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Decision analysis of dutasteride use for patients with negative prostate biopsy

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Abstract

Objective—To determine whether the additional benefits of improved prostate cancer detection associated with 5-alpha reductase inhibitors are sufficient to warrant chemoprevention in the case where the degree of prostate cancer risk reduction is deemed inadequate.

Methods—We reanalyzed data from REDUCE, a randomized trial of dutasteride for prostate cancer chemoprevention in men with prior negative biopsy. We evaluated whether statistical models utilizing PSA and PSA velocity could help predict the result of repeat prostate biopsy separately for dutasteride and placebo groups. Area-under-the-curve (AUC) was evaluated by 10-fold cross-validation.

Results—PSA velocity improved discrimination at 4 years in the dutasteride group, but not at 2 years nor in the placebo group. At 2 years, dutasteride improved discrimination of PSA slightly (0.616 vs. 0.603 for any grade cancer; 0.681 vs. 0.676 for high grade disease). Between group differences in cancer rates at 4 years were small.

Conclusion—Clinicians who are willing to treat at least 23 patients with dutasteride for two years to avoid one prostate cancer should offer dutasteride after initial negative biopsy. Clinicians not willing to do so might consider dutasteride for its additional benefit of reducing unnecessary biopsy, although this benefit is apparent only under very restrictive conditions. It is difficult to justify extending treatment with dutasteride for more than two years.

Keywords

prostate cancer; chemoprevention; prostate specific antigen; prediction; velocity

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Conflict of interest: Dr Andrew Vickers is named as a co-inventor on a patent application for a statistical method for predicting the result of a prostate cancer biopsy. The test has been commercialized by Opko: Dr Vickers has stock options in Opko and is due to receive royalty payments from sales of the test.
Daniel Sjoberg has undertaken consulting for Opko.

Introduction

Two large randomized trials have clearly demonstrated that 5α-reductase inhibitors can reduce the risk of prostate cancer. The Prostate Cancer Prevention Trial (PCPT)[1] randomized 18,882 men aged 55 or older with negative digital rectal exam (DRE) and confirmed low prostate-specific antigen (PSA) to 7 years of placebo or finasteride. Prostate cancer rates were 24% and 18% respectively, a statistically significant 25% relative risk reduction. The PCPT has not led to widespread use of finasteride as a chemopreventive[2]. This is partly due to fears that finasteride may increase the risk of high-grade cancer, with about a 15% increase in high-grade tumors. More recent research indicates that this effect is likely related to the differential sampling of high-grade disease in small prostate volumes. For example, studies of radical prostatectomy specimens, which are not subject to these sampling effects, do not find increases in the risk of high-grade disease with finasteride[3].

A second disincentive to prostate cancer chemoprevention is that the average man is at insufficient risk of prostate cancer to merit the relatively modest absolute benefits of treatment. There have been two approaches to this conundrum. The first is to define a high-risk group in terms of baseline PSA. It has been shown that, given certain reasonable assumptions about the number of patients a doctor would be willing to treat with finasteride to prevent one cancer, restricting its use to patients with PSA above 2 ng/ml would lead to a better balance of patients treated and cancers prevented than prescribing finasteride on either all or no men[4]. The alternative approach is to define high-risk in clinical terms. This was the approach taken by the investigators of the second major trial of 5α-reductase inhibitor chemoprevention, REDUCE, in which men with an initial negative prostate biopsy were randomized to receive dutasteride or placebo. The results were similar to PCPT, with a 23% relative reduction in the risk of prostate cancer within four years.[5]

The use of 5α-reductase inhibitors is known to improve the operating characteristics of the PSA test[6], an effect related to the reduction in PSA elevations associated with benign enlargement. It has been argued that, even if reductions in cancer risk are insufficiently large to warrant treatment, the added benefit of improved prostate cancer detection might encourage clinicians to prescribe a 5α-reductase inhibitor. In this paper, we present an analysis of the REDUCE trial in which the benefits of dutasteride are quantified in terms of both cancer prevention and reduction in the rates of unnecessary prostate biopsy. These benefits can then be put in the context of the harms of dutasteride, considered both in terms of medical side-effects such as decreased libido and impotence, and financial costs, around $1000 per year. Our overarching assumption is that the number of patients that a doctor would expose to the harms of dutasteride to prevent one cancer or one unnecessary biopsy is limited and quantifiable.

