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REVIEW PAPER

UROLOGICAL ONCOLOGY

Association of statins use and mortality outcomes in prostate cancer patients who received androgen deprivation therapy: a systematic review and meta-analysis

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Introduction While several recent studies investigated the influence of statins on survival outcomes in prostate cancer (PCa) patients on androgen deprivation therapy (ADT), definitive conclusions are still missing. The present systematic review and meta-analysis aimed to develop an overarching framework for the association of statins use and survival outcomes in PCa patients who receive ADT.

Material and methods We conducted a systematic review and meta-analysis of the literature assessing the survival outcomes for statin compared to non-statin users in PCa patients who received ADT. We searched PubMed and Web of Science for studies published before March 1, 2021. We used the random effect model in the presence of heterogeneity and the fixed-effects model in the absence of heterogeneity per the I^2 statistic. We did two meta-analyses; the primary meta-analysis was accomplished for articles reporting cancer-specific survival (CSS) as an outcome. A secondary meta-analysis was completed for articles reporting overall survival (OS) as an outcome.

Results Ten studies were eligible for inclusion. Nine studies included in the first meta-analysis comprising 136,285 patients showed no statistically significant difference in CSS (HR 0.77; 95% CI 0.49–1.21) between statin users and non-users in PCa patients who received ADT. In four studies included in the second meta-analysis comprising 95,032 patients, statin users had a significantly better OS compared to non-users (HR 0.67; 95% CI 0.62–0.73).

Conclusions Although the combination of statins and ADT in PCa patients significantly improves OS, it seems not to be through an effect on cancer-specific factors.

Key Words: nephron-sparing surgery ‹› training in robotic surgery ‹› robot-assisted partial nephrectomy ‹› robot-assisted partial nephrectomy ‹› learning curve in robotic surgery ‹› vascular clamping

INTRODUCTION

Statins (i.e., 3-Hydroxy-3methyl-glutaryl-CoA reductase inhibitors) are commonly used for lowering cholesterol levels and reducing the risk of cardiovascular disease [1]. However, statins can also modify the cholesterol levels needed for signal transduction and affect prostate cancer (PCa) tumor cells [2]. Statins are thought to modulate androgen receptor expression and activity, reducing PCa cell proliferation and inducing apoptosis [3, 4]. Statins may also reduce prostate-specific antigen (PSA) levels released by PCa tumor cells [5, 6]. Recently, there has been rising interest in investigating statins potential roles in preventing and treating PCa patients [7]. Indeed, cumulative evidence showed that statins might decrease the risk of PCa and delay the progression of the illness [8, 9, 10].

Androgen deprivation therapy (ADT) is the backbone treatment for men with advanced or metastatic PCa [11, 12, 13]. Despite significant efficacy, castration resistant PCa (CRPC) is the eventual outcome of all patients with long term ADT.

A series of recent studies investigate the influence of statin on survival outcomes in PCa patients who received ADT [10, 14–22]. A closer look at the literature reveals many gaps and shortcomings. Thereby, the present systematic review and meta-analysis aimed to develop an overarching framework for the association of statins use and survival outcomes in PCa patients who received ADT.

MATERIAL AND METHODS

In this meta-analysis, we followed the Meta-analyses of Observational Studies in Epidemiology (MOOSE) statement guidelines that propose a checklist of items that resemble randomized controlled trials checklist [23]. Furthermore, we used the preferred reporting items for systematic reviews and meta-analysis (PRISMA) to improve our systematic reviews and meta-analyses reporting [24].

Eligibility criteria

The question of this study was, "Do statin users have better survival outcomes compared to non-statin users in PCa patients who received ADT". We considered all studies covering our question eligible for our systematic review. We selected studies that perform quantitative synthesis according to the similarity in PICO elements to decrease the selection bias and heterogeneity. Our inclusion criteria were original studies that evaluated survival outcomes and reported an estimated risk effect [hazard ratio (HR), odds ratio (OR), relative risk (RR)] for both patient and control groups. Abstracts and animal studies were excluded. Consequently, according to the MOOSE guidelines, the more comparable original studies were included in the analyses. Moreover, we explore the heterogeneity of the population by identifying the source and origin of databases. We categorized studies according to overall survival (OS) and cancer-specific survival (CSS).

