. PSADV, defined as the change in PSA density divided by the number of days between PSA measurements (ng/mL/cc/day), was calculated and compared between the placebo and treatment groups and further stratified by prostate biopsy results. Statistical significance was

calculated using the Wilcoxon rank sum test.

**RESULTS:** Median PSA, PSA velocity, and PSADV are shown for the placebo and dutasteride treatment cohorts at 24 months in Table 1. Median PSA velocity in both the placebo and treatment groups were positive independent of a prostate cancer diagnosis. Results of PSADV stratified by treatment and biopsy results are seen in the boxplots in Figure 1. There was a significantly more robust reduction in PSADV in those without cancer on biopsy compared to those with prostate cancer in the treatment arm ( $P = 0.0019$ ).

**CONCLUSIONS:** The magnitude of change in PSADV after dutasteride therapy may be an additional diagnostic adjunct to aid in the identification of those at lower risk for prostate cancer on repeat biopsy. This measurement may reduce unnecessary prostate biopsies and the increasingly prevalent associated risks of the procedure.

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**Key Words:** Prostate cancer diagnosis; PSA; Prostate cancer; 5-alpha reductase inhibitor

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### INTRODUCTION

Prostate cancer (CaP) is the most prevalent malignancy among American men. The American Cancer Society estimates a total of 2.8 million men in the United States have CaP with 241,740 new cases diagnosed in 2012<sup>[1]</sup>. This increase in CaP detection is undoubtedly a result of prostate specific antigen (PSA) screening as well as modifications to traditional transrectal ultrasonography (TRUS) guided prostate biopsies.

TRUS guided prostate biopsies remain the mainstay of histologic diagnosis of CaP. A recent review of the SEER database revealed that of T1 prostate cancers, 94% are diagnosed by TRUS biopsy compared to only 6% by transurethral resection<sup>[2]</sup>. However, a majority of prostate biopsies fail to detect malignancy and are a source of patient discomfort, morbidity, and anxiety. Complications are not uncommon with a reported complication rate including minor complications as high as 63%<sup>[3]</sup>. In addition, prostate biopsy confers a 2.65-fold higher risk of hospital admission compared to a control population based on multivariable analysis of the SEER database<sup>[4]</sup>. This observation is likely related to the increasing prevalence of fluoroquinolone resistance within the population undergoing TRUS prostate biopsy, which is reportedly as high as 22% based on pre-biopsy rectal swab cultures<sup>[5]</sup>.

PSA screening remains a sensitive but nonspecific predictor of benign versus malignant disease. In fact, there is significant physiologic variation in serial measurements of PSA creating difficulty in interpreting the results of this screening test<sup>[6,7]</sup>. Considerable efforts to improve the performance of PSA as a screening tool have been made.

Previous reports have suggested that treatment with 5 $\alpha$ -reductase inhibitors (5aRIs) may improve the diagnostic yield of available screening tools for CaP<sup>[8-14]</sup>. In order to combine considerations of prostate volume and PSA kinetics in conjunction with 5aRI therapy, we evaluated if PSA density velocity (PSADV) further improved the ability to predict prostate cancer risk on repeat biopsy. We utilized the REDUCE trial data in order to evaluate this concept. To our knowledge, this is the only study comparing the combination of PSA kinetics with consideration of prostate volume between those on a 5aRI versus placebo.

## MATERIALS AND METHODS

The study design of the REDUCE trial has been previously described in depth<sup>[15]</sup>. The trial was a 4-year, multicenter, randomized, double-blind, placebo-controlled, parallel-group study investigating the chemoprevention effects of the non-selective 5aRI dutasteride. A total of 8 231 men aged 50 to 75 years underwent randomization to a 0.5mg daily dose of dutasteride or placebo. Men between 50 and 60 years of age were eligible if their baseline PSA value was between 2.5 and 10.0 ng per milliliter, while those men over the age of 60 years were included if the PSA value was 3.0 to 10.0 ng per milliliter. All participants had undergone a 6-12 core TRUS prostate biopsy within 6 months of enrollment without evidence of prostate cancer (pathology was centrally reviewed and confirmed). Men were excluded from participation if they had previously been biopsied more than once; had known prostate cancer of any grade, high-grade intraepithelial neoplasia, atypical small acinar proliferation, or had a prostate volume greater than 80 mL. In addition, men with severe lower urinary tract symptoms defined as an International Prostate Symptom Score (IPSS) of 25 or higher, or 20 or higher with concomitant alpha-blocker therapy were also excluded from the study.

