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The impact of statins in combination with androgen deprivation therapy in patients with advanced prostate cancer: A large observational study

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Abstract

Background: Statins are thought to possess antineoplastic properties related to their effect on cell proliferation and steroidogenesis. Progression to castrate resistant prostate cancer (CaP) includes de-regulation of androgen synthesis suggesting a role for statins in this setting. Our goal was to assess the role of statin use on oncologic outcomes in patients with advanced CaP being treated with androgen deprivation therapy (ADT).

Methods: The national VA database was used to identify all men diagnosed with CaP who were treated with ADT for at least 6 months between 2000 and 2008 with follow-up through May 2016. Our cohort was stratified based on statin use of at least 6 months duration during the same time. Multivariable Cox proportional hazards analyses with inverse propensity score weighted (IPSW) adjustment were calculated to assess for primary outcomes of CaP-specific survival (CSS), overall survival (OS) and skeletal related events (SREs).

Results: A total of 87,346 patients on ADT were included in the study cohort, 53,360 patients used statins and 33,986 did not. Statin users were younger in age (median 73 vs. 76, $P < 0.001$), more likely to have a higher Charlson comorbidity index (CCI) >3 (3.1% vs. 2.5%, $P < 0.001$) and more likely to have a high grade (Gleason score 8–10) cancer (12.3% vs. 10.9%, $P < 0.001$). Statin users had longer OS (median 6.5 vs. 4.0 years $P < 0.001$) and decreased death from CaP (5-year CSS 94.0% vs. 87.3%, $P < 0.001$). Statin use was also associated with longer time to a SRE (median 5.9 vs. 3.7 years, $P < 0.001$). On multivariable Cox proportional hazards analysis with inverse propensity score weighted, statin use was an independent predictor of improved OS (hazard ratio [HR] 0.66, confidence interval [CI] 0.63–0.68; $P < 0.001$), CSS (HR 0.56, 95% CI 0.53–0.60; $P < 0.001$), and SREs (HR 0.64, 95%CI 0.59–0.71; $P < 0.001$) when controlling for age, race, Charlson comorbidity index, prostate-specific antigen, and Gleason score.

Conclusion: The use of statins in men on ADT for CaP is associated with improved CSS and OS. Statins are inexpensive, well-tolerated medications that offer a promising adjunct to ADT, but require further prospective studies.

Keywords: Prostatic neoplasms; Hydroxymethylglutaryl-CoA reductase inhibitors; Gonadotropin-releasing hormone/analogs and derivatives; Hospitals; Veterans

Abbreviations: ADT, androgen deprivation therapy; IPSW, inverse propensity score weighted; CCI, Charlson comorbidity index; OS, overall survival; CaP, prostate cancer; CSS, prostate cancer-specific survival; PSA, prostate-specific antigen; SRE, skeletal related event; VA, Veterans Health Administration

1. Introduction

Statins are one of the most commonly prescribed medications for hypercholesterolemia worldwide, with 1 in 4 Americans over 45 taking a daily statin [1]. Statins lower cholesterol levels by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme

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A enzyme at the rate limiting step in the mevalonate pathway of cholesterol synthesis [2]. Recent research has focused on the antineoplastic role of statins through their impact on cell proliferation, inflammation, membrane organization, and steroidogenesis [3]. The androgen-dependent nature of prostate cancer (CaP) has made it a perfect candidate for study of statin based cancer prevention and therapy. Additionally, recent Phase III trials have defined a role for androgen deprivation therapy (ADT) in combination with docetaxel or abiraterone for metastatic hormone-sensitive CaP suggesting combination therapy improves the ability of ADT to lengthen survival [4,5].

Observational studies suggest that long-term statin therapy may prevent aggressive CaP [3]. The role of statins in decreasing CaP specific and overall cancer mortality is more heavily disputed [6]. Specifically, there are few studies focusing on the role of statins in advanced CaP and prevention of progression to castrate resistant CaP and subsequent death. It is now recognized that castration resistance is at least partially related to CaP cells' ability to undergo intratumoral steroidogenesis sufficient to activate the androgen receptor [3,7]. This may explain the resistance to ADT seen in many patients with advanced CaP. Statins may work synergistically with ADT by lowering cholesterol and hence, decreasing the availability of the major substrate for androgen synthesis [3]. Furthermore, statins have also been shown to down-regulate androgen receptors via proteolysis, alter cell signaling pathways, and induce apoptosis of proliferating cells [3,8]. Our goal was to assess the effect of statin use on oncologic outcomes in patients with advanced CaP at the time of ADT initiation.