Information sources

We searched PubMed and Web of Science for studies published before March 1, 2021. The search queries used were "(Hydroxymethylglutaryl-CoA Reductase Inhibitors OR HMG-CoA Reductase Inhibitors OR statin OR statins OR atorvastatin OR bervastatin OR cerivastatin OR crilvastatin OR compactin OR dalv-

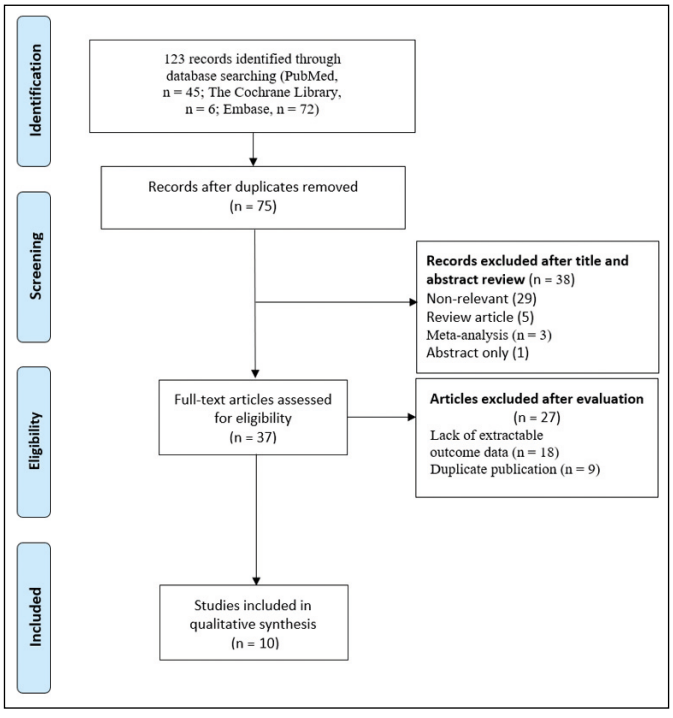

Figure 1. *The selection process of the articles that assess survival outcomes for statin user in prostate cancer patients who received androgen deprivation therapy (ADT) compared to non-user.*

astatin OR fluindostatin OR fluvastatin OR glenvastatin OR lovastatin OR mevastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin OR tenivastatin) AND (prostate cancer OR prostate carcinoma OR prostatic cancer OR prostatic carcinoma)) AND (androgen deprivation therapy OR ADT)".

The search results were restricted to English language articles. Two reviewers screened titles and abstracts independently; any disagreement about the articles eligibility was resolved by Delphi consensus with the co-authors. A data extraction sheet was developed based on the Cochrane Consumers and the Communication Review Group's (http://cccrg.cochrane.org/author-resources). We extracted the following data: first-author, type of article, year of publication, sample size, number of individuals on treatment, outcome, how the outcome was measured, type of effect statistic, effect statistic error measures and effect statistic P-value. We did not contact any authors for additional details because of no limitations in the data of the articles. We used a modified Newcastle-Ottawa Scale (NOS) criteria to evaluate the included articles quality [25]. We extracted outcomes (OS and CSS), hazard ratios (HR) and 95% confidence intervals (CI). Using Delphi consensus, we resolved all discrepancies about data extraction.

Statistical analysis

We used Forest plots to evaluate the multivariable HR. We summarized them to represent the relationship of our outcomes with statin usage. Multivariable adjusted or propensity score-matched analyses were used in the meta-analyses. The primary meta-analysis was accomplished for articles reporting CSS as an outcome. A secondary meta-analysis was completed for articles reporting OS as an outcome. Heterogeneity across the studies was assessed using p-values, Q and I2 statistics [26]. We used random-effect meta-analysis when the heterogeneity was more than 50 percent. When there was no significant heterogeneity observed, the fixed-effect model was used. We used Funnel plots to detect the risk of publication bias. If the P-value was <0.05, we con-

Table 1. *Characteristics of the included studies*

Study	Year	Type of study	Sample size (ADT)	Diagnosis	Outcomes	Treatment	Time of statin use	Follow-up	Statin users (n)	Non-statin users (n)
Hamilton et al. [14]	2020	Retrospective cohort	1,364	Advanced PCa	OS/CSS	ADT following primary or salvage RT	Post	6.9 years	585	779
Kumar et al. [15]	2020	Retrospective cohort	68,432 (14,975)	Stage I–IV PCa	CSS	RT, RP and ADT	Pre	Until death or last follow-up	40,772	27,660
Goldberg et al. [16]	2020	Retrospective cohort	21,512	Healthy men at risk for PCa	CSS	ADT	Pre	9.42 years	10,818	10,694
Wu et al. [22]	2019	Retrospective cohort	5,749	Locally advanced and metastatic PCa	OS/CSS	ADT	Post	3.6 years	2,171	3,578
Anderson-Carter et al. [17]	2018	Retrospective cohort	87,346	Advanced PCa	OS/CSS	ADT	Post	Until death or end of study	53,360	33,986
Joentausta et al. [10]	2018	Retrospective cohort	14,424 (1,335)	Localized [N0 cases], locally advanced [T3-T4, all N1 cases] and unknown)	CSS	RP ±ADT	Pre or Post	9.5 years	3,435	10,698
Mikkelsen et al. [18]	2017	Retrospective cohort	573	Most advanced PCa	OS	ADT	Post	5.7 years	141	396
Jung et al. [19]	2015	Retrospective cohort	171	Metastatic PCa	CSS	ADT	Pre or Post	52 months	46	125
Sun et al. [20]	2015	Retrospective cohort	10,358 (1,253)	PCa N/A	CSS	RT, RP and ADT	Pre	7.75 years	5179	5179
Caon et al. [21]	2014	Retrospective cohort	3,851 (2,580)	Localized prostate cancer	CSS	RT ± (ADT)	Pre	8.4 years	506	2,428

