ORIGINAL RESEARCH

Statin use and mortality of patients with prostate cancer: a meta-analysis

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Objective: The aim of this meta-analysis was to investigate the effect of statin use on the mortality of patients with prostate cancer (PCa).

Methods: An electronic search of PubMed, Embase, and CENTRAL databases from inception to August 2015 was performed to find eligible studies. Articles investigating the association between statin use and mortality of PCa were identified. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using random- or fixed-effects models.

Results: In total, 13 studies that enrolled 100,536 participants were included in this meta-analysis. Results showed that prediagnostic statin use had a significantly lower risk of both all-cause mortality (ACM; HR, 0.56; 95% CI, 0.38–0.83) and PCa-specific mortality (PCSM; HR, 0.53; 95% CI, 0.36–0.77). Similarly, postdiagnostic statin use was correlated with reductions in both ACM (HR, 0.77; 95% CI, 0.69–0.87) and PCSM (HR, 0.64; 95% CI, 0.52–0.79). When stratified by primary treatment, postdiagnostic use of statins had a 0.4-fold lower risk of ACM in patients with PCa who were treated with local therapy; both pre- and postdiagnostic use of statins was correlated with a significantly lower risk of PCSM in patients who were treated with androgen deprivation therapy.

Conclusion: Both pre- and postdiagnostic use of statins is associated with better overall survival and PCa-specific survival. This suggests a need for randomized controlled trials of statins in patients with PCa.

Keywords: prostate cancer, all-cause mortality, prostate cancer-specific mortality, statins

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are commonly used to treat hypercholesterolemia and have been demonstrated to reduce cardiovascular events and mortality.[1] Most recently, attention has focused on their potential anticancer properties. Statins have been shown to affect proliferation, induce apoptosis, and inhibit angiogenesis of tumor cells.[2–4] Several epidemiological studies have investigated the effects of statins on the risk of prostate cancer (PCa) and treatment outcomes. A recent meta-analysis of 27 observational studies revealed that statins reduced the risk of both overall PCa and clinically important advanced PCa.[5] However, the impact of statins on all-cause mortality (ACM) or PCa-specific mortality (PCSM) in patients with PCa remains debatable. Some studies have demonstrated a beneficial effect of statins in reducing ACM and PCSM,[6–8] whereas others have not revealed a significant effect.[9,10] These inconsistent conclusions may be due to relatively small sample sizes and different timings of statin use (eg, prediagnostic or postdiagnostic). Therefore, we performed a systematic review and meta-analysis of the available data to explore the association of prediagnostic and postdiagnostic statin use with the risk of death in patients with PCa.

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Materials and methods
Search strategy
An electronic search of PubMed, Embase, and CENTRAL databases for all relevant studies (the last search update was August 21, 2015) was carried out using the following search terms: "Hydroxymethylglutaryl-CoA Reductase Inhibitors or HMG-CoA Reductase Inhibitors or statin or statins or atorvastatin or bervastatin or cerivastatin or crilvastatin or compactin or dalvastatin 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 "mortality or survival or death." The search was limited to English language articles. All searches were performed independently by two investigators and any differences were resolved by discussion.

Selection criteria
Following the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines, the Population, Intervention, Comparison, Outcome, and Study design eligibility criteria were applied to define study eligibility.[11] All studies investigating the association between statin use and mortality of PCa were considered relevant to this meta-analysis. Both full-text articles and conference abstracts were eligible. Inclusion criteria were as follows: 1) the exposure of interest was statin use prior to or after diagnosis, 2) ACM and/or PCSM after PCa diagnosis according to statin use were reported, and 3) adjusted risk estimates with 95% confidence intervals (CIs; or adjusted risk estimates and P-values) were given. Case reports, letters, review articles, and comments were excluded during the process of study selection. For studies that reported results using the same or overlapping data, only the study with the largest number of patients was included.

Study quality assessment
All the finally included studies were nonrandomized studies. The quality of all studies, except the conference abstracts, was assessed according to the Newcastle–Ottawa scale,[12] which is recommended by the Cochrane Collaboration. Stars were allocated to each study in the range of 0–9, and studies with 6 or more stars were deemed of high quality.

Data extraction
Two authors (YM and JW) independently extracted the data from all the included studies, and the following information was extracted: the first author, year of publication, study location, sample size, follow-up period, patient characteristics (eg, age, pretreatment prostate-specific antigen level, tumor stage, and Gleason score), type of primary treatment, statin use, risk estimates with their corresponding 95% CIs (or P-values), and study design. Any discrepancy was resolved by discussion.