Methods

The REDUCE trial has been described previously. In brief, 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 within 6 months before enrollment. Enrolled

patients were randomized to 0.5 mg dutasteride daily or placebo. Total PSA was measured every 6 months, with a 10-core biopsy at 2 and 4 years.

In total, 8,231 men enrolled in the REDUCE trial. Our primary aim was to investigate the utility of PSA and PSA velocity (PSAv) in predicting cancer on biopsy in men with a previous negative biopsy, separately for men on dutasteride and placebo. PSAv was calculated separately as the average change per year in PSA from 6 months after study start to 2 years and 4 years. We chose 6 months to start measuring PSA velocity as dutasteride reduces PSA to a nadir within 6 months. Velocity was calculated in two ways: 1) subtracting baseline from final pre-biopsy PSA and dividing by the time between baseline and biopsy; 2) ordinary least squares (OLS) regression using all log transformed PSA values. Two separate endpoints were used: positive biopsy, and high-grade cancer, defined as Gleason score of 7 or more.

Patients with missing PSA measurements at 6 months (n=713) were omitted from all analyses; 1378 patients were omitted from the 2 years analyses due to missing biopsy information, leaving 6140 patients for the 2 year analyses. The 4 year analyses focused on patients with a confirmation of no cancer at 2 years, thus omitting the 899 patients found to have cancer at first repeat biopsy. An additional 2225 patients were omitted due to missing PSA data at the 4 year biopsy, leaving 3016 patients available for the 4 year analyses.

To assess the ability of PSA and PSAv to predict cancer on biopsy, we assessed discrimination using the area under the receiver operator curve (AUC). Statistical models were created using logistic regression. PSA was entered into the model as the log of PSA and PSAv was entered linearly. Separate models were created for the dutasteride and placebo groups. The results of digital rectal exam were not found to be predictive and so were excluded from the model. Thus the only variables in the model were PSA and PSAv. We assumed that clinicians would biopsy patients using a risk threshold from the models. We therefore compared the number of cancers found and unnecessary biopsies conducted for each group separately. Our aim was to determine the degree to which dutasteride would reduce unnecessary biopsy rates. To correct for potential overfit, repeated 10-fold cross validation was performed. All analyses were conducted in Stata 12.0 (StataCorp, College Station, TX).

Results

Characteristics of the study cohort and cancer outcomes at 2 and 4 years are shown in Table 1. Prostate cancer rates were much lower in both groups at 4 years compared to 2 years. PSA was a statistically significant predictor of cancer and high grade cancer at two and four years for both the dutasteride and placebo arms (all $p< 0.005$). When incorporating both PSA and PSAv, the value of PSAv was sensitive to the method of calculation. For example, the average change in PSA from 6 months to 2 years is a significant predictor of cancer at 2 years in the placebo group ($p=0.002$), but OLS PSAv was not ($p=0.5$). The only scenario where both PSAv calculations were significant was predicting high grade cancer at two years in the dutasteride group ($p=0.019$ for average PSA change and $p=0.045$ for OLS PSAv), and in this case OLS PSAv is only slightly less than conventional levels of

significance. OLS PSAv is a significant predictor of both cancer and high grade cancer at 4 years in the dutasteride group ($p<0.0001$ for both outcomes), while average change in PSA was not significant ($p=0.11$ for cancer and $p=1$ for high grade cancer).

Table 2 shows the discrimination of models for each set of predictors (PSA, PSAv, log PSAv, PSA + PSAv, PSA + log PSAv), for both endpoints (any or high-grade cancer), for the two treatment groups separately (dutasteride vs. placebo) at each of the two timepoints (2 and 4 years). It is clear that PSAv is not of value in the placebo group. OLS PSAv is of value in predicting the outcome of biopsy in men treated with dutasteride at four years, with statistical models incorporating both PSA and PSAv having higher AUCs than those with PSA alone for predicting both cancer and high grade cancer at biopsy. PSAv, regardless of the method of calculation, did not have a large impact on discrimination when predicting cancer or high grade cancer at 2 years in the dutasteride group.

