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ORIGINAL PAPER

Impact of statins on metastatic castration-resistant prostate cancer patients receiving new hormonal agents

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Summary *Introduction: After androgen ablation treatment for prostate cancer, virtually all patients with recurrent or advanced disease develop castration-resistance (CRPC). Abiraterone and Enzalutamide are the most common used novel antiandrogen treatments in patients with castration-resistant prostate cancer (CRPC). The solute carrier transporter (SLCO2B1) enables various anticancer compounds or hormones to enter cells, including the adrenal androgen dehydroepiandrosterone (DHEAS), a precursor to the most potent androgen dihydroxytestosterone (DHT), which is the substrate binding and activating the androgen receptor in normal and Prostate Cancer (PCa) cells. Other substrates of SLCO2B1 are statins. An in vitro-part study showed that statins, by binding to SLCO2B1, can block the uptake of DHEAS competitively, decreasing the available intratumoral androgen and improving and extending the effect of primary ADT.*

Aim: To evaluate whether the addition of statins to the new antiandrogens (Abiraterone or Enzalutamide) affects overall and progression free survival in patients with metastatic castration-resistant prostate cancer.

Materials and methods: Medical records of patients with mCRPC taking abiraterone or enzalutamide between December 2019 and January 2022 were reviewed in a tertiary hospital. Patients were assessed for statin use at the time of treatment initiation, progression free (PFS) and overall survival (OS), prostate-specific antigen (PSA) variations, and other variables of interest. Statistical analysis was performed using SPSS 22.0.

Results: A total of 107 patients receiving ADT (63 abiraterone - 59,4% - and 43 enzalutamide - 40,6%) for mCRPC in this time period were eligible for inclusion in this retrospective study. Patients had a mean age of 76,5 years (48-93). 26 patients had surgery with curative intent prior to the treatment (24,5%), 19 had previous pelvic radiotherapy with curative intent (17,9%) and 20 patients (18,9%) were previously treated with chemotherapy with docetaxel.

Statins use was a significant prognostic factor for longer PFS, with a mean time of 13,68 months for those who don't use statins and 19,62 months for those who do ($p < 0,06$). No statistically significant difference was found in OS or global mortality between the patients who use or don't use statins. Statins use also did not show any difference in the reduction of PSA values during the treatment with ADT.

Conclusions: Our study suggests a prognostic impact of statin use in the PFS in patients receiving abiraterone or enzalutamide for mCRPC. This may be related with the enhancement of the antitumor activity of the ADT drugs but also with the cardioprotective effects associated with statin use.

KEY WORDS: *Statins; Prostate cancer; Metastasis; Abiraterone; Enzalutamide.*

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INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men, accounting for approximately 15% of all cancers diagnosed (1). *Androgen deprivation therapy* (ADT) is a backbone treatment for patients with advanced prostate cancer, and although initially effective, virtually all patients eventually develop *metastatic castration-resistant prostate cancer* (mCRPC), a stage associated with poor prognosis and limited survival (2, 3). Median overall survival after mCRPC diagnosis ranges from 13 to 23 months, depending on disease burden, and the condition remains highly heterogeneous, with considerable variability in clinical outcomes (4).

Two *novel Hormonal Agents* (NHA), abiraterone and enzalutamide, have been approved to treat patients with mCRPC, improving overall and progression-free survival, yet treatment resistance is inevitable. Abiraterone works by inhibiting the enzyme CYP17A1, which is involved in androgen synthesis, decreasing its production (5), while enzalutamide blocks androgen receptor activation 6, both aiming to slow disease progression and extend survival in patients resistant to traditional hormone therapies (5, 6).

In prostate cancer, statins may have an additional benefit in improving survival due to their interaction with the solute carrier transporter SLCO2B1 (7). This transporter facilitates the entry of various substances into cells, including *dehydroepiandrosterone* (DHEAS), a precursor to the potent androgen *dihydrotestosterone* (DHT), which activates the androgen receptor in both normal and prostate cancer cells. As prostate cancer progresses to *castration-resistant stages* (CRPC), SLCO2B1 expression increases, influencing the effectiveness of ADT (7, 8). The response to ADT can vary depending on SLCO2B1 variants that differ in their ability to transport androgens into cancer cells (7).