2. Materials and methods

2.1. Data source

The study was approved by the local Institutional Review Board. The Veterans Health Administration (VA) health system is one of the largest integrated health systems in the United States. All care provided to veterans is recorded in their electronic health record—the Veterans Information System Technology Architecture. All information regarding patient care is extracted from Veterans Information System Technology Architecture systems and stored on the Corporate Data Warehouse (CDW). The Veterans Health Administration's (VA) CDW includes data from over 20 years of Electronic Health Record Use [9]. The VA is unique in that it provides an integrated way to monitor medication use as most patients receive their medications through the VA due to the lower copays. Of the 5,958,849 veterans treated in 2015, 83.8% use their VA pharmacy benefits and fill prescriptions through the VA pharmacy [10]. The CDW was used herein to characterize the effects of concurrent statin and ADT use on CaP outcomes in a large, diverse patient cohort.

2.2. Study population

We developed a cohort of men with CaP on ADT by initially identifying all men diagnosed with CaP (ICD-9 code 185) from January 1, 2000 through December 31, 2008 ($n = 558,252$). We then identified utilization of ADT within the CaP cohort ($n = 129,572$) from January 1, 2000 through May 31, 2016. Utilization of ADT was established by querying the pharmacy data for the only approved ADT medications on formulary during the study period including leuprolide, bicalutamide, flutamide, nilutamide, and goserelin. We excluded medication records with no information on supply days, quantity, or dosages. Patients that were treated with ADT $\leq$ 6 months ($n = 33,312$) or who received ADT concurrently with primary radiation therapy ($n = 10,960$) were also excluded from the final cohort. This left a final cohort of 87,346 patients for analysis. ADT was entered as a time-dependent variable in the models. The cohort population was then stratified by statin use using the pharmacy databases to identify all patients taking a statin at any dose during the study period for a minimum of 6 months ($N = 53,360$). All participants were followed until death or study end of May 31, 2016 at which point they were censored.

2.3. Outcomes of interest

The primary outcome was overall survival (OS) defined as the time from ADT initiation to death from any cause to limit the effect of lead time bias. Secondary outcomes included CaP-specific survival (CSS) and skeletal related events (SRE). CSS was defined as the time from ADT initiation to death from CaP. SRE was used as a surrogate for progression since approximately 70% of patients dying of CaP will have bone metastases [11]. We used a previously described model which identifies SREs using claims that indicate pathologic fractures, spinal cord compression, radiation, and bone surgery [12].

We adjusted for demographic and clinical characteristics of each patient including age at ADT initiation, race, Agent Orange exposure, duration of ADT use, Charlson comorbidity score (CCI), prostate-specific antigen (PSA) at initiation of ADT, year of diagnosis, and Gleason score.

2.4. Statistical analysis

Statistical analysis was performed using Stata 14 (College Station, TX). Comparison of medians was performed using the Mann-Whitney U test. Fisher's exact and chi-squared tests were used for comparison of categorical variables. Multivariable Cox proportional hazards models were performed to assess for independent predictors of OS, CSS, and SRE adjusted for potential confounding covariates included in the baseline demographic data. We then computed a propensity score by multinomial logistic regression and then utilized this for inverse propensity score weighted

(IPSW) adjustment in the final models [13]. A subset analysis was also performed in patients with PSA > 10 at time of ADT initiation. The models were limited to patients in whom all key covariates were available. We constructed IPSW Kaplan-Meier survival curves for OS, CSS, and SRE performing a log-rank test for each curve. Last, we conducted a sensitivity analysis for CSS to account for competing risks because of death from other causes using a subdistribution hazards model adapted for time-dependent covariates [14,15]. A 2-sided *P* value of < 0.05 was considered significant.

