Differences in mortality risk associated with statin use amongst Asian patients with prostate cancer undergoing androgen deprivation therapy: a retrospective cohort study

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Abstract

Background: With known anticancer properties, statins have the potential to be an adjuvant cancer therapy, but their associations with mortality in prostate cancer (PCa) remain debatable. This study investigated the associations between statin use concurrent with androgen deprivation therapy (ADT) and mortality risks in Asian patients with PCa.

Methods: Adults with PCa receiving any ADT attending public hospitals in Hong Kong between December 1999 and March 2021 were retrospectively identified, with follow-up until September 2021. Patients with <180 days of medical castration without subsequent bilateral orchidectomy, <180 days of concurrent statin use and ADT, or missing total cholesterol level at baseline were excluded. Statin users had ≥180 days of concurrent statin and ADT use, while non-users were those without any statin use. The primary outcome was PCa-related mortality. The secondary outcome was all-cause mortality. Inverse probability treatment weighting was used to balance covariates.

Results: 4920 patients were studied (2578 statin users and 2342 non-users; mean age 76.1±8.2 years). Over a mean follow-up of 4.2±3.3 years, statin users had significantly lower risks of PCa-related mortality (weighted hazard ratio (wHR) 0.56 [95% confidence interval 0.48, 0.65], p<0.001) and all-cause mortality (0.57 [0.51, 0.63], p<0.001) regardless of the type of ADT. The associations appeared stronger in patients without chemotherapy or antiandrogens use.

Conclusions: Statin use concurrent with ADT was associated with lower risks of mortality in Asian patients with PCa, warranting further studies of its role in the treatment of patients with PCa.

Introduction

Among males, prostate cancer (PCa) was the second most common cancer and fifth leading cause of death worldwide in 2012[1]. Furthermore, in recent years, the prevalence of PCa has increased in Asia[2]. Additional properties of statins have been discovered in recent years, including anticancer properties which may enable it to be used as adjuvant therapy for cancer treatment[3, 4]. Retrospective analyses suggested that statins confer survival benefit in gastric cancers and triple negative breast cancers[5, 6]. Meanwhile, the STAT-ROC phase III trial (ISRCTN98060456) is currently recruiting and aims to assess the role of adjuvant statins in the context of patients with oesophageal adenocarcinomas who have undergone surgery with curative intent[7].

However, evidence underlying the associations between statin use during androgen deprivation therapy (ADT), the gold standard treatment for PCa, and mortality risks among patients with PCa is unclear. Despite preclinical evidence suggesting that statins have the ability to initiate tumour-specific apoptosis and promote invasiveness of PCa cells [8, 9], a recent meta-analysis showed that statins was not associated with significantly different prostate-cancer specific survival among patients on ADT, despite improved overall survival[10]. Nonetheless, significant inter-study differences prevented conclusions from

being drawn [4], and studies remain much needed to bridge the gaps in our understanding of statin's possible associations with mortality risks in patients with PCa. As such, this study aimed to investigate the associations between statin use concurrent with ADT and the risks of PCa-specific and all-cause mortality in Asian patients with PCa.

Methods

This retrospective cohort study was performed in accordance with the Declaration of Helsinki and the STROBE guideline[11]. It has been approved by the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee. The requirement for patient consent has been waived because of the use of retrospective data. All data underlying this study is available on reasonable request to the corresponding author.

Source of data

All data used were retrieved from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic health records database documenting key demographics, diagnoses, procedures, and medication records of all patients that attend public healthcare institutions in Hong Kong. The *International Classification of Diseases, Ninth Revision* (ICD-9) codes were used to code all diagnoses. CDARS is linked to the Hong Kong Death Registry, a population-wide governmental registry of all Hong Kong citizens' death records, from which mortality data may be obtained and linked to CDARS records. Causes of mortality were encoded using either ICD-9 or ICD-10, depending on the year of death. CDARS and its associated mortality data have been used extensively for research[12, 13].

Patient population

The inclusion criteria were adult patients (18 years old or above) who had a diagnosis of PCa and were receiving any ADT in Hong Kong between December 1999 and March 2021. Diagnosis of prostate cancer was determined by ICD-9 codes (**Supplementary Table 1**). ADT included bilateral orchidectomy, gonadotrophin-releasing hormone agonists, and gonadotrophin-releasing hormone antagonists.

The following patients were excluded: (a) with less than 180 days of medical castration without subsequent bilateral orchidectomy, (b) with less than 180 days of concurrent statin use and ADT, and (c) with missing baseline total cholesterol level.

Definition of statin users and non-users

Statin users were defined as patients who had at least 180 days of concurrent statin and ADT use. Statin non-users were defined as patients who never used statin.

Follow-up and outcomes

All patients were followed up from the day of ADT initiation (baseline date) up until 30 September 2021. The primary outcome was PCa-related mortality. The secondary outcome was all-cause mortality. The

duration between ADT initiation and mortality was recorded, and all causes of death were ascertained by ICD codes (**Supplementary Table 2**).