Statistical analyses
The inverse variance method was used to pool the hazard ratios (HRs) for the effect of statin on mortality in patients with PCa.[13] Because outcomes were relatively rare, odds ratio (OR) was used as an estimate of HR. If studies reported risk estimates for PCSM and other-cause mortality, the risk estimates for ACM were calculated first.[14] For any study providing separate risk estimates by primary treatment, we considered the estimates as different studies.[6] Between-study heterogeneity was assessed using both Cochran's Q-test and I^2 statistics. A value of $P<0.10$ for Q-test or an $I^2>50\%$ was considered significant. A random-effects model was used if heterogeneity was significant; otherwise, a fixed-effects model was used.[15] Subgroup analyses were conducted to explore potential sources of between-study heterogeneity. The potential publication bias was assessed by funnel plot visual inspection for all comparisons. All statistical analyses were performed with RevMan software (version 5.3). P-values for all analyses were two sided.

Results
Characteristics of eligible studies
In total, 401 abstracts were identified and assessed from the initial literature search, and 24 studies were potentially eligible and were evaluated in detail. Eleven of the 24 studies were subsequently excluded from the present meta-analysis (nine did not fulfill the inclusion criteria and two were based on overlapping data). Thus, 13 studies (12 cohort studies and one case–control study) involving 100,536 participants were included in the meta-analysis.[6–10,14,16–22] The flow chart of the study selection is shown in Figure 1.

Of the 13 studies, six investigated the association of prediagnostic statin use with ACM and/or PCSM, and seven investigated the association of postdiagnostic statin use with ACM and/or PCSM. The characteristics and quality assessments of eligible studies are summarized in Table 1. Visual inspection of funnel plots did not reveal any obvious publication bias in our meta-analysis.

ACM
Eight studies[6,9,14,17,19–22] that met the inclusion criteria were included in the analysis of ACM: two focused on statin use
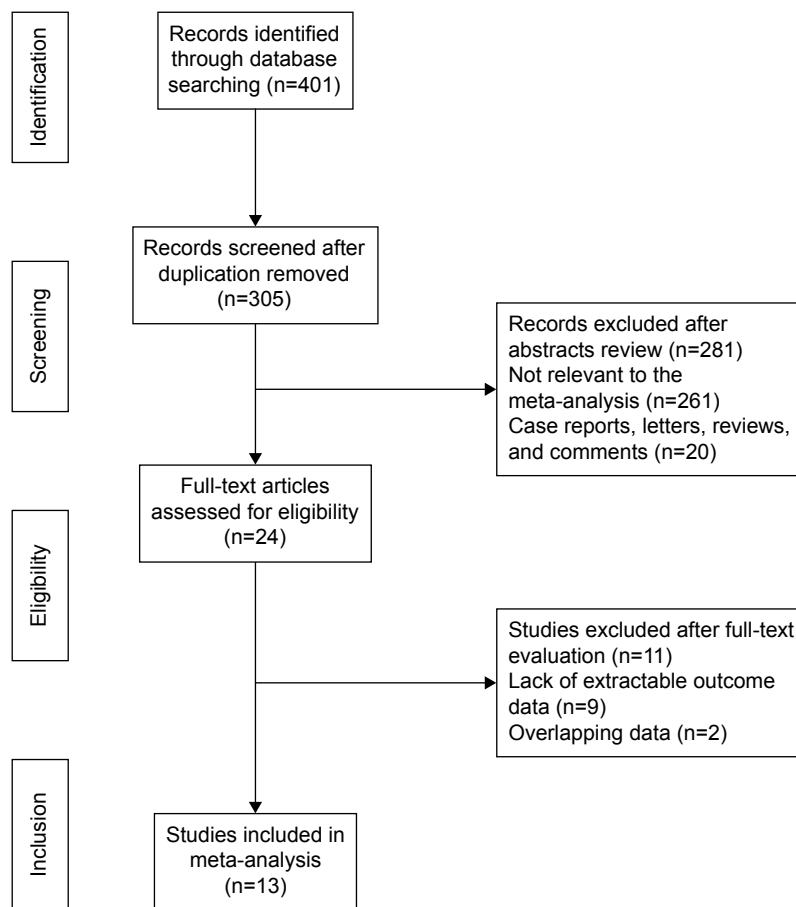
Figure 1 Flow diagram of the study selection process.

before diagnosis and six focused on statin use after diagnosis. The pooled risk estimates are shown in Table 2 and Figure 2. Both pre- (HR, 0.56; 95% CI, 0.38–0.83; $P<0.01$; $I^2=0\%$) and postdiagnostic use of statin (HR, 0.77; 95% CI, 0.69–0.87; $P<0.01$; $I^2=72\%$) was associated with a significantly reduced risk of ACM in patients with PCa.

Subgroup analysis according to the treatment strategy was then performed. Postdiagnostic statin use was significantly correlated with a decreased risk of ACM among patients with PCa who were primarily treated with local therapy (radical prostatectomy or radiotherapy; HR, 0.46; 95% CI, 0.28–0.77; $P<0.01$; $I^2=53\%$). A pooled analysis of three studies failed to distinguish primary treatment used and also revealed that postdiagnostic statin use was associated with lower ACM (HR, 0.81; 95% CI, 0.77–0.84; $P<0.01$; $I^2=22\%$).