ADT – androgen deprivation therapy; n – number of patients; N/A – not reported; PCa – prostate cancer; RT – radiotherapy; RP- radical prostatectomy; OS – overall survival; CSS – cancer-specific survival

sidered the results to be significant. Data analyses were performed using Review Manager 5.4.

RESULTS

After initial screening, we found 123 articles available for assessment. The selection process for the systematic review is shown in Figure 1. Finally, we included 10 studies for the systematic review and meta-analysis according to our inclusion and exclusion criteria; the characteristics of the included studies presented in Table 1 [10, 14–22].

All included studies in our review were retrospective cohort studies. Out of 10 included, nine studies evaluated CSS and four assessed OS. According to the NOS, the included studies quality assessment is summarized in Table 2. The results showed that all included studies had a good quality.

Association of statins and cancer-specific survival

In the first meta-analysis, we included nine studies comprising 136,285 patients. We found no significant CSS difference between statin using PCa patients on ADT compared to PCa patients on ADT who did not use statins with an HR of 0.77 (95% CI 0.49–1.21) (Figure 2A). However, the nine studies included in the meta-analysis demonstrated high heterogeneity (I^2 = 99%, p = 0.00001), so we used a random-effect model. The funnel plot was asymmetrical (Figure 2B).

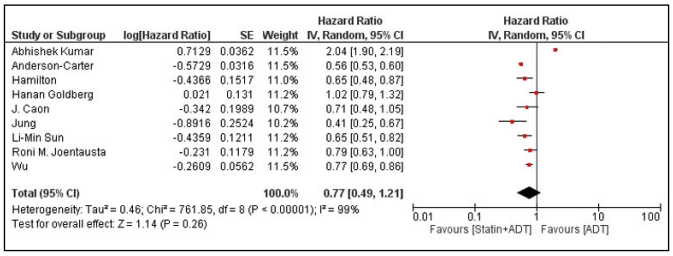

Figure 2A. *Forest plots with summary hazard ratios (all included study) for cancer-specific survival (CSS) of statin group vs non-statin (reference group) for prostate cancer patients who received ADT.*

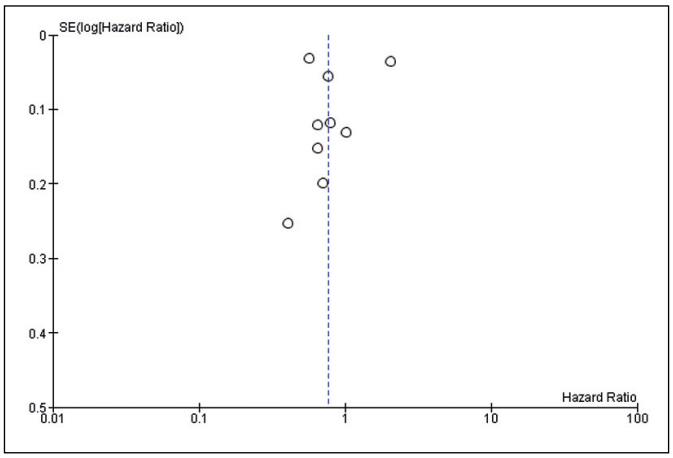

Figure 2B. *Funnel plots of the cancer-specific survival (CSS) meta-analyses.*

Association of statins and overall survival

In the second meta-analysis, we included four studies comprising 95,032 patients. We found that statin using PCa patients on ADT had significantly better OS compared to PCa patients on ADT who did not use statins with an HR of 0.67 (95% CI 0.62–0.73) (Figure 3A). The four studies included in the meta-analysis showed high heterogeneity (I^2 = 57%, p = 0.07), so we used a random-effect model. The funnel plot was asymmetrical (Figure 3B).

