European Urology

The association between statin use and outcomes in patients initiating androgen deprivation therapy.

--Manuscript Draft--

Manuscript Number:	EURUROL-D-20-00113
Article Type:	Original Article
Section/Category:	Prostate Cancer (PRO)
Keywords:	prostatic neoplasms; drug therapy; androgen antagonists; statins; quality of life
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Abstract:	Background Studies are conflicting regarding the association between statin use and biochemical recurrence after surgery or radiotherapy for prostate cancer (PCa). The few studies examining statins in advanced stages are positive, with few specifically examining statins and androgen deprivation therapy (ADT).

Objective

To examine the association between statin use and outcomes among men initiating ADT nested in a randomized controlled trial (RCT).

Design, setting, and participants

Patients with PSA >3 ng/mL, >1 year following primary/salvage radiotherapy were enrolled in a RCT of intermittent vs. continuous ADT (NCT00003653). Baseline and on- study statin use modeled as a time-dependent covariate.

Outcome measurements and statistical analysis

Primary end-point was overall survival. Models were adjusted for age, time from radiotherapy to ADT, baseline PSA and prior ADT use.

Results and limitations

Of 1364 patients, statin users (585/43%) were younger (72.7 vs. 73.8, p=0.001) and less likely to have PSA >15 (20 vs. 25%, p=0.04). After median follow-up of 6.9 years, statin use was associated with a reduced risk of overall (HR: 0.64; 95% C.I. 0.53-0.78, p<0.001) and PCa-specific mortality (HR: 0.63, 95% C.I. 0.47-0.85, p=0.002). Statin users had 14% longer time to castration resistance but this did not reach statistical

significance (p=0.13). In the IAD arm, statin users had more off-treatment intervals (p=0.03) and longer time off-treatment (median: 0.85 vs. 0.64 years, p=0.06). Across 6 functional domains, statin users reported better quality-of-life scores.

Conclusions

In men treated with ADT following primary or salvage radiotherapy, statin use was associated with improved overall and PCa-specific survival and improved quality-of-life. In patients treated with IAD, statin use was associated with more off-treatment intervals and longer time off-treatment. A prospective trial of statins in men commencing ADT is warranted to confirm our observations.

Patient summary

	We found a favourable association between statin use and survival outcomes in patients initiating ADT.
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The association between statin use and outcomes in patients initiating androgen deprivation therapy.

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Key words: prostatic neoplasms, drug therapy, androgen antagonists, statins, quality of life

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Word count of text: 2477

Word count of the abstract: 300

ABSTRACT:

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Objective: To examine the association between statin use and outcomes among men initiating ADT nested in a randomized controlled trial (RCT).

Design, setting, and participants: Patients with PSA >3 ng/mL, >1 year following primary/salvage radiotherapy were enrolled in a RCT of intermittent vs. continuous ADT (NCT00003653). Baseline and on-study statin use modeled as a time-dependent covariate.

Outcome measurements and statistical analysis: Primary end-point was overall survival. Models were adjusted for age, time from radiotherapy to ADT, baseline PSA and prior ADT use.

Results and limitations: Of 1364 patients, statin users (585/43%) were younger (72.7 vs. 73.8, p=0.001) and less likely to have PSA >15 (20 vs. 25%, p=0.04). After median follow-up of 6.9 years, statin use was associated with a reduced risk of overall (HR: 0.64; 95% C.I. 0.53-0.78, p<0.001) and PCa-specific mortality (HR: 0.63, 95% C.I. 0.47-0.85, p=0.002). Statin users had 14% longer time to castration resistance but this did not reach statistical significance (p=0.13). In the IAD arm, statin users had more off-treatment intervals (p=0.03) and longer time off-

treatment (median: 0.85 vs. 0.64 years, p=0.06). Across 6 functional domains, statin users reported better quality-of-life scores.

Conclusions: In men treated with ADT following primary or salvage radiotherapy, statin use was associated with improved overall and PCa-specific survival and improved quality-of-life. In patients treated with IAD, statin use was associated with more off-treatment intervals and longer time off-treatment. A prospective trial of statins in men commencing ADT is warranted to confirm our observations.

Patient summary: We found a favourable association between statin use and survival outcomes in patients initiating ADT.