Covariates

All included patients' age at baseline, type of ADT received, other comorbidities at baseline as determined by ICD-9 codes (hypertension, ischaemic heart disease, myocardial infarction, heart failure, stroke, diabetes mellitus, chronic kidney disease, anaemia, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, hyperlipidaemia, any malignancy; codes detailed in **Supplementary Table 1**), use of other medications (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, beta-blocker, dihydropyridine calcium channel blocker, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitor, glucagon-like peptide 1 receptor agonist, insulin, corticosteroid, antiplatelet, anticoagulant, and androgen receptor antagonists (abiraterone, enzalutamide, and bicalutamide)), ever underwent radiotherapy, ever underwent radical prostatectomy, prior chemotherapy (docetaxel, cabazitaxel, mitoxantrone, and estramustine), chemotherapy concurrent with ADT, and total cholesterol level at baseline were recorded.

Subgroup analyses

Due to the nature of our data source, cancer staging is unavailable. To mitigate this limitation, we considered the use of androgen receptor antagonists or chemotherapy, typical treatments of metastatic PCa, as a surrogate marker of metastatic PCa[14]. An *a priori* subgroup analysis was performed, comparing patients with and without the use of these medications, to explore whether the associations between statin use and mortality risks would apply to patients with metastatic PCa. A second *a priori* subgroup analysis was performed for each type of ADT given to investigate whether the associations between statin use and mortality risks remained significant for different types of ADT.

Sensitivity analyses

To investigate the effects of statin use at the time of ADT initiation on the observations, a sensitivity analysis was performed where patients who were not using statin at the time of ADT initiation were excluded from the statin user group, such that only statin users who had statin use at the time of ADT initiation were compared against patients who never used statin.

Whilst the present study included a mix of hydrophilic and lipophilic statins, a sensitivity analysis was performed by excluding patients who had any hydrophilic statin exposure from the user group in order to investigate the mortality effects of lipophilic statin use.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation. Logistic regression-based inverse probability treatment weighting (IPTW) using the aforementioned covariates was used to balance the treatment groups. Standardized mean difference (SMD) was used to examine the balance of covariates between treatment groups, with values < 0.1 considered to represent good balance.

IPTW-weighted univariable Cox regression was used to assess the association of statin treatment with the risks of the outcomes. Weighted hazard ratios (wHR) with 95% confidence intervals (CI) were used as the summary statistics. Kaplan-Meier curves were used to visualize the cumulative freedom from the outcomes.

All p values were two-sided, with values < 0.05 considered statistically significant. All statistical analyses were performed on SPSS (version 25.0, IBM Corp, USA) or Stata (Version 13.0, StataCorp LLC, USA).

Results

In total, 13481 patients fulfilled the inclusion criteria. After applying the exclusion criteria, the study cohort consisted of 4920 patients (Fig. 1), of which 2578 were statin users and 2342 were non-users. The mean age was 76.1 ± 8.2 years; 2870 patients (58.3%) received only medical castration, 1681 (34.2%) received only bilateral orchidectomy as ADT, and 369 (7.5%) received both. Among those who received only medical castration, the mean duration of treatment was 3.1 ± 2.5 years. Baseline characteristics of all included patients are summarized in Table 1, which also demonstrates good balance of all covariates by IPTW (SMD < 0.1 for all).

Table 1
Baseline characteristics with standardized mean differences (SMD) before and after inverse probability treatment weighting (IPTW).

	Statin non-users (N = 2342)	Statin users (N = 2578)	Unweighted SMD	SMD with IPTW
Age, years	76.4 ± 8.6	75.8 ± 7.8	0.08	< 0.01
Use of GnRH agonist or antagonist, N (%)	1418 (60.5)	1821 (70.6)	0.21	< 0.01
Bilateral orchidectomy, N (%)	1195 (51.0)	855 (33.2)	0.37	< 0.01
Hypertension, N (%)	759 (32.4)	1263 (49.0)	0.34	< 0.01
Ischaemic heart disease, N (%)	148 (6.3)	693 (26.9)	0.57	0.07
Myocardial infarction, N (%)	46 (2.0)	232 (9.0)	0.31	0.07
Heart failure, N (%)	147 (6.3)	207 (8.0)	0.07	0.04
Stroke, N (%)	189 (8.1)	471 (18.3)	0.30	< 0.01
Diabetes mellitus, N (%)	539 (23.0)	1154 (44.8)	0.47	0.03
Chronic kidney disease, N (%)	90 (3.8)	140 (5.4)	0.08	0.04
Anaemia, N (%)	215 (9.2)	202 (7.8)	0.05	0.03
Atrial fibrillation, N (%)	144 (6.1)	190 (7.4)	0.05	0.05
Chronic liver disease, N (%)	35 (1.5)	40 (1.6)	< 0.01	0.01
Chronic obstructive pulmonary disease, N (%)	156 (6.7)	129 (5.0)	0.07	0.01
Hyperlipidaemia, N (%)	91 (3.9)	721 (28.0)	0.69	< 0.01
Ever underwent radiotherapy, N (%)	490 (20.9)	477 (18.5)	0.06	< 0.01
Ever underwent radical prostatectomy, N (%)	772 (33.0)	753 (29.2)	0.08	< 0.01
Any malignancy, N (%)	344 (14.7)	249 (9.7)	0.16	< 0.01
ACEI/ARB use, N (%)	693 (29.6)	1371 (53.2)	0.49	< 0.01
Beta-blocker use, N (%)	864 (36.9)	1427 (55.4)	0.38	0.03
Dihydropyridine calcium channel blocker, N (%)	1232 (52.6)	1673 (64.9)	0.25	0.02
Metformin use, N (%)	278 (11.9)	720 (27.9)	0.41	0.03