Study protocol called for assessments every 6 months with PSA and IPSS measurements. PSA levels in patients taking dutasteride were adjusted by a factor of two. Prostate biopsies were performed at 2 and subsequently 4 years or if clinically indicated as judged by the study physician (protocol-independent).

Of the 8 231 men originally randomized, prostate volume, PSA and biopsy results at 24 months were available for 1 074 subjects (after excluding measurements on or up to 42 days after biopsy, or

after prostate cancer diagnosis or final biopsy) PSADV, defined as the change in PSA density divided by the number of days between PSA measurements (ng/ml/cc/day), was calculated and compared between the placebo and treatment groups and further stratified by prostate biopsy results. Statistical significance was calculated using the Wilcoxon rank sum test performed at the significance level of 0.05.

## RESULTS

Data were analyzed from the 1 074 patients with available PSA values, prostate volumes and biopsy results at the 2-year interval of the study. A total of 532 patients in the placebo group were compared to 542 patients in the dutasteride treatment arm. Because the aim of this subset analysis of the REDUCE trial was to investigate the discriminatory ability of PSADV (compared to other PSA parameters) to predict biopsy-detected CaP, the placebo and treatment groups were then stratified into those with a negative or positive TRUS biopsy. Within the placebo cohort, 95 patients received a diagnosis of CaP while 437 patients remained without evidence of malignancy. The dutasteride cohort was comprised of 58 patients with biopsy-proven prostate cancer and 484 patients without CaP at 2 years.

Median baseline PSA was similar in the placebo and dutasteride groups irrespective of a CaP diagnosis and were 5.8 (placebo with CaP), 5.6 (placebo without CaP), 5.2 (dutasteride with cancer) and 5.5 (dutasteride without CaP) ng/mL. Median PSA at 24 months in the placebo group increased to 6.6 and 5.7 ng/mL for those with and without cancer respectively, which correlated to median PSAVs (ng/mL per day  $\times 10^4$ ) of 15.8 and 5.2  $P = 0.0002$ . (As expected, the median PSA at 24 months in those on dutasteride decreased to 3.0 (dutasteride with cancer) and 2.2 (dutasteride without cancer) ng/mL. The calculated median PSAVs for these two cohorts were -34.9 and -37.9 ng/mL per day  $\times 10^4$  in patients with and without CaP on 2-year TRUS biopsy respectively  $P = 0.03$ ).

In order to account for the dual effect of 5aRI on PSA and prostate volume, we calculated the PSADV (ng/mL/cc per day  $\times 10^6$ ) at 24 months for each group. The median PSADV was positive ( $> 0$ ) only in the group of patients on placebo who were diagnosed with CaP and was 15.9. The remainder of the groups had a negative ( $< 0$ ) median PSADV, with values of -4.8 (placebo without cancer), -46.3 (dutasteride with cancer) and -73.2 (dutasteride without cancer). The results of PSA, PSAV, and PSADV among the subgroups are summarized in Table 1. Using the Wilcoxon rank sum test, there was a significant difference in PSADV between those patients taking dutasteride with CaP at 2 years and those without CaP (median of -46.3 vs -73.2,  $P = 0.0019$ ). Results of PSADV stratified by treatment and biopsy results are seen in the boxplots in Figure 1.