Introduction:

Emerging data suggests statins may prevent cancer development and progression. Laboratory studies in prostate cancer (PCa) have found statins inhibit inflammation, angiogenesis, cell proliferation, migration/adhesion, invasion and promote apoptosis.[1-4] Clinical evidence suggests statins may lower PSA,[5] have a modest inverse association with overall cancer and a 20% reduction in the risk of high-grade or advanced PCa.[6] Observational studies are conflicting as to whether statin use at the time of primary treatment is associated with improved outcomes.[7] A few studies looked at PCa-specific and overall mortality and observed favourable associations with statin use , including potential synergy with castration-resistant PCa (CRPC) treatments however most of these studies were limited by few mortality events.[8-10]

Because statins improve cardiovascular health, they may combat some of the metabolic changes induced by androgen deprivation therapy (ADT),[11] In a handful of observational studies that have examined statin use in combination with ADT favourable outcomes have been observed.[12-14]

Thus, we sought to examine the association between statin use and outcomes among men initiating ADT nested in a randomized controlled trial (RCT).

Methods:

This is a secondary analysis of the Canadian Cancer Trials Group (CCTG) PR-7 trial of intermittent (IAD) vs. continuous ADT (CAD) in men with biochemical recurrence (BCR) having completed radiotherapy.[15]

Eligibility criteria

Details of the study and main results have been published elsewhere,[15] but briefly, eligibility criteria included histologically confirmed adenocarcinoma of the prostate having completed definitive primary/salvage radiotherapy >12 months prior to enrolment, a rising PSA level ≥3 ng/mL above the post-radiotherapy nadir and no evidence of distant metastatic disease. Prior ADT was allowed provided it was <12 months duration, a part of the definitive radiotherapy, and completed >12 months prior to enrolment.

Treatment schema

Patients were assigned 1:1 to either CAD (using a luteinizing hormone- releasing hormone (LHRH) agonist with or without a nonsteroidal antiandrogen or orchiectomy) or IAD (8-month treatment cycles using an LHRH agonist with a nonsteroidal antiandrogen for 4 weeks). After 8 months, if the PSA was <4 ng/mL without evidence of distant metastases, an off-treatment interval commenced and was continued until the PSA reached 10 ng/mL or clinical/radiographic disease progression detected.

End-points

The primary end-point was overall survival (OS). Secondary end-points included prostate cancer-specific survival (PCSS), time to CRPC, number of off- treatment intervals, off-treatment duration and quality-of-life. The individual study sites

reported cause of death; no central review was undertaken. CRPC was defined as 3 consecutive increases in PSA, at least 1 month apart or new clinical disease detected while the patient was receiving ADT and the testosterone level was

castrate (<3nmol/L or 85 ng/dL). After development of CRPC, management was according to the local physician. Quality-of-life was assessed with The European Organization for Research and Treatment of Cancer quality-of-life core questionnaire (QLQ-C30)[16] administered at baseline, every 4 months for 2 years, then every 8 months until CRPC developed, then annually thereafter. An *a priori* decision was made to focus only on functional domains (physical, role, emotional, cognitive, social) and symptoms (fatigue, hot flashes, urinary problems, and interest in sexual activity).

Determining statin use

At enrolment and every subsequent clinical visit, medication history was obtained. However, collecting information on statin use was only initiated after June 25th 2004. Statin users enrolled prior to this date who subsequently stopped statin use could potentially be classified as nonusers.

Thus, for our main analysis we made the assumption that absence of any report of statin use during the study period equated to a nonuser. We also performed a landmark analysis whereby all patients who died or were lost to follow-up before June 25th 2004 were excluded. Anyone enrolled prior to this date and still alive was classified as enrolled on June 25th 2004.

Statistical analysis

The trial began in January 1999 and was closed to accrual in November 2005.

The disposition of patients is shown in the CONSORT diagram (Figure 1).

A priori it was determined that separate analyses would be done within the two arms of the trial (i.e. CAD vs. IAD) and if similar, both arms would be pooled and

analyzed together with the exception of end-points specific to the intermittent arm (e.g., off-treatment intervals and duration).