Statins are also substrates for SLCO2B1, which may explain why statin use has been linked to a lower incidence and better outcomes in prostate cancer (7). Recent studies, such as one by *Harshman et al.* (9), showed that statins taken alongside ADT were associated with a longer time to cancer pro-

gression and that statins competitively inhibit DHEAS uptake by binding to SLCO2B1, reducing the androgen supply within tumors and enhancing the effectiveness of ADT (9). As recent reports highlight the potential PCa protective effects of statins, and given their generally favorable toxicity profile, an increasing number of men with PCa appear to be treated with statins to enhance their outcomes, even in the absence of hypercholesterolemia (10, 11). To date, limited evidence exists regarding the impact of statins in patients undergoing treatment with NHAs. We aim to evaluate whether the use of statins concomitantly with the NHA (*Abiraterone or Enzalutamide*) affects *overall* (OS) and *progression free survival* (PFS) in patients with mCRPC.

Patients and methods

A retrospective study was carried out involving all patients diagnosed with mCRPC who were followed in a urological oncology consultation at a tertiary hospital in Portugal between December 2019 and January 2022. A total of 106 patients were included, all of whom underwent systemic therapy with NHA (63 received Abiraterone and 43 Enzalutamide) for mCRPC.

Castration resistance was defined according to the *European Association of Urology* criteria as follows: 1) three consecutive PSA increases at least one week apart, resulting in two 50% rises from the nadir and a PSA level > 2 ng/mL; 2) the appearance of new lesions-either two or more new bone lesions or a soft tissue lesion per RECIST (*Response Evaluation Criteria in Solid Tumors*); or 3) clinical deterioration. Patients with mCRPC were randomly prescribed either Abiraterone or Enzalutamide, as long as there were no contraindications.

OS was measured from the start date of treatment with either Abiraterone or Enzalutamide to the date of death from any cause or the last follow-up. PFS was measured from the same starting point to the occurrence of clinical or radiological progression, or a rise in PSA levels that resulted in a change of treatment, or the final date of follow up if the patient remained stable.

The database used was unstructured and anonymized. Patient's characteristics were extracted from the electronic medical records including age, histological grade - ISUP score, previous treatment with surgery, radiotherapy or chemotherapy, statin use and PSA levels at 0, 1, 2 and 6 months after the start of the NHA. Regarding statin use, all hMG-CoA reductase inhibitors (including combination therapies) were considered, but duration of use, dosing or indication were not. The follow-up data was collected until 1st January 2022.

The primary endpoints of this study were OS and PFS.

Statistical analysis

Descriptive statistics were calculated for all patients included in the study. Group comparisons were conducted using independent samples t-tests. Associations between statin use and PFS and OS were evaluated. OS and PFS curves were generated using the Kaplan–Meier method.

To assess the potential impact of statin use on *prostate-specific antigen* (PSA) response, we calculated the percentage change in PSA from baseline (month 0) to 1, 2, and 6 months after initiation of treatment with abiraterone or enzalutamide. For each time point, PSA reduction was computed as:

[(PSA at baseline - PSA at follow-up)/PSA at baseline] × 100. Mann-Whitney U test was used to compare PSA reduction between statin users and non-users.

A Cox proportional hazards regression analysis was also performed to evaluate the association between statin use and PFS and OS, with statin use included as a covariate in the model. To further explore whether clinical or demographic characteristics influenced outcomes differently based on statin use, separate models were applied to the subgroups of patients receiving and not receiving statins.

Statistical significance was set at $p < 0.05$

All analyses were performed using SPSS software, version 27.0 (*IBM Corp., Armonk, NY, USA*).

Results

A total of 106 patients receiving NHA (63 abiraterone - 59.4% - and 43 enzalutamide - 40.6%) for mCRPC in this time period were included in this retrospective study.

Table 1.
Patients' characteristics and comparison between studied groups.

Variables	Non-statin users (n = 63)	Statin users (n = 43)	P-value
Mean age (years)	77.37 ± 10.05	75.40 ± 7.84	n.s.
Median basal PSA (ng/mL)	43.85 (IQR: 0.09-1664.00)	20.0 0 (IQR: 0.25-2871.00)	n.s.
Median basal testosterone (ng/mL)	0.75 (IQR: 0.22-2.45)	0.55 (IQR: 0.200-1.30)	n.s.
ISUP Score (%)			
- ISUP 1	9.5%	6.9%	n.s.
- ISUP 2	17.5%	30.2%	n.s.
- ISUP 3	49.2%	44.4%	n.s.
- ISUP 4	7.9%	6.9%	n.s.
- ISUP 5	15.9%	11.6%	n.s.
Previous treatment (%)			
- Surgery	17.5%	34.88%	n.s.
- Radiotherapy	15.9%	20.9%	n.s.
- Docetaxel (mHSPC)	20.6%	16.3%	n.s.

n.s.: non significant.