3. Results

A total of 87,346 patients on ADT were included in the study cohort, of which 53,360 patients used statins and 33,986 did not. The statin cohort was younger in age (median 73, interquartile range [IQR] 67–78) at ADT initiation than the nonstatin cohort (median 76, IQR 70–81), *P* < 0.001. Both nonstatin and statin cohorts were composed of primarily Caucasians (60.5 and 65.2%, *P* < 0.001). Individuals taking statins were more likely to have a CCI > 3 (3.1%) compared to nonstatin users (2.5%), *P* < 0.001. Statin users at the time of initiating ADT were more likely to have a high-grade cancer (12.3%) than nonstatin users (10.9%), *P* < 0.001 (Table 1).

The median OS was 4.0 years (IQR 1.98–7.25) in the nonstatin group and 6.5 years (IQR 3.41–9.98) in the statin group (*P* < 0.001; Table 1; Fig. 1). Analysis of OS from the Cox proportional hazards model demonstrated increased OS in the statin group as compared to the nonstatin group (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.63–0.68; *P* < 0.001) after IPSW and in the subset analysis in patients with PSA > 10 (HR 0.65, 95%

Table 1
Cohort characteristics: 87,344 patients with prostate cancer on ADT.

	Nonstatin *N* = 33,986	Statin *N* = 53,360	*P* value
Age, median (IQR)	76 (70–81)	73 (67–78)	<0.001
Race, *n* (%)			<0.001
White	20,565 (60.5)	34,766 (65.2)	
Black	6,811 (20.0)	10,028 (18.8)	
Other	6,610 (19.5)	8,566 (16.1)	
Charlson comorbidity score, n (%)			<0.001
<=1	26,414 (77.7)	41,102 (77.0)	
2–3	6,724 (19.8)	10,627 (19.9)	
>3	848 (2.5)	1,631 (3.1)	
Agent Orange exposure, *n* (%)	999 (2.9)	2,477 (4.6)	<0.001
Duration ADT use			<0.001
<12 mo	11,632 (34.2)	14,337 (26.9)	
12–24 mo	9,713 (28.6)	13,329 (25.0)	
24–36 mo	4,986 (14.7)	8,063 (15.1)	
≥36 mo	7,655 (22.5)	17,631 (33.0)	
Prostate-specific antigen[a], median (IQR)	9.18 (1.53–30.5)	6.5 (1.24–16.8)	<0.001
Prostate-specific antigen[a], *n* (%)			<0.001
<4	8,159 (24.0)	15,956 (29.9)	
4–10	4,079 (12.0)	9,438 (17.7)	
>10	11,281 (33.2)	15,661 (29.4)	
Missing	10,467 (30.8)	12,305 (23.1)	
Year of diagnosis, *n* (%)			<0.001
2000–2004	27,381 (80.6)	39,795 (74.6)	
2005–2008	6,605 (19.4)	13,565 (25.4)	
Gleason score, *n* (%)			<0.001
<=6	1,852 (5.5)	4,486 (8.4)	
7	2,523 (7.4)	5,381 (10.1)	
8–10	3,693 (10.9)	6,549 (12.3)	
Missing	25,918 (76.3)	36,944 (69.2)	
Local therapy, *n* (%)	2,144 (6.3)	4,995 (9.4)	<0.001
Docetaxel, *n* (%)	1,195 (3.5)	1,700 (3.2)	0.008
Vital status, *n* (% deceased)	29,547 (86.9)	37,721 (70.7)	<0.001
Overall survival, median, years (IQR)	4.0 (1.98–7.25)	6.5 (3.41–9.98)	<0.001
Death from prostate cancer, *n* (%)	4,275 (12.6)	4,752 (8.9)	<0.001
Skeletal related event, *n* (%)	3,124 (9.2)	5,181(9.7)	0.011
Time to skeletal related event, years, median (IQR)	3.7 (1.75–6.85)	5.9 (2.85–9.42)	<0.001

ADT = androgen deprivation therapy; IQR = interquartile range; PSA = prostate-specific antigen.
[a] PSA at initiation of ADT (ng/dl).