ACEI, angiotensin converting enzyme inhibitor. ADT, androgen deprivation therapy. ARB, angiotensin receptor blocker. GnRH, gonadotropin hormone-releasing hormone. HbA1c, haemoglobin A1c

	Statin non-users (N = 2342)	Statin users (N = 2578)	Unweighted SMD	SMD with IPTW
Sulfonylurea use, N (%)	331 (14.1)	689 (26.7)	0.31	0.04
DPP-4 inhibitor use, N (%)	20 (0.9)	90 (3.5)	0.18	0.06
GLP-1 receptor agonist use, N (%)	0 (0)	2 (0.1)	0.04	0.03
Insulin use, N (%)	153 (6.5)	279 (10.8)	0.15	0.04
Corticosteroid use, N (%)	452 (19.3)	476 (18.5)	0.02	0.02
Antiplatelet use, N (%)	491 (21.0)	1265 (49.1)	0.61	0.06
Anticoagulant use, N (%)	79 (3.4)	157 (6.1)	0.13	< 0.01
Androgen receptor antagonist use, N (%)	940 (40.1)	1235 (47.9)	0.16	0.01
Prior chemotherapy, N (%)	11 (0.5)	15 (0.6)	0.02	0.02
Chemotherapy concurrent with ADT, N (%)	238 (10.2)	265 (10.3)	< 0.01	< 0.01
Total cholesterol, mmol/L	4.6 ± 0.9	4.2 ± 1.0	0.35	0.06

ACEI, angiotensin converting enzyme inhibitor. ADT, androgen deprivation therapy. ARB, angiotensin receptor blocker. GnRH, gonadotropin hormone-releasing hormone. HbA1c, haemoglobin A1c

Over a mean follow-up duration of 4.2 ± 3.3 years, PCa-related mortality occurred in 1206 patients (14.5%) and all-cause mortality in 2944 (59.8%). Overall, statin users had significantly lower risks of PCa-related mortality (wHR 0.56 [0.48, 0.65], p < 0.001; Fig. 2) and all-cause mortality (wHR 0.57 [0.51, 0.63], p < 0.001; Fig. 3).

Subgroup analyses

Among patients with or without androgen receptor antagonists or chemotherapy use (N = 1872 and N = 2620, respectively), statin users had significantly lower risks of PCa-related mortality and all-cause mortality, with stronger associations observed in patients without androgen receptor antagonist or chemotherapy use (p value for interaction = < 0.001 for both; Table 2). This may suggest that the survival benefits associated with statin may be more pronounced among patients without metastatic PCa.

Table 2
Weighted comparisons of outcomes by statin usage with subgroups for androgen receptor blocker or chemotherapy usage. Hazard ratios were referenced against statin non-users.

	Never received androgen receptor blocker or chemotherapy (N = 2620)		Received androgen receptor blocker or chemotherapy (N = 1872)		p value for interaction
	Weighted hazard ratio [95% confidence interval]	p value	Weighted hazard ratio [95% confidence interval]	p value	
Prostate cancer-related mortality	0.39 [0.31, 0.50]	< 0.001	0.69 [0.56, 0.87]	0.001	< 0.001
All-cause mortality	0.47 [0.41, 0.55]	< 0.001	0.69 [0.60, 0.80]	< 0.001	< 0.001

Statin users had significantly lower risks of PCa-related mortality and all-cause mortality among those who received bilateral orchidectomy only (N = 1681) or medical castration only (N = 2870), as summarized in **Supplementary Table 3**. With numerical trends for lower mortality risks, the statistical significance for patients who received both bilateral orchidectomy and medical castration was likely dampened by the small number of patients in this subgroup (N = 369).

Sensitivity analyses

Statin use remained associated with significantly lower risks of all outcomes when statin users who had statin use at the time of ADT initiation were compared against patients who never used statin (N = 4436; $p < 0.001$ for all; **Supplementary Table 4**). These suggested that the aforementioned associations were unlikely to be confounded by statin use at the time of ADT initiation.

When patients who received lipophilic statins were only compared against patients who never used statin, the observed associations remained (N = 4686; $p < 0.001$ for all; **Supplementary Table 5**).

Discussion

This population-based retrospective cohort study showed that concurrent statin and ADT use in an Asian population with PCa was associated with significantly lower risks of PCa-related mortality and all-cause mortality, with stronger associations observed in patients without androgen receptor antagonist or chemotherapy use.