PCSM

In total, ten studies[7,8,10,14,16–20,22] were included in the analysis of PCSM: six were based on prediagnostic statin use and four on postdiagnostic statin use. The pooled risk estimates are shown in Table 2 and Figure 3.

The results demonstrated that patients who used statins before diagnosis had a 0.5-fold lower risk of PCSM (HR, 0.53; 95% CI, 0.36–0.77; $P<0.01$; $I^2=77\%$). When stratified by primary treatment, prediagnostic statin use was still associated with a decreased risk of PCSM among patients who were treated with androgen deprivation therapy (HR, 0.53; 95% CI, 0.29–0.98; $P=0.043$). The pooled risk estimate from studies that did not distinguish primary treatment was also correlated with a significantly lower risk of PCSM (HR, 0.44; 95% CI, 0.20–0.95; $P=0.04$; $I^2=88\%$), whereas prediagnostic statin use among patients who were primarily treated with local therapy showed only a trend toward decreased risk (HR, 0.52; 95% CI, 0.17–1.58; $P=0.25$; $I^2=61\%$).

Similarly, a significant correlation of postdiagnostic statin use with a reduced risk of PCSM was found (HR, 0.64; 95% CI, 0.52–0.79; $P<0.01$; $I^2=79\%$). When stratified by primary treatment, postdiagnostic statin use was associated with a significantly decreased risk of PCSM in patients who were treated with androgen deprivation therapy (HR, 0.64; 95% CI, 0.48–0.86; $P=0.003$). A pooled analysis of those studies could not distinguish primary treatment (HR, 0.73; 95% CI,

Table 1 Characteristic of the included studies

Study	Year	Follow-up period	Study design	Patient characteristics	Primary treatment	Statin use	PCSM	ACM	Adjusted for
Katz et al[6]	2010	1990–2006; median 4 years	Cohort	7,042 patients who received RP or RT for prostate cancer	RP (n=4,611) or RT (n=2,431)	Postdiagnostic		RP: HR: 0.35 (0.21–0.58); RT: HR: 0.59 (0.37–0.94)	Use of NSAIDs, mean office visits/year, age, cardiovascular disease, year of diagnosis, pathological T stage, diabetes, biopsy Gleason grade, and smoking
Hamilton et al[7]	2011	Not reported	Cohort	782 men with prostate cancer underwent local treatment	Local treatment	Prediagnostic	HR: 0.23 (0.05–0.95)		Age, year of diagnosis, PSA, Gleason grade, clinical stage, and treatment
Nielsen et al[16]	2012	1995–2009; median 2.6 years	Cohort	27,752 Danish men with a diagnosis of prostate cancer	Failed to distinguish	Prediagnostic	HR: 0.81 (0.75–0.88)		Age at diagnosis, cancer stage, treatment with chemotherapy, treatment with radiotherapy, cardiovascular disease before cancer, diabetes mellitus before cancer, birth year, sex, descent, highest obtained level of education, and size of residential area
Marcella et al[8]	2012	1997–2002	Case–control	380 cases aged 55 years to 79 years who died from prostate cancer and 380 matched controls	Failed to distinguish	Prediagnostic	OR: 0.37 (0.23–0.60)		Education level, body mass index, waist size, number of comorbidities, matched for race and age, and antihypertensive medication use
Geybels et al[14]	2013	2002–2011; mean 7.5 years	Cohort	1,001 patients with prostate cancer of all stages	Failed to distinguish	Prediagnostic	HR: 0.19 (0.06, 0.56)	HR: 0.45 (0.10–2.01)	Age, Gleason score, stage, diagnostic PSA level, primary treatment approach, race, first-degree family history of PCa, body mass index, smoking, lifetime alcohol consumption, aspirin use, nonaspirin NSAID use, history of diabetes mellitus, and history of PCa screening
Niraula et al[9]	2013	2000–2003; mean 20.7 months	Cohort	1,006 patients with castration-refractory metastatic prostate cancer treated with docetaxel	Docetaxel	Postdiagnostic		HR: 0.97 (0.76–1.23)	Not stated
Dehlendorff et al[17]	2014	Mean 4 years	Cohort	34,284 Danish men with a first-time diagnosis of prostate cancer	Failed to distinguish	Postdiagnostic	HR: 0.74 (0.70–0.79)	HR: 0.79 (0.75–0.83)	Age, year of prostate cancer diagnosis, stage (localized, nonlocalized, or unknown), education, income, Charlson Comorbidity Index score, diabetes, chronic obstructive lung disease, aspirin, 5-alpha-reductase inhibitors, nonaspirin NSAIDs, ACEIs, and angiotensin-II antagonists
Murtola et al[18]	2014	1996–2009	Cohort	6,220 finish men diagnosed with prostate cancer	Failed to distinguish	Postdiagnostic	HR: 0.33 (0.23–0.49)		Age at diagnosis, use of other drug groups (aspirin and NSAIDs, antihypertensive and antidiabetic drugs, 5a-reductase inhibitors and alpha-blockers), tumor stage and grade, primary treatment selection (active surveillance, surgery, radiation therapy or hormonal therapy), statin usage before the diagnosis