Baseline characteristics were compared between statin ever users and non- users using chi-square test (for categorical data), and t-test (for continuous data). OS and PCSS were calculated from the date of randomization to date of death from any cause (for OS) and death due to PCa or complications of PCa treatment (for PCSS), or censored at the last known alive date. To avoid immortal time bias for statin users, Kaplan-Meier curves compared all patients and those who did not receive a statin during the trial as described by Anderson et al.[17] The non-statin user curve consisted of patients never using statins during the trial and patients not on a statin at baseline but censored the date they started a statin. Cox proportional hazards models (CPHM) employed statin use as time-dependent covariate as per Crowley and Hu.[18] Multivariate CPHM were used including baseline factors found significantly associated with statin use in bivariate analyses.

Analyses of time to castration-resistance were performed similarly to OS and PCSS. CRPC was defined as: 1) bilateral orchiectomy or castrate level testosterone (< 3 nmol/L or 85 ng/dl) measured within 6 weeks of the qualifying event; and 2)

three successive PSA rises (≥1 month apart and during ADT treatment) with the highest PSA > 4 ng/ml; and/or 3) new evidence of clinical disease on imaging.

Patients not meeting the above criteria but with cause of death attributable to PCa or PCa treatment were declared to be castration-resistant at the time of death.

For patients on the IAD arm, the median, min and max of number of off- treatment intervals were compared between statin ever and never users by the

Wilcoxon rank sum test**.** A linear regression model was used to compare the number of off-treatment intervals adjusting for the confounding factors as above. To compare the total time off ADT between statin users and non-users each off- treatment interval was summated and modeled as a time-to-event analysis from treatment initiation using CPHM adjusting for confounding variables as above.

Finally, for quality-of-life, responses were assessed using area-under-the- curve (AUC) analyses whereby scores at each time-point between baseline and 5 years were multiplied by the duration of the interval and then summed and compared between statin ever users and nonusers with the Wilcoxon rank-sum test. Linear regression models were used to compare the AUC between statin users and nonusers while adjusting for confounding factors as above.

P-values are based on two-sided comparisons and analyses performed using SAS software, version 9.2 (SAS Institute).

Results:

Table 1 summarizes the distribution of baseline characteristics between statin users and never users. There was similar distribution of statin users in the intermittent and continuous arms (42% vs. 44%).

Overall Survival (Figure 2)

At a median follow-up of 6.9 years, a total of 513 patients died. CPHM with statin as a time-dependent covariate found a 38% (95% C.I. 25% - 49%, $p < 0.0001$) reduction in the risk of death associated with statin use, which remained after adjusting for potential confounding factors (HR 0.64, 95% CI 0.53-0.78, $p<0.001$, table 2)

Prostate cancer-specific survival (Figure 3)

Of the deaths, 219 (43%) were attributable to PCa or PCa treatment. CPHM with statin use as a time-dependent covariate found that statin use was associated with a 36% reduction in the risk of PCa-specific death and this held after adjusting for confounding factors (HR 0.63, 95% CI 0.47 – 0.85, p=0.002, table 2)

Time to CRPC

CRPC developed in 441 (32%) of patients with a median of 10 years. CPHM with statin use as a time-dependent covariate illustrated that statin use trended towards a prolonged time to CRPC but this did not reach statistical significance. This trend held after adjusting for potential confounding variables (HR 0.86, 95% CI 0.70 – 1.04, p=0.13, table 2).

Time off ADT

Among patients on the IAD (n=681) statin users had significantly more off- treatment intervals than nonusers (mean 2.2 vs. 2.0, p=0.03), and this difference held after adjusting for confounding variables (statin use associated with 0.2 more off-treatment intervals, p=0.04). When total time off treatment was modeled as a time-to-event analysis, statin users had more total time off treatment as represented in figure 4, (median 0.85 years vs. 0.64 years, p=0.06). This difference held after adjusting for confounding variables.

Quality-of-Life

Statin users had significantly better quality-of-life scores across all domains with the exception of interest in sexual activity. These differences held after adjusting for confounding variables (supplementary Table 3).

Landmark analysis

In excluding patients who died or were lost to follow-up prior to June 25, 2004, the date we started collecting detailed information on statin use, 1263 patients were analyzed. In this sub-cohort, 412 deaths occurred, 187 due to PCa. Statin use remained significantly associated with an improved OS (HR 0.62, 95% CI 0.47 – 0.82, p<0.001), and PCSS (HR 0.65, 95% CI 0.43 – 097, p=0.035). Statin use

was not significantly associated with prolonged time to CRPC, however, the point estimate did not vary substantially from the main analysis (HR 0.94, 95% CI 0.72 – 1.23, p=0.66).