Underlying mechanisms

The major cholesterol-mediated mechanism through which statins inhibit PCa tumour growth is by reducing androgen receptor (AR) signalling independent of circulating androgen[15]. PCa cells proliferate in an androgen-sensitive manner, and the activation of AR alters cell cycle control[16] and increases oncogene

expression by direct interaction with transcriptional cofactors[17]. AR signalling is vital in the PCa progression regardless of castration status[18], which makes androgen deprivation therapy the first-line treatment of PCa. Statins could be a useful adjuvant agent to ADT by further dampening AR signalling. Furthermore, the cholesterol-lowering properties of statins, mediated by inhibition of the 3-hydroxy-3-methylglutaryl–coenzyme A reductase, disrupt the organisation of lipid raft[19], the specialized cholesterol-rich domains of the cell membrane that facilitate the signalling pathways of membrane receptors such as AR[20], thereby inhibiting the survival and proliferation of PCa cells. In addition, statin counteracts the upregulation of intracellular cholesterol metabolism in CRPC cell lines, which is vital for the development of castration-resistance during long-term usage of ADT[21]. Therefore, the cholesterol-lowering ability of statins is desirable in delaying the development of castration resistant prostate cancer, a state with limited treatment options and higher risk for mortality[22].

Non-cholesterol-mediated mechanisms may also contribute to the protective effects of statins in patients with PCa. *In vitro* studies showed that statins competitively reduce dehydroepiandrosterone sulphate (DHEAS) uptake. Since DHEAS is a substrate for testosterone synthesis, statins can effectively reduce the level of intratumoral androgen[23]. In addition, statins are well-known for its apoptosis-inducing effect in tumour cells. With less mevalonate activating cyclin-dependent kinase 2, cell cycle progression in PCa cells is reduced[8]. Lower levels of mevalonate also leads to reduced inhibition and thus increased activity of caspace-7, a critical protease in apoptotic pathways[24]. Statin's apoptosis-inducing ability is further attributable to a downregulation of phosphorylation pathways mediated by AKT kinase in PCa cells[9]. These non-cholesterol-mediated mechanisms may thereby confer antineoplastic properties in PCa through their intramural androgen-lowering and apoptotic effects.

Prior studies and future directions

While some studies also suggested an association between statin use and improved survival in patients on ADT, others did not observe any[25, 26]. Mikkelsen et al observed no relationship between statin use at the time of PCa diagnosis and time to progression defined as CRPC development or PCa death among patients using ADT[25]. That study, however, was limited by its small sample size (N = 537). Although Mikkelsen et al explained that the protective effect of statin against mortality in other studies is likely confounded by selection bias as statin users were more health-aware and had lower incidence of metastasis because of better treatment options, i.e. the "healthy user effect"[25], another large observational studies (N = 87,346) observed the contrary, with statin users being more likely to have higher Charlson comorbidity index and high grade cancer[27]. Ultimately, the risk of "healthy user effect" can only be thoroughly eliminated by randomised controlled trials (RCTs). A small RCT by Murtola et al had attempted to address statin's role in patients with PCa, with initial findings suggesting that atorvastatin does not lower the proliferation rate of PCa[28]. Nonetheless, this trial did not investigate statin's effect on mortality, and the short duration of statin exposure (median of 27 days) severely limited its practical implications. More clinical trials are still required to better delineate the association between statin use and mortality risk in patients with PCa. The ongoing PEACE-4 trial (NCT03819101), which is a

2x2 factorial phase III RCT aimed to evaluate the effects of acetylsalicylic acid and atorvastatin on overall survival in patients with CRPC initiating first-line treatment, may provide critical insights into the captioned topic.

In addition, few studies investigated the effect of statin usage at different time relative to ADT. Peltomaa et al found that statin use after initiation of ADT, but not before, was associated with lower PCa death[26]. However, such finding should be interpreted with caution as the study could not account for the numerous reasons underlying discontinuation of statins, such as having poor lipid-wise treatment effects, adverse reactions to statins, or requiring other medications that may interact with statins, all of which may confound the above observations. This issue was circumvented in the present study by only including patients with statin use concurrent with ADT. Furthermore, the sensitivity analysis restricting statin users to those with statin use at ADT initiation further reinforced the analysis' validity and minimized any effects that the timing of stating use may have had on the observations.

Although there is laboratory evidence suggesting that statins may delay the development of castration resistance[21], the corresponding clinical evidence is far from conclusive. In a post hoc analysis of RCT data, Hamilton et al did not observe any significant difference in the time to CRPC on patients with biochemical recurrence after radiotherapy[29]. Meanwhile, another retrospective study by Jung et al supported statin's possible use to delay progression to CRPC in metastatic prostate cancer patients[30]. These highlight the need for further studies in this area. Furthermore, few studies compared mortality effects between hydrophilic and lipophilic statins. Whilst initial reports suggested that hydrophilic statins may possess stronger protective effects[31], most existing studies only included patients receiving lipophilic statins[32, 33], probably due to the relatively high potency of lipophilic statins and their consequently limited indications. For the same reason, whilst the present study included a mix of hydrophilic and lipophilic statins, the number of patients on hydrophilic statins was too small for any meaningful subgroup analysis to be performed. This gap in evidence remains open and await further investigations.