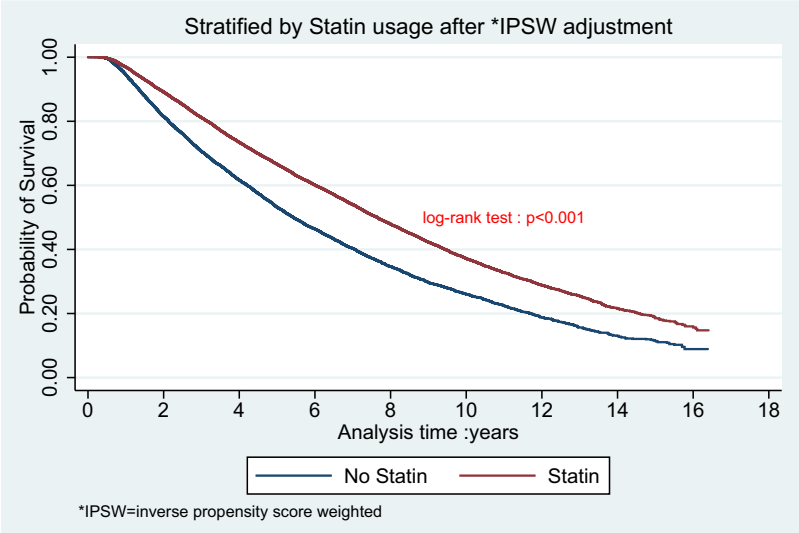

Fig. 1. Kaplan-Meier of overall survival.

CI 0.62–0.69; $P < 0.001$). All analyses adjusted for age at ADT initiation, duration of ADT use, race, CCI, Agent Orange exposure, year of diagnosis, PSA at initiation of ADT, and Gleason score (Table 2).

The 5-year freedom from SRE was 92.9% (95% CI 92.6–93.2) in the nonstatin group and 95.6% (95% CI 95.4–95.8) in the statin group, ($P = 0.011$; Fig. 2). After adjusting for similar potentially confounding variables, Cox proportional hazards model analysis for SRE demonstrated a decreased risk of SRE in the statin group as compared to the referent nonstatin group (HR 0.64, 95% CI 0.58–0.70; $P < 0.001$) after IPSW (Table 3) and even more so in the subset analysis in patients with PSA > 10 (HR 0.58, 95% CI 0.52–0.66; $P < 0.001$).

The 5-year CSS was 87.3% (95% CI 86.9–87.8) in the nonstatin users and 94.1% (95% CI 93.8–94.3) in the statin users ($P < 0.001$; Fig. 3). Statin use was associated with a reduced risk of death from CaP in the Cox proportional hazards multivariable analysis (HR 0.56 95% CI 0.53–0.60; $P < 0.001$) after IPSW (Table 4) and in the subset analysis in patients with PSA > 10 (HR 0.56, 95% CI 0.52–0.61; $P < 0.001$). After accounting for competing risks as a result of death from other causes, the decreased risk observed between statin use and CaP mortality remained statistically significant (HR 0.66, 95% CI 0.63–0.70; $P < 0.001$).

4. Discussion

Advanced CaP has classically been treated with ADT with a median survival of less than 2 years once castration resistance develops [16]. Recent research has led to the understanding that despite "castration resistance," progression of CaP may continue to be driven by androgen signaling suggesting the existence of a de novo intracellular androgen synthesis pathway [2,3]. This has led to the

Table 2
Cox proportional hazards multivariable analysis assessing predictors of overall survival after inverse propensity score weighted (IPSW) adjustment.

	HR	95% CI	*P* value
Statin			
Nonstatin	Referent	Referent	
Statin	0.66	(0.63–0.68)	<0.001
Duration ADT use			
<12 mo	Referent	Referent	
12–24 mo	0.87	(0.83–0.92)	<0.001
24–36 mo	0.66	(0.62–0.69)	<0.001
≥36 mo	0.39	(0.37–0.41)	<0.001
Age (continuous)	1.04	(1.03–1.04)	<0.001
Race			
White	Referent	Referent	
Black	0.94	(0.90–0.98)	<0.001
Other	0.95	(0.90–1.01)	0.10
Charlson comorbidity score			
≤1	Referent	Referent	
2–3	1.16	(1.10–1.21)	<0.001
>3	1.81	(1.63–2.01)	<0.001
Agent Orange exposure			
No	Referent	Referent	
Yes	0.98	(0.89–1.08)	0.70
Year of diagnosis			
2000–2004	Referent	Referent	
2005–2008	0.83	(0.80–0.87)	<0.001
Prostate-specific antigen (category)[a]			
<4	Referent	Referent	
4–10	0.97	(0.92–1.03)	0.36
>10	1.44	(1.37–1.51)	<0.001
Gleason score			
6	Referent	Referent	
7	1.10	(1.05–1.16)	<0.001
8–10	1.58	(1.50–1.66)	<0.001

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] PSA at initiation of ADT (ng/dl).