Discussion:

Interest in statins as a potential chemopreventive agent has grown and there exist biological rationale, laboratory and clinical data that support our findings. Observational studies examining statin use and PCa risk have shown a modest (≈7%) but statistically significant reduction in the risk of overall PCa and a more clinically meaningful (20%) reduction in the risk of advanced or high-grade disease.[6]

Similarly, studies assessing the influence of statin use on BCR risk after primary treatment also had mixed results. The meta-analysis of 34 observational studies by Raval et al found statin use was associated with reduced recurrence risk after radiation, but not after radical prostatectomy.[19]

Thus, the data in these "earlier" disease endpoints such as primary prevention and BCR, are promising but less impressive. Possible explanations include

heterogeneity of patients, varying statin doses/duration of use, measuring different outcomes (e.g. overall vs. high-grade PCa), and low event rates. In the case of preventing BCR, for the majority of patients there may be no viable tumour mass upon which the statins can exert their antineoplastic effects.

Indeed the bulk of the laboratory data suggests statins may be most effective in preventing progression, and thus looking in a cohort that has recurred after primary treatment, as we have done in our study, may be more revealing. Several large cohort and case-control studies have observed significant statin-associated reductions in PCa-specific death.[8,9]

One reason for this is that statins may be synergistic with ADT – as suggested by our study as well as other recent ones. [12-14] In the retrospective cohort study conducted by Harshman et al, statin use was associated with longer time to progression in both patients with and without metastases at ADT initiation. [12] Statins appear to prevent cancer progression through both cholesterol-dependent and cholesterol-independent mechanisms.[20] They may work in concert with ADT by combatting some mechanisms of CRPC. For example, though statins do not alter serum testosterone,[2132] by reducing intracellular cholesterol levels statins may reduce intratumoral androgen production.[22] Also, as inhibiting the androgen axis leads to reciprocal activation of other pathways, statins may assist in blocking these escape pathways.[23] By lowering systemic cholesterol, statins alter the cholesterol composition of portions of the lipid bilayer called lipid rafts.[24] This lipid raft depletion has been shown to attenuate Akt signalling and induce apoptosis of PCa

cells.[25] Cholesterol depletion in rafts also inhibits EGFR signaling which mediates PI3, Akt, Ras and Raf and thus inhibits growth and survival.[25, 26]

Recently an additional potential mechanism was discovered. Harshman et al., showed that statins inhibit PCa cell androgen uptake by competing for intracellular transport sites at solute carrier organic anion transporter family, member 2B1

(SLCO2B1).[12] Specifically, dehydroepiandrosterone sulphate (DHEAS) uptake, a precursor to potent androgens like dihydroxytestosterone (DHT), is dramatically reduced by statin exposure. Thus, statin use may be reducing the intracellular androgen supply for PCa cells. During ADT, testicular androgens are depleted.
However adrenal androgens persist, particularly DHEAS.[27] This mechanism may provide the basis for synergy between statins and ADT.

A recent analysis of PCa transcriptomes observed that in a relatively prevalent subset of cancers, there were perturbations in expression of genes involving lipid and steroid biosynthetic processes.[28] This could be a signal for statin susceptibility. Studies are ongoing into whether a germline (i.e. host) genetic signature can predict statin sensitivity. Well characterized genes predict lipid, cardioprotective and adverse effect response of statins.[29] Though not reported in PCa, a germline genetic signature has been identified, predicting the statin chemopreventative efficacy in colorectal cancer.[30]

Patient selection may, however, not be relevant. Statins are safe with a favourable side-effect profile; they are low cost relative to current cancer therapeutics; and they dramatically improve cardiovascular outcomes, even among men without elevated cholesterol. Men with advanced PCa are most likely to die of

PCa. However, those not dying of PCa are likely to die of cardiovascular disease[4] Thus, statins could address the two most common threats to life for men with advanced PCa.

The main limitation of our study is the potential for confounding bias: statin users may be more connected with the health care system or have better baseline health and thus intrinsically have better outcomes. However, this study is nested in an RCT and thus the patient groups are likely healthier and more homogenous than other retrospective cohort studies. This is supported by the relative similarities in baseline characteristics between statin users and nonusers as compared to other studies. Moreover, the multivariate model did not change the associations between statin use and outcome significantly, and similar results have been observed in three other studies, suggesting our results are robust.