Mean age of the patients was 76.57 ± 9.23 years. After a median follow up of 30 months, 22 patients (20.8%) had died. The majority of the patients was not under treatment with statins when they started NHA therapy (56.6%). Mean PSA at the start of the treatment was 152.16 mg/dL, and most of the patients had an ISUP 3 score (46.2%) on histology (biopsy or surgery), with the second most common being ISUP 2 (23.6%).

Forty-five patients had been previously submitted to therapy with curative intent (26 (24.5%) surgery, 19 (17.9%) radiotherapy) and 20 patients (18.9%) had been previously treated with docetaxel chemotherapy for *metastatic hormone-sensitive prostate cancer* (mHSPC).

Regarding PFS, patients on statins showed a significantly longer mean PFS compared to the other group (19.62 *vs* 13.68 months, $p < 0.006$).

Regarding *overall survival* (OS) or all-cause mortality, no statistically significant differences were observed between statin users and non-users, as shown on Table 1 below. Survival curves are shown in Figures 1, 2.

When comparing OS only in patients under statins, no difference was found between Abiraterone and Enzalutamide use ($p > 0.05$) (Figure 3).

In the multivariate Cox proportional hazards model, patients receiving statins had a 34.5% reduction in the risk of disease progression compared to non-users (HR = 0.655,