Strengths and limitations

This study used a large and representative territory-wide database with long follow-up duration. The results are thus widely generalizable and reflect real-world practice. Additionally, sensitivity analyses based on different approaches were performed showing consistent results, indicating robustness of our findings. Nevertheless, this study has several limitations. As an observational study, residual confounding cannot be excluded. Additionally, the included diagnostic data could not be adjudicated. Nonetheless, the codes were input by treating clinicians for clinical use, independent of the authors. Lastly, details on cancer staging were unavailable due to the nature of the database. We attempted to address this by using antiandrogens or chemotherapy as a surrogate for metastatic PCa.

Conclusions

Statin use concurrent with ADT in Asian patients with PCa was associated with significantly lower risks of PCa-related mortality and all-cause mortality. Such protective effects may be more pronounced in patients with less advanced PCa.

Declarations

Funding

No funding was received for conducting this study.

Conflicts of interest/ Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Data access and responsibility

The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing

Data are available for bona fide researchers who request it from the authors.

Ethics approval

This study was approved by the Joint Chinese University of Hong Kong– New Territories East Cluster Clinical Research Ethics Committee (reference number: 2022.051). The study was performed in accordance with the Declaration of Helsinki.

Consent to participate

Not applicable.

Consent to publication

All authors consent to publication of this manuscript.

Authorship

Lee Yan Hiu Athena contributed to conceptualization, study design, and writing of the original draft. Jeffrey Shi Kai Chan contributed to conceptualization, and writing of the original draft. Jeremy Man Ho Hui contributed to conceptualization, formal analysis, and writing of the original draft. Pias Tang contributed to study design. Kang Liu contributed to data curation. Edward Christopher Dee and Kenrick Ng contributed to review and editing of the draft. Gary Tse and Chi Fai Ng contributed to supervision, review and editing od the draft.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
2. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020;77(1):38–52.
3. Jiang W, Hu JW, He XR, Jin WL, He XY. Statins: a repurposed drug to fight cancer. J Exp Clin Cancer Res. 2021;40(1):241.
4. Yang H, Pang L, Hu X, Wang W, Xu B, Zhang X, et al. The effect of statins on advanced prostate cancer patients with androgen deprivation therapy or abiraterone/enzalutamide: A systematic review and meta-analysis. J Clin Pharm Ther. 2020;45(3):488–95.
5. Yang PR, Tsai YY, Chen KJ, Yang YH, Shih WT. Statin Use Improves Overall Survival of Patients with Gastric Cancer after Surgery and Adjuvant Chemotherapy in Taiwan: A Nationwide Matched Cohort Study. Cancers (Basel). 2020;12(8).
6. Nowakowska M, Lei X, Thompson MR, Shaitelman SF, Wehner M, Woodward WA, et al. Association of statin use with clinical outcomes in patients with triple-negative breast cancer. Journal of Clinical Oncology. 2021;39(15_suppl):523-.
7. Alexandre L, Clark AB, Walton S, Lewis MP, Kumar B, Cheong EC, et al. Adjuvant statin therapy for oesophageal adenocarcinoma: the STAT-ROC feasibility study. BJS Open. 2020;4(1):59–70.
8. Alfaqih MA, Allott EH, Hamilton RJ, Freeman MR, Freedland SJ. The current evidence on statin use and prostate cancer prevention: are we there yet? Nat Rev Urol. 2017;14(2):107–19.
9. Deng JL, Zhang R, Zeng Y, Zhu YS, Wang G. Statins induce cell apoptosis through a modulation of AKT/FOXO1 pathway in prostate cancer cells. Cancer Manag Res. 2019;11:7231–42.
10. Aydh A, Motlagh RS, Alshyarba M, Mori K, Katayama S, Grossmann N, et al. Association of statins use and mortality outcomes in prostate cancer patients who received androgen deprivation therapy: a systematic review and meta-analysis. Cent European J Urol. 2021;74(4):484–90.
11. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7.
12. Chou OHI, Zhou J, Lee TTL, Kot T, Lee S, Wai AKC, et al. Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study. Clin Res Cardiol. 2022.
13. Chan JSK, Zhou J, Lee S, Li A, Tan M, Leung KSK, et al. Fragmented QRS Is Independently Predictive of Long-Term Adverse Clinical Outcomes in Asian Patients Hospitalized for Heart Failure: A Retrospective Cohort Study. 2021;8.
14. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019;17(5):479–505.