We did not control for subsequent treatments after CRPC developed. These may have differed between statin users and nonusers and could have influenced survival. However, during the period of this study the only approved therapy was docetaxel, which has a 3-month survival benefit. Therefore, this potential confounder is not likely to explain the greater than 1 year difference in survival observed in our study.

Finally, our study is weakened by the lack of detailed information on statin use prior to June 25th 2004. Our main analysis has made assumptions regarding statin use, but these assumptions would influence the results towards null rather than induce the protective effect we observed. Our landmark analysis, whereby these patients are excluded, confirms our results are robust.

Conclusions:

In a secondary analysis of the PR7 randomized trial of intermittent vs. continuous ADT, we observed statin use was associated with significantly improved OS and PCSS. In patients treated with IAD, statin use was associated with more off-treatment intervals and longer time off treatment. Finally, men taking statins reported significantly better quality-of-life throughout the duration of the study.

This study supports the benefit of statins in men on ADT. A prospective trial of statins in men commencing ADT is warranted.

Acknowledgements:

DD acknowledges NHS funding to the NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and Institute of Cancer Research. RH acknowledges support from the Canadian Urological Association Scholarship Fund.

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Figures:

Figure 1: PR-7 CONSORT diagram. ADT, androgen-deprivation therapy; CAD, continuous androgen deprivation

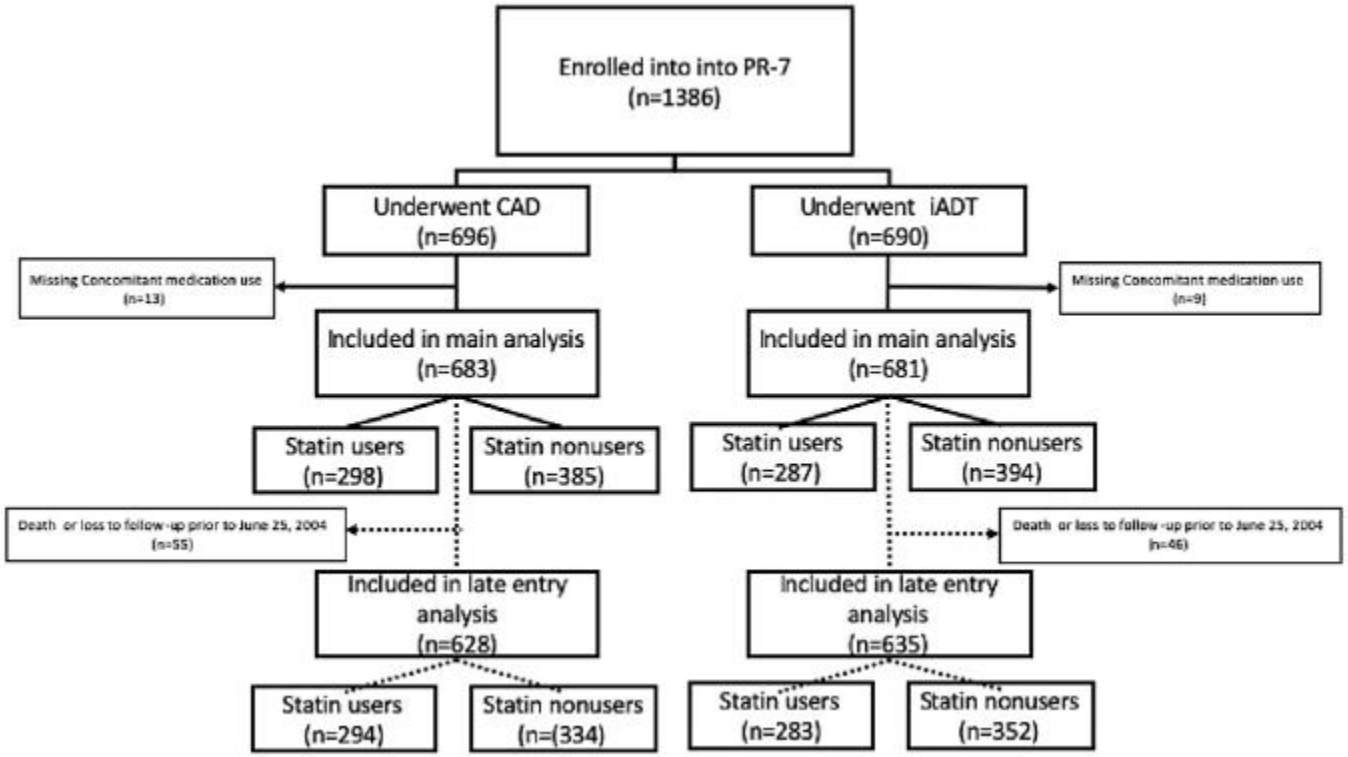


Figure 2: Overall survival (OS) comparing statin nonusers with all patients.