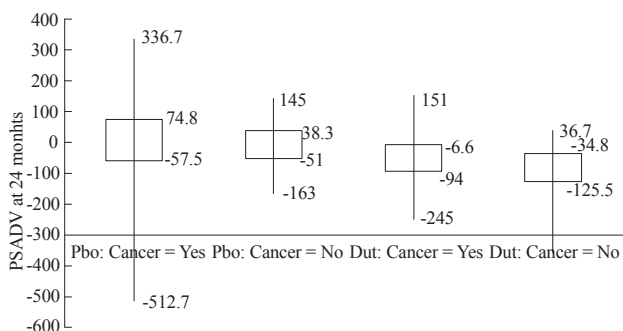
Figure 2 depicts ROC curves for PSADV.

## DISCUSSION

Prostate cancer remains a very commonly encountered clinical entity for primary care physicians and urologists alike. We have seen an increased detection of CaP as a result of early screening efforts in the PSA era. However, PSA is a non-specific marker for prostate cancer and may be increased for a variety of reasons, most notably due to CaP or BPH<sup>[16]</sup>. This inevitably creates the difficult diagnostic quandary engendering considerable patient anxiety and physician uncertainty.

Contemporary extended prostate biopsy schemes have significantly improved the cancer detection rates compared to the historical sextant

Endpoint	Visit	Placebo w Pca	Placebo w/o Pca	Dutasteride w/ Pca	Dutasteride w/o Pca	P value
PSA (ng/mL)	Entry	5.8	5.6	5.2	5.5	
	24 months	6.6	5.7	3	2.2	
PSAV (ng/mL/day × 10 <sup>4</sup> )	24 months	15.8	5.2	-34.9	-37.9	0.03
PSADV (ng/mL/cc/day × 10 <sup>6</sup> )	24 months	15.9	-4.8	-46.3	-73.2	0.002



**Figure 1** PSADV with Confidence Intervals at 24 months in Patients with and without CaP on and not on Dutasteride.

biopsy scheme<sup>[17]</sup>. The unifying theme of extended biopsies is one of maximizing cores taken from the lateral peripheral zone, the most common site of CaP. Extended, saturation, and transperineal biopsy templates have been studied and CaP detection rates range from 29-43%<sup>[18-20]</sup>. Regardless of the approach to biopsy, there remains a majority of patients at risk for CaP with a negative biopsy.

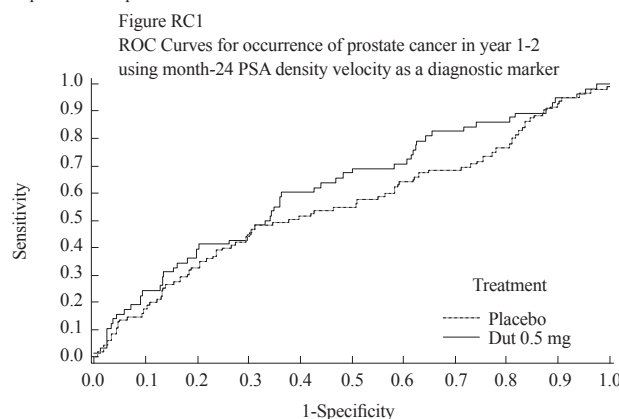
Knowing the limitations of PSA as a screening test for the detection of prostate cancer, many have investigated refinements in PSA including corrections for volume (PSAD), molecular forms (F/T PSA), and kinetics (PSAV) to improve the predictive value of CaP detection of TRUS biopsy. In a study of 1,708 men referred for prostate biopsy, Elliott et al. determined that PSAD had a significantly higher area under the curve (AUC) than PSA for detecting all CaP (0.737 vs 0.633,  $P < 0.001$ ) as well as for detecting high grade (0.766 vs 0.673,  $P < 0.001$ ) and high volume (0.843 vs 0.755,  $P < 0.001$ ) disease<sup>[21]</sup>. Similarly, in a large study of 1,051 men with a PSA between 4 to 10 ng/mL undergoing TRUS biopsy, the AUC for percent free PSA (0.745) was higher than transition zone PSAD (0.691), PSAD (0.618), and total PSA (0.603)<sup>[22]</sup>.