15. Skara L, Hudek Turkovic A, Pezelj I, Vrtaric A, Sincic N, Kruslin B, et al. Prostate Cancer-Focus on Cholesterol. Cancers (Basel). 2021;13(18).
16. Knudsen KE, Arden KC, Cavenee WK. Multiple G1 regulatory elements control the androgen-dependent proliferation of prostatic carcinoma cells. J Biol Chem. 1998;273(32):20213–22.
17. Wasmuth EV, Hoover EA, Antar A, Klinge S, Chen Y, Sawyers CL. Modulation of androgen receptor DNA binding activity through direct interaction with the ETS transcription factor ERG. Proc Natl Acad Sci U S A. 2020;117(15):8584–92.
18. Green SM, Mostaghel EA, Nelson PS. Androgen action and metabolism in prostate cancer. Mol Cell Endocrinol. 2012;360(1–2):3–13.
19. Simons K, Ikonen E. Functional rafts in cell membranes. Nature. 1997;387(6633):569–72.
20. Freeman MR, Cinar B, Lu ML. Membrane rafts as potential sites of nongenomic hormonal signaling in prostate cancer. Trends Endocrinol Metab. 2005;16(6):273–9.
21. Han W, Gao S, Barrett D, Ahmed M, Han D, Macoska JA, et al. Reactivation of androgen receptor-regulated lipid biosynthesis drives the progression of castration-resistant prostate cancer. Oncogene. 2018;37(6):710–21.
22. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract. 2011;65(11):1180–92.
23. Harshman LC, Wang X, Nakabayashi M, Xie W, Valenca L, Werner L, et al. Statin Use at the Time of Initiation of Androgen Deprivation Therapy and Time to Progression in Patients With Hormone-Sensitive Prostate Cancer. JAMA Oncol. 2015;1(4):495–504.
24. Marcelli M, Cunningham GR, Haidacher SJ, Padayatty SJ, Sturgis L, Kagan C, et al. Caspase-7 is activated during lovastatin-induced apoptosis of the prostate cancer cell line LNCaP. Cancer Res. 1998;58(1):76–83.
25. Mikkelsen MK, Thomsen FB, Berg KD, Jarden M, Larsen SB, Hansen RB, et al. Associations between statin use and progression in men with prostate cancer treated with primary androgen deprivation therapy. Scand J Urol. 2017;51(6):464–9.
26. Peltomaa AI, Raittinen P, Talala K, Taari K, Tammela TLJ, Auvinen A, et al. Prostate cancer prognosis after initiation of androgen deprivation therapy among statin users. A population-based cohort study. Prostate Cancer Prostatic Dis. 2021;24(3):917–24.
27. Anderson-Carter I, Posielski N, Liou JI, Khemees TA, Downs TM, Abel EJ, et al. The impact of statins in combination with androgen deprivation therapyin patients with advanced prostate cancer: A large observational study. Urol Oncol. 2019;37(2):130–7.
28. Murtola TJ, Syvala H, Tolonen T, Helminen M, Riikonen J, Koskimaki J, et al. Atorvastatin Versus Placebo for Prostate Cancer Before Radical Prostatectomy-A Randomized, Double-blind, Placebo-controlled Clinical Trial. Eur Urol. 2018;74(6):697–701.
29. Hamilton RJ, Ding K, Crook JM, O'Callaghan CJ, Higano CS, Dearnaley DP, et al. The Association Between Statin Use and Outcomes in Patients Initiating Androgen Deprivation Therapy. Eur Urol. 2021;79(4):446–52.

30. Jung J, Lee C, Lee C, Kwon T, You D, Jeong IG, et al. Effects of statin use on the response duration to androgen deprivation therapy in metastatic prostate cancer. Korean J Urol. 2015;56(9):630–6.
31. Goldberg H, Mohsin FK, Saskin R, Kulkarni GS, Berlin A, Kenk M, et al. The Suggested Unique Association Between the Various Statin Subgroups and Prostate Cancer. Eur Urol Focus. 2021;7(3):537–45.
32. Sun LM, Lin MC, Lin CL, Chang SN, Liang JA, Lin IC, et al. Statin Use Reduces Prostate Cancer All-Cause Mortality: A Nationwide Population-Based Cohort Study. Medicine (Baltimore). 2015;94(39):e1644.
33. Yu O, Eberg M, Benayoun S, Aprikian A, Batist G, Suissa S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol. 2014;32(1):5–11.