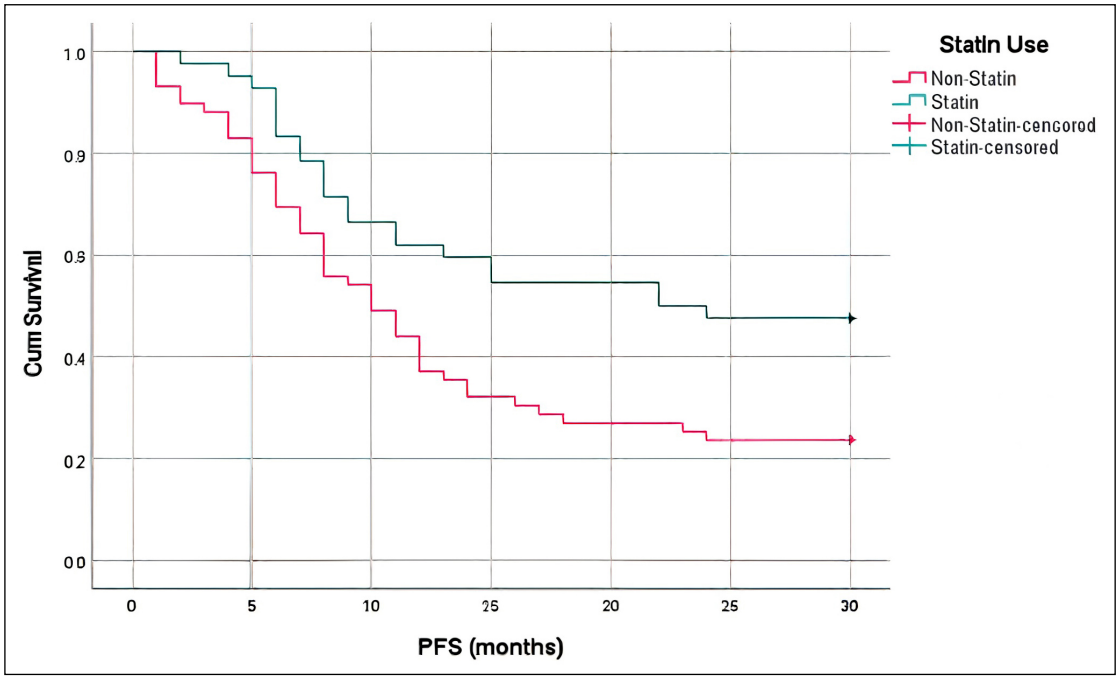

Figure 1. *Comparing PFS between statin users and non-users.*

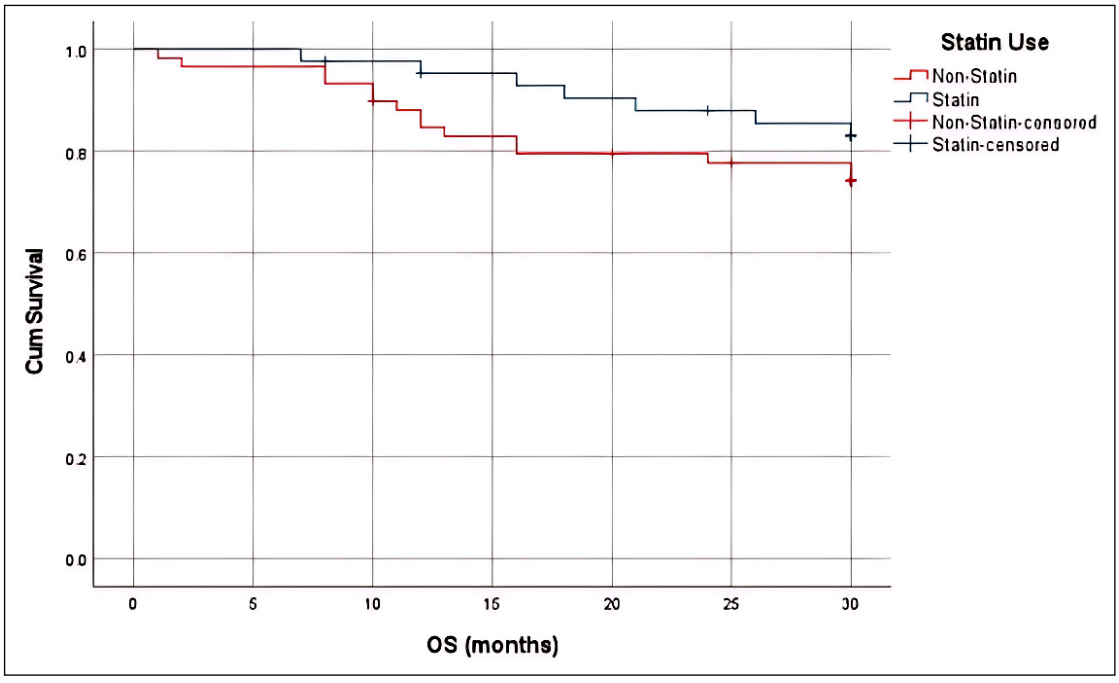

Figure 2. *Comparing OS between statin users and non-users.*

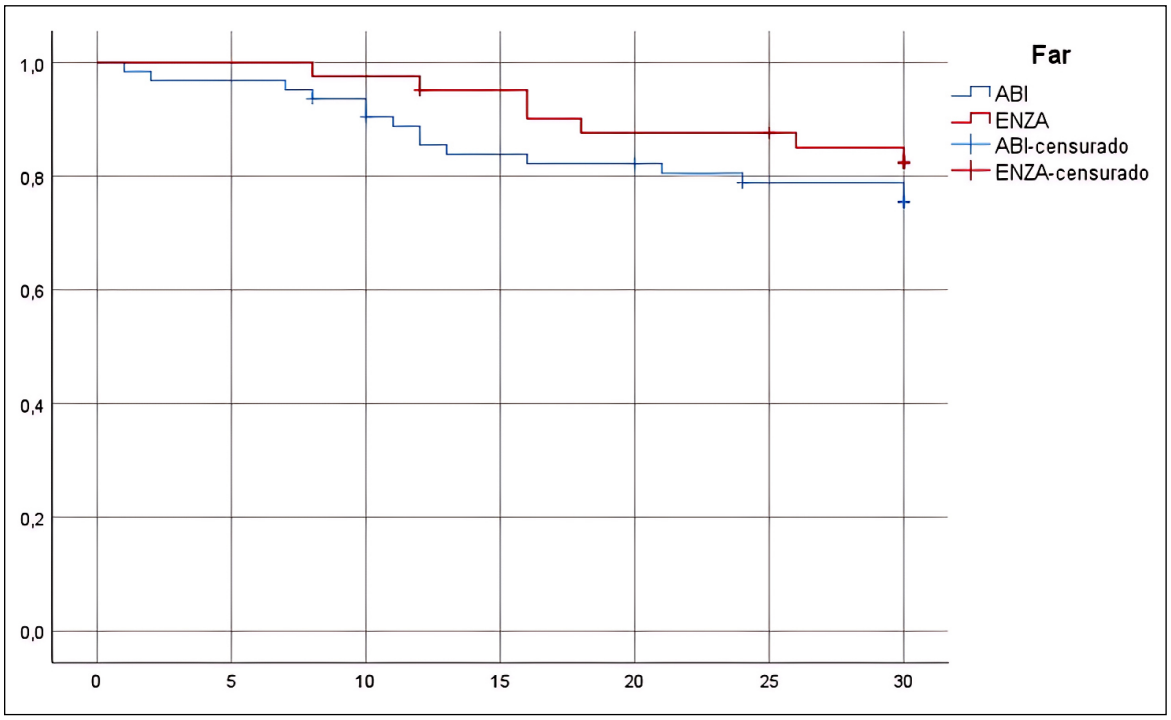

Figure 3.
Comparison of overall survival (OS) between Abiraterone and Enzalutamide in patients using statins.

95% CI not shown, p = 0.034), but no significant association was shown with OS (HR = 0.934, p = 0.731).
In a multivariate analysis performed separately for statin users and non-users, none of the evaluated clinical or demographic variables – including age, ISUP score, prior prostatectomy, radiotherapy, or prior docetaxel – were significantly associated with PFS or OS in either group. Detailed results are presented in Table 3.
PSA reduction at 1, 2, and 6 months after initiation of treatment with abiraterone or enzalutamide was compared between statin users and non-users. No statistically significant differences were observed between the two groups at any of the evaluated time points, indicating that statin use was not associated with a greater reduction in PSA levels over time. Results are shown in Table 4.

Table 2.
Comparison of PFS, OS, and overall mortality between statin users and non-users.

Time point	Non-statin users	Statin users	P-value
PFS (months)	13.68	19.62	0.006
OS (months)	25.22	27.07	0.219
Overall mortality	0.25	0.16	0.279

Table 3.
Multivariate Cox regression analysis for PFS and OS in statin users and non-users.

Variable	Statin users – PFS (HR-[95%CI], p)	Non-users – PFS (HR-[95%CI], p)	Statin users – OS (HR-[95%CI], p)	Non-users – OS (HR-[95%CI], p)
Age (years)	1.017 [0.976-1.060], p = 0.429	1.009 [0.980-1.039], p = 0.553	1.009 [0.970-1.049], p = 0.660	1.021 [0.978-1.066], p = 0.203
ISUP score	1.156 [0.810-1.649], p = 0.425	0.981 [0.733-1.313], p = 0.899	1.011 [0.729-1.403], p = 0.553	1.098 [0.861-1.400], p = 0.467
Prior surgery	0.960 [0.502-1.836], p = 0.903	0.831 [0.378-1.830], p = 0.646	1.017 [0.520-1.989], p = 0.520	1.033 [0.429-2.486], p = 0.930