Table 2. *The Newcastle-Ottawa Scale for all studies in the quantitative synthesis*

Study	Selection	Comparability	Outcome	Total
Hamilton, et al. 2020 [14]	****	**	***	9
Kumar, et al. 2020 [15]	****	**	**	8
Goldberg, et al. 2020 [16]	****	**	**	8
Wu, et al. 2019 [22]	****	**	***	9
Anderson-Carter, et al. 2018 [17]	****	**	**	8
Joentausta, et al. 2018 [10]	****	**	**	8
Mikkelsen, et al. 2017 [18]	****	**	**	8
Jung, et al. 2015 [19]	****	**	**	8
Sun, et al. 2015 [20]	****	**	*	7
Caon, et al. 2014 [21]	****	**	*	7

*According to Newcastle-Ottawa scale, stars were awarded for each quality item such that highest quality studies were awarded up to 9 stars

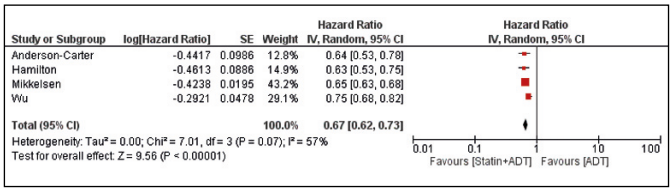

Figure 3A. *Forest plots with summary hazard ratios (all included study) of overall survival (OS) of statin group vs non-statin (reference group) for prostate cancer patients who received androgen deprivation therapy (ADT).*

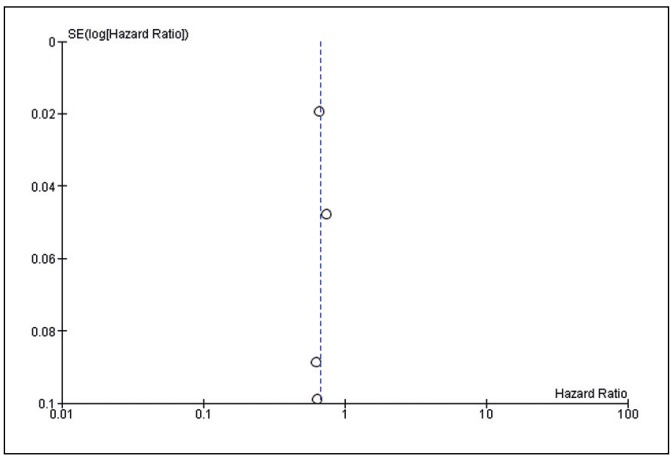

Figure 3B. *Funnel plots of the overall survival (OS) meta-analyses.*

DISCUSSION

According to the present systematic review and meta-analyses results, we found that using statins significantly improve OS of PCa patients on ADT. While CSS was also better in patients on statins, the association did not reach statistical significance.

It is not fully elucidated yet by which mechanism statins improve OS. It is surely a multifactorial effect of statins on the adverse events of ADT [27]. It has been confirmed that long-term ADT is related to cardiometabolic conditions such as diabetes mellitus, hyperinsulinemia, lipid metabolism disturbances, cardiovascular diseases and dementia [28, 29, 30]. Low testosterone levels secondary to ADT are associated with decreased higher triglycerides, density lipoprotein, and cholesterol levels [31, 32]. A lipid profile and metabolism possibly improved among PCa patients who receive ADT and on statins could explain the OS benefit in those patients compared to ADT PCa patients without statins.

Four studies found that statins significantly improved CSS in patients who received ADT [14, 17, 19, 22]. The same phenomenon has also been shown in breast cancer patients [33]. Conversely, in our CSS meta-analysis, we could not confirm this CSS improvement statistically. This suggests that statins do not significantly impact the molecular PCa mechanism but rather impact the cardiovascular component which is assumed by ADT [5, 6].

There are different types of statins (hydrophilic and lipophilic) with distinct effects in PCa patients. However, of included studies in the present meta-analysis, only three studies showed the results for different statin types. All three studies showed that hydrophilic statin (e.g., rosuvastatin, atorvastatin and pravastatin) were associated with better survival outcomes for PCa patients treated with ADT [16, 20, 22]. Prior studies primarily described results from patients who received lipophilic statin [34, 35]. Furthermore, the statin dosage and duration are other critical points to the efficacy of statin use as demonstrated in some studies [20, 36]. Few studies examined the duration and dose of statins [10, 20, 22]. The variances in the dose and duration of statins among included studies might justify the pooled study estimates heterogeneity. We believe that statin use dosage and duration are important confounding factors in the assessment of statin effect on survival outcomes of PCa patients who receive ADT.

The present study suffers from some limitations that should be acknowledged. The main limitation is that all included studies were of retrospective cohort design. Second, important potential confounding factors such as dosage and duration might result in heterogeneity. Finally, the effect of pre- or post-diagnostic statin use on survival outcomes is scarce.

CONCLUSIONS

Although the use of statins in PCa patients on ADT could significantly improve OS, statins seem not to improve CSS. Better management of ADT adverse and secondary effects in addition to better management of the general health of the elderly PCa population would help improve OS in these patients [37]. Better designed prospective studies are necessary to validate our results while controlling for all potential confounding factors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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