Figures

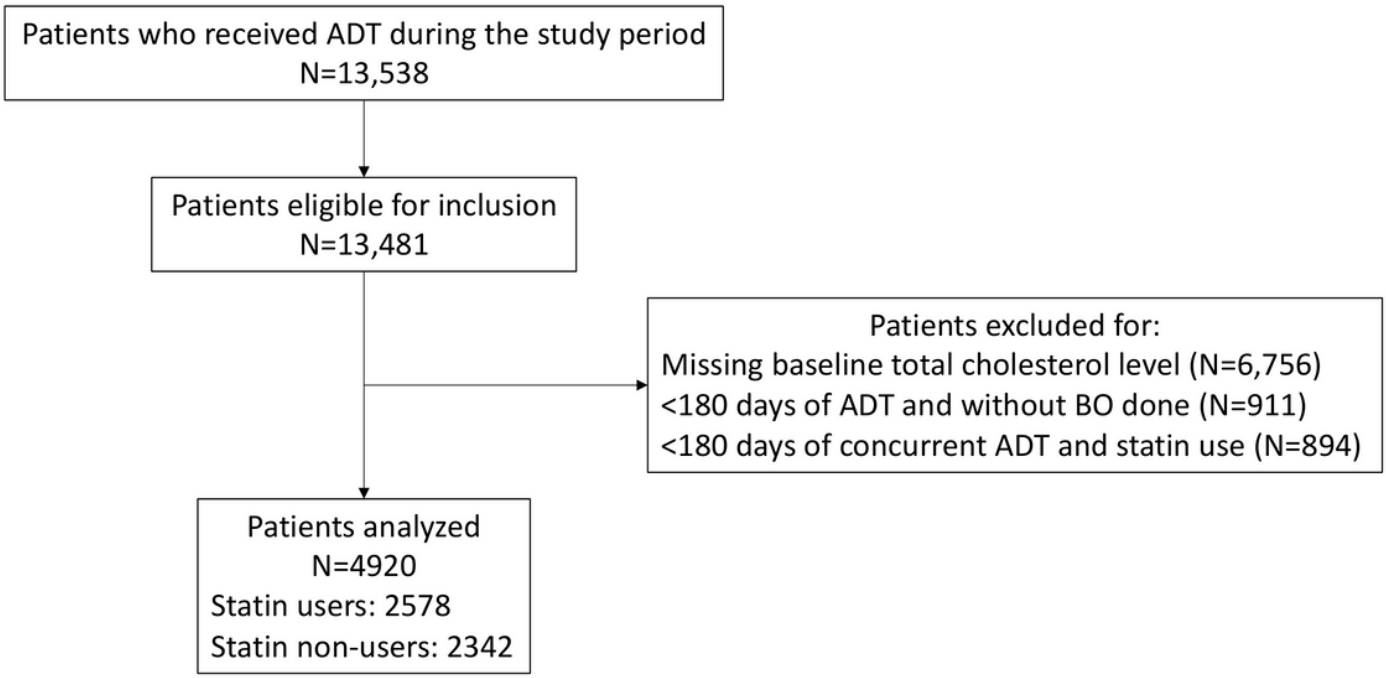

Figure 1

Study flow chart. ADT, androgen deprivation therapy. BO, bilateral orchidectomy.

ADT, androgen deprivation therapy. BO, bilateral orchidectomy. HbA1c, haemoglobin A1c.