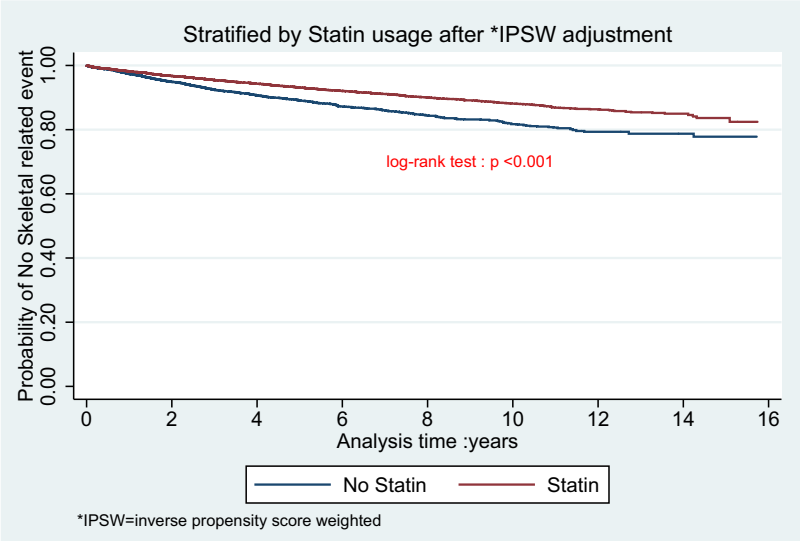

Fig. 2. Kaplan-Meier of skeletal related events.

Table 3
Cox proportional hazards multivariable analysis assessing predictors of skeletal related events after inverse propensity score weighted (IPSW) adjustment.

	HR	95% CI	*P* value
Statin			
Nonstatin	Referent	Referent	
Statin	0.64	(0.59–0.71)	<0.001
Duration ADT use			
<12 mo	Referent	Referent	
12–24 mo	0.95	(0.83–1.08)	0.41
24–36 mo	0.83	(0.71–0.96)	0.02
≥36 mo	0.56	(0.49–0.65)	<0.001
Age (continuous)	1.01	(1.00–1.01)	0.11
Race			
White	Referent	Referent	
Black	1.00	(0.89–1.12)	1.00
Other	0.90	(0.77–1.06)	0.22
Charlson comorbidity score			
≤1	Referent	Referent	
2–3	1.09	(0.97–1.23)	0.16
>3	1.53	(1.18–1.99)	<0.001
Agent Orange exposure			
No	Referent	Referent	
Yes	1.05	(0.86–1.27)	0.66
Year of diagnosis			
2000–2004	Referent	Referent	
2005–2008	1.05	(0.95–1.17)	0.34
Prostate-specific antigen (category)[a]			
<4	Referent	Referent	
4–10	1.26	(1.07–1.50)	0.01
>10	1.98	(1.73–2.27)	<0.001
Gleason score			
6	Referent	Referent	
7	0.96	(0.83–1.12)	0.62
8–10	1.61	(1.40–1.85)	<0.001

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] PSA at initiation of ADT (ng/dl).

discovery of new therapeutic agents such as enzalutamide and abiraterone which target the androgen synthesis pathway [16] as well as generated interest in the use of statins to prevent CaP progression. This study demonstrates for the first time that statin use, at the time of ADT initiation, was associated with improved oncological outcomes in patients with advanced CaP. The initiation of ADT represents a novel therapeutic niche with cancer cells developing altered signaling and metabolism that may be exploited.

Our study of 87,346 patients on ADT, of which more than 53,000 took a statin for at least 6 months during the study period, found that statins use was associated with a significant improvement in oncological outcomes. We showed that patients with CaP on ADT who were concurrently taking statins had increased OS (HR 0.66 $P < 0.001$), decreased CaP-specific mortality (HR 0.56 $P < 0.001$) and fewer SRE (HR 0.64 $P < 0.001$). These observations were notable given increased rates of high grade cancers in the statin group that was adjusted for in the multivariable models which were performed in patients in whom all key covariates were available. Higher Gleason score is one of the strongest predictors of CaP-specific death in advanced CaP and this observation emphasizes the potential advantage of combining ADT and statins [17].