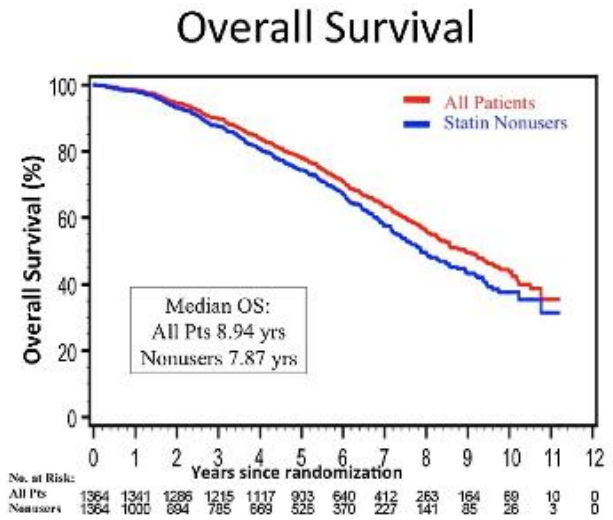


Figure 3: Prostate-cancer specific survival (PCSS) comparing statin nonusers with all patients. N/A, not applicable.

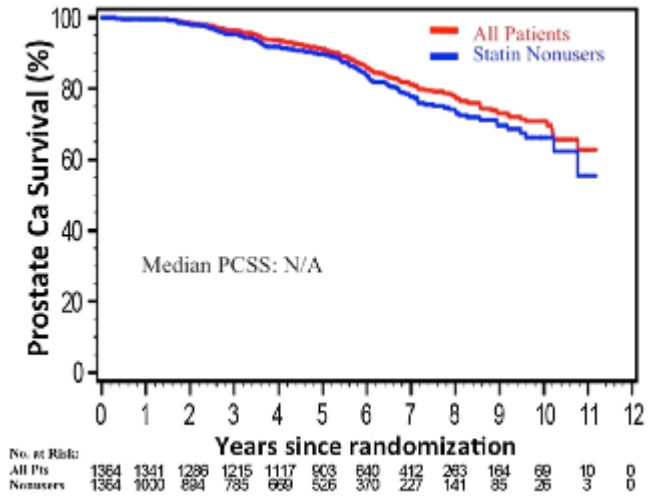
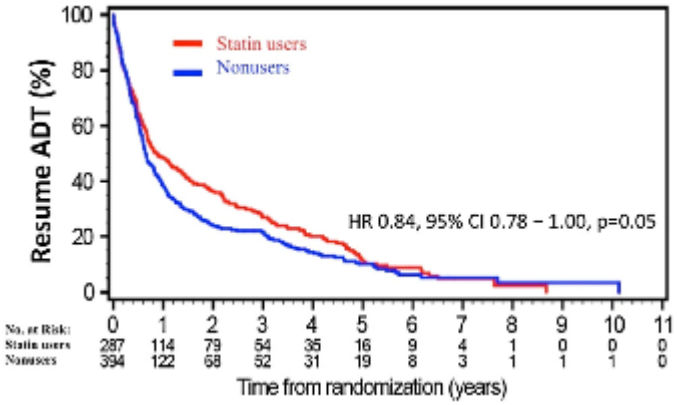


Figure 4: Sum of duration of off-treatment intervals modeled as time-to-event from ADT initiation. Comparison is between statin users and non-users and only among men on the intermittent arm of ADT. HR, hazard ratio.



Tables:

Table 1: Baseline Characteristics.