Prior radiotherapy	1.126 [0.490-2.585], p = 0.780	1.313 [0.579-2.978], p = 0.514	1.207 [0.557-2.616], p = 0.557	1.220 [0.613-2.432], p = 0.593
Prior Docetaxel	0.638 [0.260-1.561], p = 0.325	0.727 [0.379-1.392], p = 0.336	1.207 [0.557-2.616], p = 0.634	1.069 [0.521-2.195], p = 0.847

HR: Hazard Ratio; CI: Confidence Interval.

Table 4.
Comparison of PSA reduction (%) at 1, 2, and 6 months between statin users and non-users.

Time point	Non-statin users	Statin users	P-value
Median reduction of PSA at 1 month (%)	51.38% (IQR: -548.81-99.91%)	51.99% (IQR: -69.61-98.93%)	0.688
Median reduction of PSA at 2 months (%)	73.37% (IQR: -1973.25-98.93%)	72.55% (IQR: -336.30-99.70%)	0.397
Median reduction of PSA at 6 months (%)	70.64% (IQR: -2670.70-99.88%)	91.58% (IQR: -160.61-99.70%)	0.158

IQR: Interquartile Range.

Discussion

In this study, we evaluated the impact of statins on PFS and OS in patients with mCRPC who were receiving either Abiraterone or Enzalutamide.

Our study suggested that patients on statins had a longer PFS compared to those not receiving statin therapy. There are two possible explanations for this finding: first androgens are steroid hormones, and their basic component is cholesterol, so by reducing the available cholesterol in PCa cells, statins may reduce their activity and proliferation; and second, the impact of statins on the SLCO2B1 transporter may add to this potential effect (7). Another potential mechanism underlying this observation could be related to the pleiotropic effects of statins beyond their lipid-lowering properties. Statins have been shown to possess anti-inflammatory, pro-apoptotic, and anti-angiogenic effects, which may contribute to the inhibition of cancer cell growth and metastasis. These findings are consistent with previous studies indicating that statins can modulate the tumor microenvironment and inhibit cancer progression, particularly in prostate cancer models (12, 13).