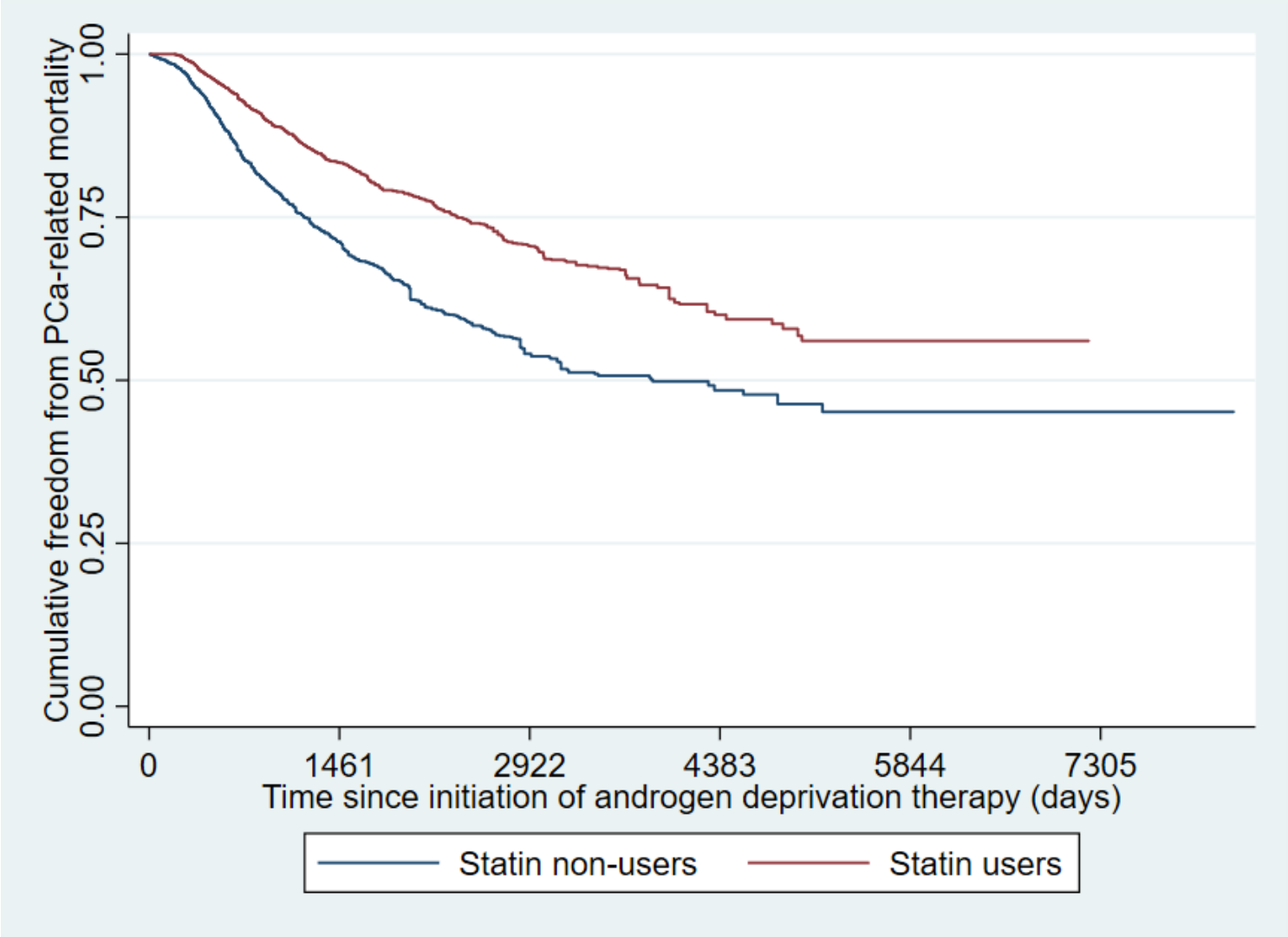

Figure 2

Kaplan-Meier curve showing the cumulative freedom from prostate cancer (PCa)-related mortality.

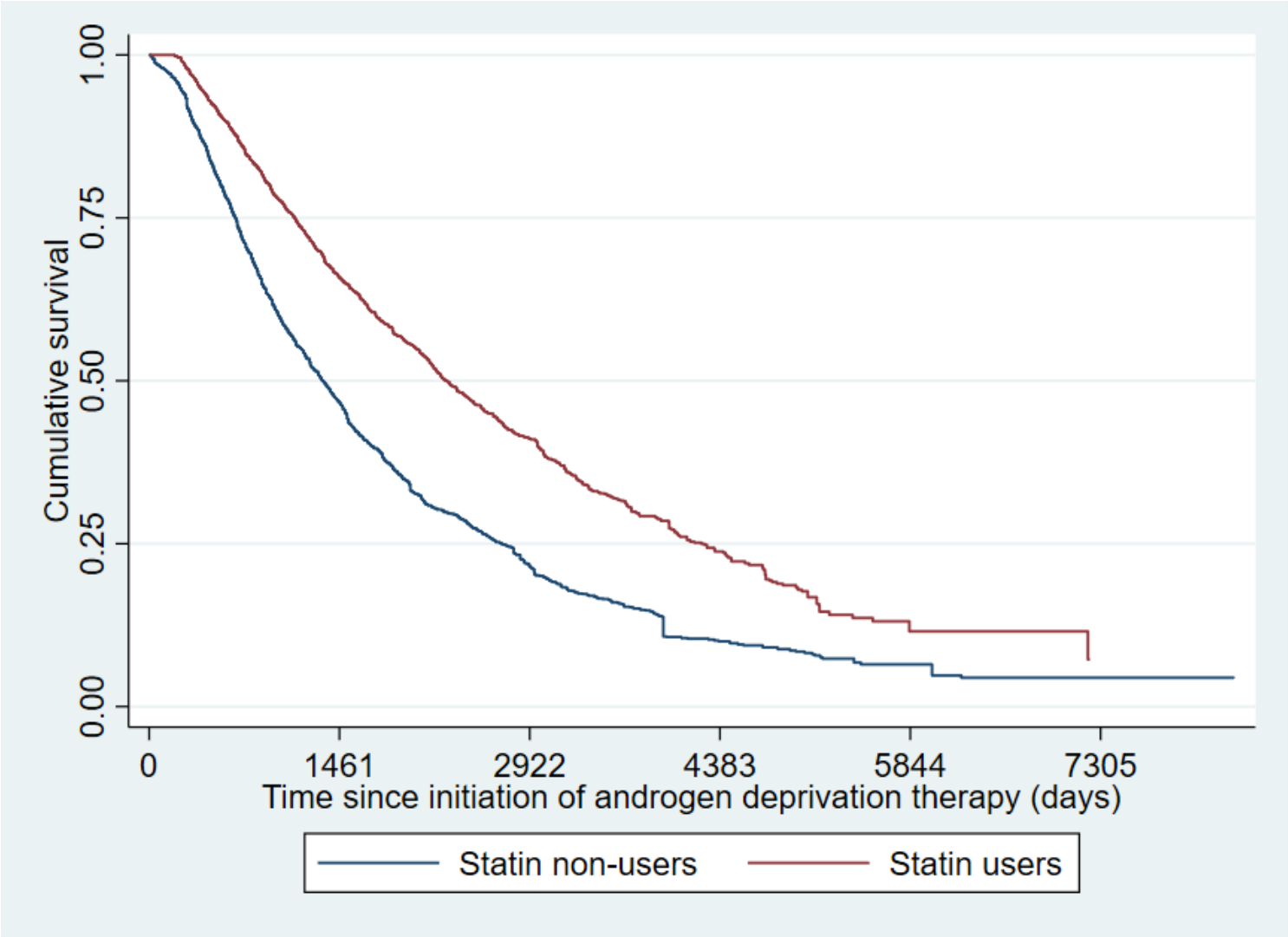

Figure 3

Kaplan-Meier curve showing the cumulative freedom from all-cause mortality.

Supplementary Files

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- Supplementarymaterial.docx