Statins are commonly used to lower cholesterol levels and decrease cardiovascular risk. Many studies have shown that cholesterol is a crucial component of cell membranes and that its absence is sufficient to cause a halt in cell cycle progression. This is especially important in rapidly proliferating cancer cells, which require increased levels of cholesterol to sustain their growth. By reducing available substrate, cholesterol synthesis inhibitors may be able to induce significant apoptosis [2]. Cholesterol is also a major precursor in androgen synthesis. Castration resistance in CaP is thought to develop due to the ability of tumor cells

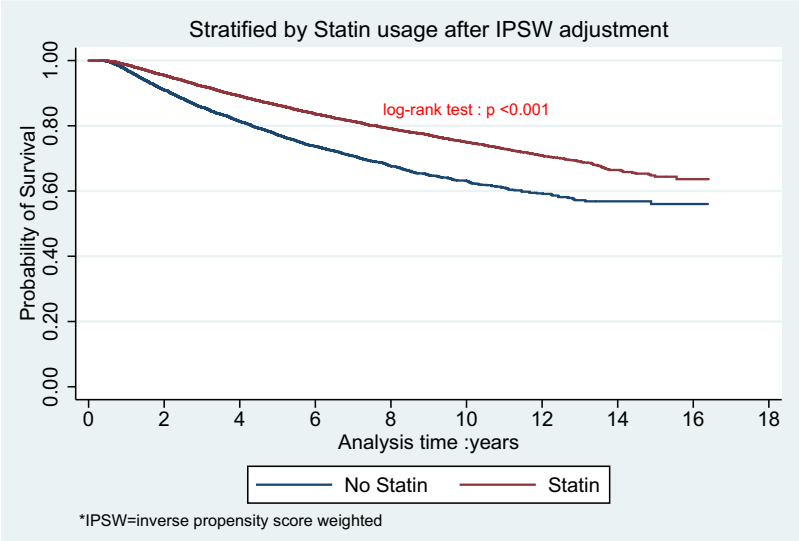

Fig. 3. Kaplan-Meier of prostate cancer specific survival.

Table 4
Cox proportional hazards multivariable analysis assessing predictors of prostate cancer specific survival after inverse propensity score weighted (IPSW) adjustment.

	HR	95% CI	*P* value
Statin			
Nonstatin	Referent	Referent	
Statin	0.56	(0.53–0.60)	<0.001
Duration ADT use			
<12 mo	Referent	Referent	
12–24 mo	0.78	(0.72–0.84)	<0.001
24–36 mo	0.58	(0.53–0.64)	<0.001
≥36 mo	0.29	(0.26–0.31)	<0.001
Age (continuous)	1.02	(1.01–1.02)	<0.001
Race			
White	Referent	Referent	
Black	1.02	(0.95–1.10)	0.55
Other	0.94	(0.86–1.04)	0.26
Charlson comorbidity score			
≤1	Referent	Referent	
2–3	1.14	(1.06–1.23)	<0.001
>3	1.60	(1.35–1.91)	<0.001
Agent Orange exposure			
No	Referent	Referent	
Yes	0.94	(0.80–1.10)	0.42
Year of diagnosis			
2000–2004	Referent	Referent	
2005–2008	0.76	(0.71–0.81)	<0.001
Prostate-specific antigen (category)[a]			
<4	Referent	Referent	
4–10	1.04	(0.93–1.16)	0.49
>10	1.92	(1.76–2.09)	<0.001
Gleason score			
6	Referent	Referent	
7	1.18	(1.07–1.30)	<0.001
8–10	2.24	(2.05–2.45)	<0.001

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.
[a] PSA at initiation of ADT (ng/dl).

to continue to synthesize testosterone and dihydrotestosterone despite the use of ADT [2]. Locke et al. showed that androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant CaP [18]. Furthermore, circulating cholesterol levels have also been shown to be associated with intratumoral levels of testosterone and tumor size [3]. Like cell membrane synthesis, by decreasing available intermediates, statins may reduce the ability of CaP cells to perform this "de novo" steroidogenesis. In vitro experiments have shown that statins decrease levels of androgen receptor expression by proteolysis resulting in decreased androgen sensitivity and indicating a possible role in regulatory as well as synthetic processes [8]. Other hypotheses as to the antineoplastic role of statins relate to their anti-inflammatory properties, cell signaling effects via protein expression on lipid rafts [3], and up-regulation of genes associated with CaP migration and invasion [19].