Cancer rates at two years are 14.4% and 18.8% in the dutasteride and placebo groups respectively. This absolute risk difference of 4.4% means that a clinician would have to be willing to treat 23 men with dutasteride for two years in order to prevent one cancer. Table 3 shows the result of applying the models to predict the risk of high-grade disease at various illustrative cut-points. The models used included only PSA for the placebo group and for the dutasteride group at two years on the grounds that PSAv either failed to improve discrimination or improvements in discrimination were sensitive to the method of analysis; for the dutasteride group at four years, OLS PSAv clearly improved predictiveness and so was included in the model alongside PSA.

One point immediately apparent from table 3 is that the statistical model would only influence clinical practice if a urologist believed that cut-points should be very low. Using a 6% or 8% risk of high-grade disease as the threshold for biopsy would typically mean avoiding biopsy for 90% of patients or more, roughly equivalent to a clinical rule of advising patients against biopsy except in unusual circumstances. It is only for cut-points such as 2% and 4% that use of a model would lead to different recommendations for different patients. Yet a risk of 4% for high-grade cancer is equivalent to a 65 year-old Caucasian man with negative DRE, no family history, and a PSA of around 2.5 ng/ml, an individual who few urologists would chose to biopsy. It is difficult to see a role for the model in clinical practice given that it only helps clinical decision-making if questionable cut-points are used.

The difference in cancer rates at four years is much lower than at two years (9.2% in the dutasteride group and 10.8% placebo group, absolute risk difference of 1.6%). This means that a clinician would need to treat 65 patients with dutasteride for two years (i.e. between two and four years after negative biopsy) in order to prevent one cancer diagnosis. This is a very high number and it is difficult to see how advantages in terms of reduced unnecessary biopsies would shift a clinician towards dutasteride treatment. As shown in table 3, most reasonable cut-points for biopsy would involve avoiding biopsy in all but a handful of men.

Discussion

There are two separate reasons why a clinician might consider use of dutasteride in a patient with a negative prostate biopsy: to reduce the risk of cancer and to improve the ability to predict the result of subsequent prostate biopsy. We have attempted to quantify these two separate effects. We have shown that a clinician might consider use of dutasteride for two years after negative biopsy, even if the effects in terms of reduced cancer risk are deemed insufficient, on the grounds that dutasteride lowers the number of unnecessary biopsies. That said, doing so would involve use of a statistical model and would have a substantive effect across a very limited range of threshold risks for biopsy, threshold risks that are lower than typical. It is difficult to justify the use of dutasteride for more than two years, even though doing so allows good predictions as to the outcome of biopsy at four years.

Our results on PSA velocity are worthy of further comment. PSA velocity has been widely promoted as a prognostic factor in prostate cancer[7], despite a dearth of evidence that it aids prediction[8]. In brief, while most papers show a statistically significant association between PSA velocity and outcome, few if any show that adding information on PSA velocity to PSA alone materially aids prediction or decision-making. In a typical study, PSA velocity was an independent predictor of biopsy outcome after adjusting for PSA, family history, DRE and prior biopsy. However, the AUC of the model increased from 0.702 to only 0.709 with the addition of PSA velocity[9]. In this paper, we confirmed prior data showing lack of benefit for PSA velocity in untreated men, including previously published analyses of the REDUCE trial[10]. Our AUC values are slightly different from those previously published - predominately because we log transformed PSA and used crossvalidation to correct for optimism when developing and testing a model on the same data set – but the overall conclusions are similar. We clearly demonstrate that PSA velocity does add prediction for patients treated by dutasteride for four years: PSA velocity was not only a statistically significant predictor of biopsy outcome, but it importantly increased AUC compared to PSA alone (e.g. from 0.63 to 0.71 for high grade cancer).

