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.
INTRODUCTION

Statins (i.e., 3-Hydroxy-3-methyl-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-
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://ccrg.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.

**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               |

**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-

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).

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.
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., rosvastatin, 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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