In recent years, there has been an increasing focus on the possible chemopreventative and therapeutic roles of statins in CaP. Several retrospective cohort studies including a VA Hospitals study of 55,875 men have shown decreased incidence of CaP and high-grade CaP with statin use [20–23]. The VA study was notable as a commonly cited limitation of many of these studies is that statin users may have more access to health care and hence are diagnosed before the disease has progressed. The VA statin cohort was compared to patients taking antihypertensives who we could assume have similar access to health care as those taking statins. They found that statin users were 31% less likely to be diagnosed with CaP, as well as 60% less likely to be diagnosed with high-grade CaP [24]. This was supported by a meta-analysis of 27 studies which showed a reduced risk of total CaP by 7% and clinically important advanced CaP by 20% [20]. These studies focused on early disease have a

number of confounders such as increased numbers of comorbidities in statin users, inconsistent dosages and duration of statin use, trends in PSA screening and statins effect on PSA level, but the accumulating evidence for its preventative role appears promising.

Statins may also impact biochemical recurrence and mortality. A longitudinal study published in 2012 assessed the impact of statins on 13 cancer types within the entire Danish population from 1995 to 2007. They found a HR of 0.81 for death from CaP in statin users vs. nonstatin users [25]. Similar findings were seen in a longitudinal study done on 4 major United Kingdom databases. In a cohort of 11,772 men with newly diagnosed nonmetastatic CaP, upon follow-up 4.4 years later it was found that statin use after diagnosis was associated with an increased CSS producing a HR of 0.76 [26]. This finding has been replicated in other observational studies [26]. In addition, a 2017 study from nationwide Danish registries identified 31,790 men with CaP who utilized statins post diagnosis. Cox proportional hazards regression models computing CaP specific and all-cause mortality found an adjusted HR of 0.83 for CaP mortality and 0.81 for all-cause mortality [27].

When similar outcomes have been investigated in patients undergoing treatment of CaP with radical prostatectomy or radiotherapy, the data is conflicting. Two recent meta-analysis have shown that there may be an advantageous effect on biochemical free recurrence in patients treated with radiotherapy but not radical prostatectomy [28]. This raises the question of whether the impact of statins varies based on treatment modality. Statin use has not been as thoroughly studied in patients with advanced disease undergoing treatment with ADT.

Although our study design has many strengths, there are several inherent limitations that deserve mention. While the VA CDW dataset allows us to capture an abundance of information on a particular set of individuals, aspects of data collection where information is missing is not within our control. This includes but is not limited to data regarding Gleason score and PSA for both groups of patients. Additionally, given the retrospective nature of our study design, we are not able to adjust for all potential confounding variables that are not present or easily attainable in the dataset such as miscoding of key variables, body mass index, socioeconomic status, local therapies received outside the VA, exercise, smoking status, family history, and complete laboratory data for the entire cohort. In addition, there were significant differences in baseline characteristics between both groups specifically the statin group which was younger with lower PSAs potentially biasing the results in favor of the statin group. However, our large sample size and our propensity score matching allows us to control for these important confounding factors but potentially some of this confounding could remain. In addition, with this being a retrospective observational study, we are unable to account for other potential health benefits of statins that may have impacted our results including improvement in hypercholesterolemia and cardiovascular health. It is also important to note that we could not verify that all patients had advanced CaP based on staging as this data is not readily available in VA databases. We assumed advanced disease was likely present for those patients on ADT for at least 6 months and excluded those that received ADT concurrently with local radiation therapy. Last, while we could identify patient's filling their statin prescriptions, we could not verify compliance with taking their medications or ascertain reasons for discontinuation.

5. Conclusion

Statins are widely available, low-risk medications with increasing evidence of antineoplastic properties in the setting of CaP. Our study adds to the existing literature on the role of statins in progression of advanced CaP and is the largest study to date to look at statin use in the setting of ADT. Through demonstrating improved OS, decreased death from CaP, and increased time to SRE, our research suggests that statin use in conjunction with ADT offer a promising adjunct to ADT in the management of biochemically recurrent CaP. These results may support future prospective studies on the matter.