5-alpha reductase (5aR) is the enzyme expressed in prostate tissue responsible for the conversion of testosterone to dihydrotestosterone (DHT) (the more potent ligand for androgen receptors within the prostate) and exists in two isoforms, type 1 and type 2. Research has shown that 5aR levels are disproportionately expressed in patients with prostate cancer, with increased levels detected in men with localized high grade CaP. 5aR levels are higher in benign tissue adjacent to foci of prostate cancer<sup>[23]</sup>. Given the shortcomings of PSA as a predictor of CaP on prostate biopsy coupled with the incongruous expression of 5aR in prostate glands harboring cancer, others have investigated the ability of 5aRI therapy to differentially alter PSA in a manner to improve its ability to predict the presence of cancer on subsequent prostate biopsy.

Two large randomized, double-blind, placebo-controlled trials, the Prostate Cancer Prevention Trial (PCPT) and the REDUCE trial have reported on the role of 5aRI therapy for chemoprevention of CaP<sup>[24,25]</sup>. Both trials showed a significant reduction in overall prostate detection risk, but concerns regarding an increased proportion of high grade CaP have rendered 5aRI therapy controversial for chemoprevention. However, on subset analyses of both trials, PSA demonstrated

Dutasteride  
Protocol: ARI40006  
Population: Biopsied

Page 1 and 1  
Year 4 + 4-Mo FU



**Figure 2** ROC Curve for CaP using PSADV as Diagnostic Marker. Note: Analysis excludes measurement occurring on or after the prostate cancer diagnosis date, as well as those occurring on or after the last cancer assessment biopsy in year 1-2. PSA measurement on the date of a biopsy (or within 42 days after) have been deleted.

**Figure 2** ROC Curve for CaP using PSADV as Diagnostic Marker.

improved sensitivity in overall prostate cancer detection as well as high grade CaP compared to those treated with placebo<sup>[10-12]</sup>.

In the present study, the REDUCE trial data was utilized in order to evaluate a novel PSA parameter, PSADV, as a test to further discriminate between those patients with an elevated PSA due to CaP versus BPH. We found that in those patients treated with 0.5mg of dutasteride daily over a 2-year period, those with an ultimate diagnosis of prostate cancer demonstrated a significantly less pronounced decrease in PSADV compared to those without CaP. In this subset analysis, the PSADV was statistically different in the treatment arm subjects depending on the presence of prostate cancer and therefore warrants further study of its ability to guide decision-making in the difficult clinical scenario of patients with an elevated PSA after previous negative prostate biopsy.

Andriole et al published a report describing that dutasteride decreased the number of false positive PSA signaling low grade cancer diagnosis and enhancing the high grade identification<sup>[26]</sup>.

There are several limitations of the study. The retrospective nature introduces many potential biases. The fact that only a subgroup of patients initially registered in the study were included inherently adds selection bias. Given that PSADV is influenced by several variables most substantially by the addition of an alpha reductase inhibitor it is not an independent tumor marker. Finally, the ability to practically calculate a “reduction” in PSADV in clinical practice and where to set the optimal “cutoff” point to prevent repeat prostate biopsies requires further investigation.

## CONCLUSION

We postulate that PSADV may be an invaluable diagnostic adjunct to help urologists decide which patients will benefit from repeat biopsy

versus those that are more appropriately managed without biopsy. PSADV therefore may reduce not only unnecessary prostate biopsies but also may assist in identifying higher grade clinical significant prostate cancer.

## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

## REFERENCES

1. Siegel R, Desantis C, Virgo K *et al.* Cancer treatment and survivorship statistics, 2012. *CA: a cancer journal for clinicians* 2012; **62**: 220-241.
2. Meeks JJ, Maschino AC, Mcvary KT, Sandhu JS. Clinically significant prostate cancer is rarely missed by ablative procedures of the prostate in men with prostate specific antigen less than 4ng/ml. *J Urol* 2013; **189**: 111-115.
3. Rodriguez LV, and Terris MK. Risks and complications of tranrectal ultrasound guided prostate needle biopsy: a prospective study and review of the literature. *J Urol* 1998; **160**: 2115-2120.
4. Loeb S, Carter HB, Berndt SI *et al.* Complications after prostate biopsy: data from SEER-Medicare. *J Urol* 2011; **186**: 1830.
5. Liss MA, Chang A, Santos R *et al.* Prevalence and significance of fluoroquinolone resistant Escherichia coli in patients undergoing transectral ultrasound guided prostate needle biopsy. *J Urol* 2011; **185**: 1283.
6. Roehrborn CG, Pickens GJ, Carmody T. Variability of repeated serum prostate-specific antigen (PSA) measurements within less than 90 days in a well-defined population. *Urology* 1996; **47**: 59-66.
7. Brawer MK, Daum P, Petteway JC, Wener MH. Assay variability in serum prostate-specific antigen determination. *Prostate* 1995; **27**: 1-6.
8. Kaplan SA, Ghafar MA, Volpe MA *et al.* PSA response to finasteride challenge in men with a serum PSA greater than 4ng/ml and previous negative prostate biopsy: Preliminary study. *Urology* 2002; **60**: 464-468.
9. Handel LN, Agarwal S, Schiff SF, Kelty PJ, Cohen SI. Can effect of finasteride on prostate-specific antigen be used to decrease repeat prostate biopsy? *Urology* 2006; **64**
10. Thompson IM, Chi C, Ankerst DP *et al.* Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. *J Natl Cancer Inst* 2006; **98**: 1128-1133.
11. Andriole GL, Bostwick D, Brawley OW *et al.* 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. *J Urol* 2011; **185**: 126-131.
12. Andriole GL, Guess HA, Epstein JI *et al.* Treatment with finasteride preserves usefulness of prostate-specific antigen in the detection of prostate cancer: Results of a randomized double-blind, placebo-controlled clinical trial. *Urology* 1998; **52**: 195-202.
13. Roehrborn CG, Andriole GL, Wilson TH *et al.* Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the combination of Avodart and tamsulosin trial. *Eur Urol* 2011; **59**: 244-249.
14. Kaplan SA, Lee RK, Chung DE *et al.* Prostate biopsy in response to a change in nadir prostate specific antigen of 0.4 ng/ml after treatment with 5 $\alpha$ -reductase inhibitors markedly enhances the detection rate of prostate cancer. *J Urol* 2012; **188**: 757-761.
15. Andriole G, Bostwick D, Brawley O *et al.* Chemoprevention of prostate cancer in men at high risk: rationale and design of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. *J Urol* 2004; **172**: 1314-1317.
16. Stamey TA, Yang N, Hay AR *et al.* Prostate specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med* 1987; **317**: 909.
17. Hong YM, Lai FC, Chon CC *et al.* Impact of prior biopsy scheme on pathologic features of cancers detected on repeat biopsies. *Urol Oncol* 2004; **22**: 7.
18. Babaian RJ, Toi A, Kamoi K *et al.* A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol* 2000; **163**: 152.
19. Stewart CS, Leibovich BC, Weaver AL *et al.* Prostate cancer diagnosis using a saturation needle biopsy technique after previous negative sextant biopsies. *J Urol* 2001; **166**: 86.
20. Igel TC, Knight MK, Young PR *et al.* Systematic transperineal ultrasound guided template biopsy of the prostate in patients at high risk. *J Urol* 2001; **165**: 1575.
21. Elliott CS, Shinghal R, Presti JC. The performance of prostate specific antigen, prostate specific antigen density and transition zone density in the era of extended biopsy schemes. *J Urol* 2008; **179**: 1756.
22. Djavan B, Zlotta A, Remzi M *et al.* Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men. *J Urol* 2000; **163**: 1144.
23. Thomas LN, Douglas RC, Lazier CB *et al.* Levels of 5 $\alpha$ -reductase type 1 and type 2 are increased in localized high grade compared to low grade prostate cancer. *J Urol* 2008; **179**: 147.
24. Thompson IM, Goodman PJ, Tangen CM *et al.* The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215-224.
25. Andriole GL, Bostwick DG, Brawley OW *et al.* Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010; **362**: 1192-1202.
26. Andriole GL, Bostwick DG, Brawley OW *et al.* 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. *Journal of Urology* 2011; **185**: 126-131.

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