While the impact of statins on PFS is promising, it is important to note that statin therapy did not significantly affect OS in our cohort. This suggests that although statins may slow tumor progression, they may not provide a long-term survival benefit in the context of mCRPC. The lack of OS benefit could be attributed to several factors. For instance, mCRPC is an advanced stage of prostate cancer where disease progression is often driven by complex mechanisms that may not be fully addressed by statin therapy alone. Furthermore, enzalutamide and abiraterone, which were used in our study, are effective in prolonging OS, potentially overshadowing any survival advantage that statins might offer (5, 6).

Some epidemiological studies show significant association between statins use and lowering of PSA levels, reducing incidence of clinically significant and advanced PCa (14, 15). However, *Murtola et al.* showed that statins only inhibited hormone-sensitive *prostate cancer* (PCa) cell lines, but not CRPC cell lines (10). *Boegemann et al.* demonstrated that in mCRPC patients treated with Abiraterone, statins as concomitant medication do not seem to improve the best clinical benefit under Abiraterone and does not improve survival outcomes (15). A systemic review and meta-analysis by *Yang H et al.* suggests that the use of statins in combination with ADT or Abiraterone/Enzalutamide was associated with better all cause survival and cancer specific survival in patients with advanced PCa (17).

Our results support the hypothesis that the effect of statins, by reducing the available cholesterol and interfering with the SLCO2B1 transporter, adds a beneficial effect to Abiraterone and Enzalutamide alone.

No clinical or demographic variables, such as age, ISUP score, or prior treatments, appeared to independently influence PFS or OS within either group. This reinforces the idea that the longer PFS observed in statin users is not readily explained by differences in baseline characteristics or treatment history.

Moreover, PSA reduction at 1, 2, and 6 months did not significantly differ between statin users and non-users, suggesting that the potential benefit of statins may not be fully captured by short-term PSA kinetics alone.

Our study has some limitations due to the challenges inherent to its retrospective design, which may also have introduced selection bias, as patients who were prescribed statins may have had other health conditions that influenced their response to treatment. Also, we did not collect data specific to statin-related toxicity and comorbidities of statin users, that could introduce bias into the results, and also did not differentiate between the various statins, which may have different potencies and pharmacokinetic profiles, potentially influencing the outcomes of our study. Additionally, while statins were shown to influence PFS, the effect on quality of life and adverse events was not assessed, which warrants further investigation.

Conclusions

In conclusion, our study suggests that statins may have a beneficial effect on PFS in patients with mCRPC receiving new hormonal agents, although they do not appear to impact OS. These findings provide a foundation for future prospective studies to investigate the potential of statins as adjunctive therapy in mCRPC. Future trials should focus on elucidating the underlying biological mechanisms of statins in prostate cancer, examining their impact on the different existing subtypes, and assessing

Declarations

Ethical approval and consent for participate: *Not applicable.*

Consent for publication: *Not applicable.*

Availability of data and material: *The datasets generated and/or analyzed during the current study are not publicly available due to ethical and legal restrictions imposed by the hospital's data protection policies, but de-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.*

Competing interests: *The authors declare that they have no competing interests.*

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Authors' contributions: *Study conception and design; acquisition of clinical data; data curation; data analysis and interpretation; drafting of the original manuscript; critical revision for important intellectual content; TS: Data curation; data analysis and interpretation; statistical analyses; preparation of tables and figures; review and editing of the manuscript; RJ: Data curation; data analysis and interpretation; statistical analyses; validation of results; review and editing of the manuscript; VQ: Substantial contribution to manuscript writing; critical revision for important intellectual content; language editing; ETS: Study concept and design; supervision; contribution to manuscript writing; critical revision for intellectual content; approval of the final version; PN: Study concept and design; supervision; contribution to manuscript writing and editing; overall project administration; approval of the final version; AF: Study concept and design; supervision; contribution to manuscript writing and editing; overall project administration; approval of the final version. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.*

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their safety profile in combination with newer agents. Additionally, randomized controlled trials are needed to determine whether statins can provide long-term survival benefits when combined with contemporary prostate cancer therapies.

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