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References

[1] High Cholesterol Overview. Available at: http://www.statinusage.com/Pages/cholesterol-overview.aspx, accessed August 8, 2017.
[2] Kim JH, Cox ME, Wasan KM. Effect of simvastatin on castration-resistant prostate cancer cells. Lipids Health Dis. 2014;13:56.
[3] Pelton K, Freeman MR, Solomon KR. Cholesterol and prostate cancer. Curr Opin Pharmacol 2012;12:751–9.
[4] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone—sensitive prostate cancer. N Engl J Med 2015;373:737746.
[5] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
[6] Sun L-M, Lin M-C, Lin C-L, et al. Statin use reduces prostate cancer all-cause mortality. Medicine 2015;94:Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4616817/.
[7] Schweizer MT, Yu EY. Persistent androgen receptor addiction in castration-resistant prostate cancer. J Hematol Oncol 2015;8:128.
[8] Yokomizo A, Shiota M, Kashiwagi E, et al. Statins reduce the androgen sensitivity and cell proliferation by decreasing the androgen receptor protein in prostate cancer cells. Prostate 2011;71:298–304.

[9] Price LE, Shea K, Gephart S. The Veterans Affairs's Corporate Data Warehouse: uses and implications for nursing research and practice. Nurs Adm Q 2015;39:311–8.
[10] Webmaster PBM: Pharmacy Benefits Management Services Home. Available at: https://www.pbm.va.gov/, accessed February 27, 2018.
[11] Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12:6243s–9s.
[12] Aly A, Onukwugha E, Woods C, et al. Measurement of skeletal related events in SEER-medicare: a comparison of claims-based methods. BMC Med Res Methodol 2015;15:65.
[13] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 2011;46:399–424.
[14] Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
[15] Ruan PK, Gray RJ. Analyses of cumulative incidence functions via non-parametric multiple imputation. Stat Med 2008;27:5709–24.
[16] American Urological Association - Castration-Resistant Prostate Cancer. Available at: http://www.auanet.org/guidelines/castration-resistant-prostate-cancer-(2013-amended-2015), accessed August 8, 2017.
[17] Sogani PC, Israel A, Lieberman PH, Lesser ML, Whitmore WF Jr. Gleason grading of prostate cancer: a predictor of survival. Urology 1985;25:223–7.
[18] Locke JA, Guns ES, Lubik AA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. Cancer Res 2008;68:6407–15.
[19] Miyazawa Y, Sekine Y, Kato H, et al. Simvastatin up-regulates annexin a10 that can inhibit the proliferation, migration, and invasion in androgen-independent human prostate cancer cells. Prostate 2017;77:337–49.
[20] Bansal D, Undela K, D'Cruz S, et al. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One 2012;7:Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3462187/.
[21] Chen-Pin W, Javier H, Lorenzo C, et al. Statins and finasteride use differentially modify the impact of metformin on prostate cancer incidence in men with type 2 diabetes. Ann Transl Med Epidemiol 2014;1:Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4300536/.
[22] Mondul AM, Han M, Humphreys EB, et al. Association of statin use with pathological tumor characteristics and prostate cancer recurrence after surgery. J Urol 2011;185:1268–73.
[23] Breau RH, Karnes RJ, Jacobson DJ, et al. The association between statin use and the diagnosis of prostate cancer in a population based cohort. J Urol 2010;184:494–9.
[24] Farwell WR, D'Avolio LW, Scranton RE, et al. Statins and prostate cancer diagnosis and grade in a veterans population. J Natl Cancer Inst 2011;103:885–92.
[25] Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792–802.
[26] Yu O, Eberg M, Benayoun S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol 2014;32:5–11.
[27] Larsen SB, Dehlendorff C, Skriver C, et al. Postdiagnosis statin use and mortality in danish patients with prostate cancer. J Clin Oncol 2017;35:3290–7.
[28] Scosyrev E, Tobis S, Donsky H, et al. Statin use and the risk of biochemical recurrence of prostate cancer after definitive local therapy: a meta-analysis of eight cohort studies. BJU Int 2013;111:E71–7.