	Statin Users 585 (43%)	Nonusers 779 (57%)	P-value
Median age (range)	73.4 (51.4, 89.7)	74.9 (29.4, 89.3)	0.001
ECOG Performance Status			
0	480 (82.1)	623 (80.0)	
1	105 (17.9)	156 (20.0)	0.33
Median Weight, Kg (range)	84.6 (55.6, 165.6)	83.95 (45, 204)	0.08
Gleason Score			
<7	85 (14.5)	138 (17.7)	
7	191 (32.6)	262 (33.6)	
>7	267 (45.6)	314 (40.3)	
Missing	42 (7.2)	65 (8.3)	0.11
Prior prostatectomy			
No	522 (89.2)	689 (88.4)	
Yes	63 (10.8)	90 (11.6)	0.65
Baseline PSA			
3 – 15 ng/mL	466 (79.7)	583 (74.8)	
>15 ng/mL	119 (20.3)	196 (25.2)	0.04
Time since radiotherapy			
1-3 yrs	129 (22.1)	164 (21.1)	
>=3 yrs	456 (77.9)	614 (78.8)	0.67
Prior ADT			
No	356 (60.9)	471 (60.5)	
Yes	229 (39.1)	308 (39.5)	0.88

ECOG, Eastern Cooperative Oncology Group; PSA, prostate specific antigen; ADT, androgen deprivation therapy.

Table 2: Crude and multivariate associations of statin use and outcomes

	Overall Survival	Prostate Cancer-Specific Survival	Time to CRPC	Total Time off ADT				
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Crude: Statin use	0.62 (0.51–0.75)	<0.001	0.64 (0.48–0.86)	0.003	0.87 (0.71–1.06)	0.15	0.84 (0.71–1.00)	0.06
Multivariate: **Statin use**	**0.64 (0.53–0.78)**	**<0.001**	**0.63 (0.47–0.85)**	**0.002**	**0.86 (0.70–1.05)**	**0.13**	**0.85 (0.71-1.01)**	**0.06**
Age	1.05 (1.04–1.07)	<0.001	1.05 (1.03–1.07)	<0.001	1.01 (0.99 – 1.02)	0.24	0.99 (0.98–1.01)	0.19
Time since RT(<3yrs)	0.63 (0.51–0.77)	<0.001	0.36 (0.27–0.48)	<0.001	0.46 (0.37 – 0.57)	<0.001	0.78 (0.62–0.97)	0.03
PSA (>15)	1.34 (1.11–1.62)	0.003	1.97 (1.50–2.60)	<0.001	2.01 (1.65 – 2.46)	<0.001	1.57 (1.29–1.91)	<0.001
Prior ADT use	1.27 (1.06–1.53)	0.01	1.70 (1.29–2.25)	<0.001	1.45 (1.19 – 1.76)	<0.001	1.06 (0.88–1.27)	0.56

CRPC, castration-resistant prostate cancer; ADT, androgen deprivation therapy; HR, hazard ratio; RT, radiation therapy; PSA, prostate specific antigen.

Take Home Message:

We conducted a retrospective study of men initiating androgen deprivation therapy (ADT) following primary/or salvage radiotherapy. Statin use was associated with longer overall survival and prostate cancer specific survival. A prospective trial of statins in men commencing ADT is warranted.

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_ drafting of the manuscript	Robert J. Hamilton
_ critical revision of the manuscript for important intellectual content	Keyue Ding, Juanita M. Crook, Christopher J. O'Callaghan, Celestia S. Higano, David P. Dearnaley, Eric M. Horwitz, S. Larry Goldenberg, Mary K. Gospodarowicz and Laurence Klotz.
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_ administrative, technical, or material support	Robert J. Hamilton, Keyue Ding, Laurence Klotz
_ supervision	Robert J. Hamilton, Laurence Klotz
_ other (specify)	

Financial Disclosure

None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Funding Support and Role of the Sponsor

I certify that all funding, other financial support, and material support for this research and/or work are clearly identified in the manuscript.

The name of the organization or organizations which had a role in sponsoring the data and material in the study are also listed below:

Canadian urological association scholarship fund
NHS funding to the NIHR Biomedical Research Centre at the Royal Marsden NHS Foundation Trust and Institute of Cancer Research

All funding or other financial support, and material support for this research and/or work, if any, are clearly identified hereunder:

The specific role of the funding organization or sponsor is as follows:

Design and conduct of the study Collection of the data Management of the data Analysis
Interpretation of the data Preparation
Review
Approval of the manuscript

OR

No funding or other financial support was received.

Acknowledgment Statement

This corresponding author certifies that:

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