There is a clear biologic rationale as to why PSA velocity is helpful only in patients treated by a 5α reductase inhibitor for four years. In an untreated man, especially those with the sort of high PSAs that lead to biopsy, PSA levels often include PSA associated with benign inflammation. Variation in benign disease therefore leads to variation in PSA, and disproportionate variation in PSA velocity, which is a combination of absolute PSA levels. In the dutasteride treated prostate, benign inflammation is reduced, with concomitant large reductions in the variation in PSA associated with benign disease. In simple terms, if PSA rises in an untreated man, this may be due to either benign or malignant processes; for a man undergoing dutasteride treatment, increases due to benign disease are unlikely, meaning that a rise in PSA is probably cancer related. The time period of four years allows a sufficient PSA history for accurate determination of velocity.

That said, it is difficult to justify 4 rather than just 2 years of treatment on dutasteride, on the grounds that the decrease in risk between 2 and 4 years is very small, just 1.6%. Thus, unless a clinician was willing to treat more than 60 patients with dutasteride to prevent one cancer, the predictive value of PSA velocity in this setting has no clinical implications.

The main limitation of our paper is that it presents very much a “best case” scenario for dutasteride. We report that a clinician who was not willing to prescribe dutasteride for its effects on cancer risk at two years, might consider doing so for added benefit in terms of reducing unnecessary biopsy. However, the effects on unnecessary biopsy are based on a statistical model. For clinical benefit, we would need to assume that the model retains validity in the population of patients seen by the clinician, that the clinician would have easy access to the model and would use it rationally. All of these assumptions would have to be tested. A further limitation of our study is that any added benefits of biopsy prediction associated with dutasteride would be retained with the addition of other markers, such as free-to-total PSA ratio.

In conclusion, for the many patients who meet the REDUCE criteria – aged 50 to 75 with moderately elevated PSA following a recent initial negative prostate biopsy – dutasteride is a possible therapeutic option. Clinicians who are willing to treat at least 23 patients with dutasteride for two years to avoid one cancer should offer dutasteride. Clinicians who did not believe that the relative harms of dutasteride relative to a prostate cancer diagnosis justified treating 23 patients, should consider dutasteride for reduction of unnecessary biopsy only under restrictive conditions: that they would be willing to use a statistical model in practice, and if their threshold for biopsy was around a 4% risk of high grade disease. It is difficult to justify extending treatment with dutasteride for more than two years.

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Table 1

Patient Characteristics. Statistics presented are median (IQR) or frequency (percent)

	Dutasteride		Placebo	
2 Year (n=4296)	**No Cancer (N=1823; 85.6%)**	**Cancer (N=307; 14.4%)**	**No Cancer (N=1759; 81.2%)**	**Cancer (N=407; 18.8%)**
Age at Treatment Start	63 (58, 67)	64 (60, 68)	63 (58, 67)	65 (59, 69)
PSA at 6 Months	3 (2, 4)	3 (2, 4)	5 (4, 7)	6 (4, 7)
Year 2				
Year 2 DRE Result				
Normal	1706 (94%)	249 (81%)	1666 (95%)	312 (77%)
Abnormal	76 (4%)	11 (4%)	56 (3%)	23 (6%)
Unknown	41 (2%)	47 (15%)	37 (2%)	72 (18%)
PSA at 2 Yr Study Biopsy	2 (2, 3)	3 (2, 4)	6 (4, 8)	7 (5, 10)
PSA velocity from 6 months to 2 years (per year)	-0.21 (-0.64, 0.13)	0.06 (-0.34, 0.71)	0.46 (-0.13, 1.32)	0.80 (0.13, 1.91)
Bx Gleason Grade				
<=6		209 (68%)		293 (72%)
7		86 (28%)		105 (26%)
>=8		12 (4%)		9 (2%)
4 Years (n=3016)	**No Cancer (N=1421; 90.7%)**	**Cancer (N=145; 9.3%)**	**No Cancer (N=1294; 89.2%)**	**Cancer (N=156; 10.8%)**
Age at Treatment Start	63 (58, 67)	65 (60, 68)	62 (58, 67)	63 (58, 68)
PSA at 6 Months	3 (2, 4)	3 (2, 4)	5 (4, 7)	5 (4, 6)
Year 4				
Year 4 DRE Result				
Normal	1358 (96%)	131 (90%)	1239 (96%)	145 (93%)
Abnormal	42 (3%)	13 (9%)	38 (3%)	8 (5%)
Unknown	21 (1%)	1 (1%)	17 (1%)	3 (2%)
PSA at 4 Yr Study Biopsy	2 (1, 3)	3 (2, 4)	6 (4, 9)	7 (5, 10)
PSA velocity from 6 months to 4 years (per year)	-0.14 (-0.35, 0.03)	0.00 (-0.23, 0.34)	0.36 (0.00, 0.77)	0.57 (0.20, 1.15)
Bx Gleason Grade				
<=6		101 (70%)		123 (79%)
7		41 (28%)		32 (21%)

	Dutasteride		Placebo	
>=8		3 (2%)		1 (1%)

Table 2

AUC of PSA and PSA velocity

	Dutasteride		Placebo	
2 years	**Any cancer**	**High grade**	**Any cancer**	**High grade**
PSA	0.616 (0.582, 0.650)	0.681 (0.627, 0.735)	0.603 (0.573, 0.632)	0.676 (0.628, 0.725)
PSAv	0.631 (0.596, 0.666)	0.710 (0.657, 0.763)	0.584 (0.554, 0.615)	0.658 (0.608, 0.708)
OLS Log PSAv	0.621 (0.587, 0.655)	0.709 (0.659, 0.758)	0.571 (0.541, 0.600)	0.634 (0.585, 0.683)
PSA+PSAv	0.605 (0.571, 0.639)	0.663 (0.609, 0.718)	0.598 (0.568, 0.628)	0.671 (0.621, 0.721)
PSA+ OLS Log PSAv	0.626 (0.592, 0.661)	0.706 (0.652, 0.759)	0.595 (0.565, 0.625)	0.656 (0.606, 0.706)
4 years				
PSA	0.600 (0.550, 0.650)	0.634 (0.540, 0.729)	0.584 (0.539, 0.629)	0.697 (0.615, 0.779)
PSAv	0.636 (0.586, 0.686)	0.724 (0.643, 0.804)	0.609 (0.563, 0.655)	0.722 (0.639, 0.805)
OLS Log PSAv	0.658 (0.609, 0.707)	0.716 (0.629, 0.804)	0.598 (0.550, 0.645)	0.653 (0.556, 0.750)
PSA+PSAv	0.610 (0.560, 0.660)	0.626 (0.529, 0.723)	0.576 (0.531, 0.620)	0.680 (0.598, 0.761)
PSA+ OLS Log PSAv	0.654 (0.605, 0.703)	0.707 (0.618, 0.796)	0.590 (0.543, 0.638)	0.679 (0.584, 0.774)

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Table 3

Clinical implications of using statistical models to determine biopsy in the dutasteride and placebo groups, per 10,000 men

Dutasteride at 4 years uses PSA+OLS PSAv, all others use PSA alone. The columns “found” and “delayed” illustrate the clinical implications for each strategy. For instance, if a doctor prescribed dutasteride for 2 years and then biopsied men if they had a 4% or greater risk of cancer, 5529 would be biopsied with 359 high grade cancers identified; 134 men would have high-grade cancer but would not be biopsied.

		Dutasteride			Placebo		
Risk of high grade cancer		**Biopsied**	**Found**	**Delayed**	**Biopsied**	**Found**	**Delayed**
Year 2							
≥ 2%	High Grade	9866	460	33	9889	493	0
	Any Cancer		1431	231		1662	0
≥ 4%	High Grade	5529	359	134	9350	493	0
	Any Cancer		979	683		1662	0
≥ 6%	High Grade	570	82	411	1156	148	346
	Any Cancer		181	1481		321	1341
≥ 8%	High Grade	330	46	447	379	34	460
	Any Cancer		89	1573		81	1581
Year 4							
≥ 2%	High Grade	4981	203	53	6330	196	60
	Any Cancer		617	381		803	195
≥ 4%	High Grade	1589	134	121	395	13	242
	Any Cancer		324	674		51	947
≥ 6%	High Grade	680	79	177	57	0	255
	Any Cancer		172	826		3	995
≥ 8%	High Grade	399	52	203	35	0	255
	Any Cancer		108	890		0	998

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