Study	Year	Design	Population	Treatment	Timing	HR	HR	Adjustments
Caon et al[10]	2014	Cohort	3,851 patients with prostate cancer treated with external beam radiation therapy ± ADT	External beam radiation therapy	Prediagnostic	HR: 0.77 (0.55–1.08)		Age, acetylsalicylic acid, year of treatment, radiation dose, ADT, PSA, T stage, Charlson Index, and Gleason score
Yu et al[19]	2014	Cohort	11,772 patients newly diagnosed with nonmetastatic prostate cancer	Failed to distinguish	Postdiagnostic	HR: 0.76 (0.66–0.88)	HR: 0.86 (0.78–0.95)	Age, year of prostate cancer diagnosis, ethnicity, excessive alcohol use, smoking status, obesity, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancers, PSA, Gleason score, metformin, sulfonylureas, thiazolidinediones, insulins, other oral antihypoglycemic agents, ACEIs, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other nonsteroidal anti-inflammatory drugs, 5-alpha − reductase inhibitors, prediagnostic statin use, PSA testing activity, prostatectomy, radiation therapy, chemotherapy, and ADT
Hamilton et al[22]	2015	Cohort	1,364 patients with prostate cancer treated with ADT	ADT	Postdiagnostic	HR: 0.64 (0.48–0.86)	HR: 0.64 (0.53–0.78)	Age, time from RT to ADT and PSA
Chan et al[21]	2015	Cohort	3,949 men diagnosed with localized prostate cancer	Failed to distinguish	Postdiagnostic		HR: 0.84 (0.71–0.99)	Age, time period, time since diagnosis to questionnaire, body mass index, vigorous physical activity, smoking, aspirin use, clinical stage, PSA at diagnosis, Gleason score, treatment, stroke, myocardial infarction, hypertension, and diabetes
Calais Da Silva et al[20]	2015	Cohort	336 patients with prostate cancer treated with ADT	ADT	Prediagnostic	HR: 0.53 (0.28–0.98)	HR: 0.57 (0.38–0.85)	Metastatic status and age

Abbreviations: ACM, all-cause mortality; ACEIs, angiotensin-converting enzyme inhibitors; ADT, androgen deprivation therapy; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PCa, prostate cancer; PCSM, prostate cancer-specific mortality; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy.

Table 2 Main results of meta-analysis for the effect of statin use on ACM and PCSM

Statin use	Mortality	Groups/subgroups	Studies, n	Heterogeneity test		Pooled risk estimates		
				I^2 (%)	P-value	HR	95% CI	P-value
Prediagnostic statin use	ACM	Overall	2	0	0.77	0.56	0.38–0.83	0.003
Postdiagnostic statin use	ACM	Overall	7	72	0.002	0.77	0.69–0.87	<0.001
		Local therapy	2	53	0.14	0.46	0.28–0.77	0.003
		Failed to distinguish primary treatment	3	22	0.28	0.81	0.77–0.84	<0.001
		Androgen deprivation therapy	1	–	–	0.64	0.53–0.78	<0.001
		Chemotherapy	1	–	–	0.97	0.72–1.23	0.80
Prediagnostic statin use	PCSM	Overall	6	77	<0.001	0.53	0.36–0.77	0.001
		Androgen deprivation therapy	1	–	–	0.53	0.29–0.98	0.043
		Local therapy	2	61	0.11	0.52	0.17–1.58	0.25
		Failed to distinguish primary treatment	3	88	<0.001	0.44	0.20–0.95	0.04
Postdiagnostic statin use	PCSM	Overall	4	82	<0.001	0.64	0.52–0.79	<0.001
		Androgen deprivation therapy	1	–	–	0.64	0.48–0.86	0.003
		Failed to distinguish primary treatment	3	88	<0.001	0.73	0.69–0.78	<0.001

Abbreviations: ACM, all-cause mortality; CI, confidence interval; HR, hazard ratio; PCSM, prostate cancer-specific mortality.

0.69–0.78; $P<0.01$; I^2=88%) and also showed a significant correlation.

Discussion

The main results of the present meta-analysis are as follows: 1) both pre- and postdiagnostic use of statins was associated with a decreased risk of ACM and PCSM, 2) postdiagnostic use of 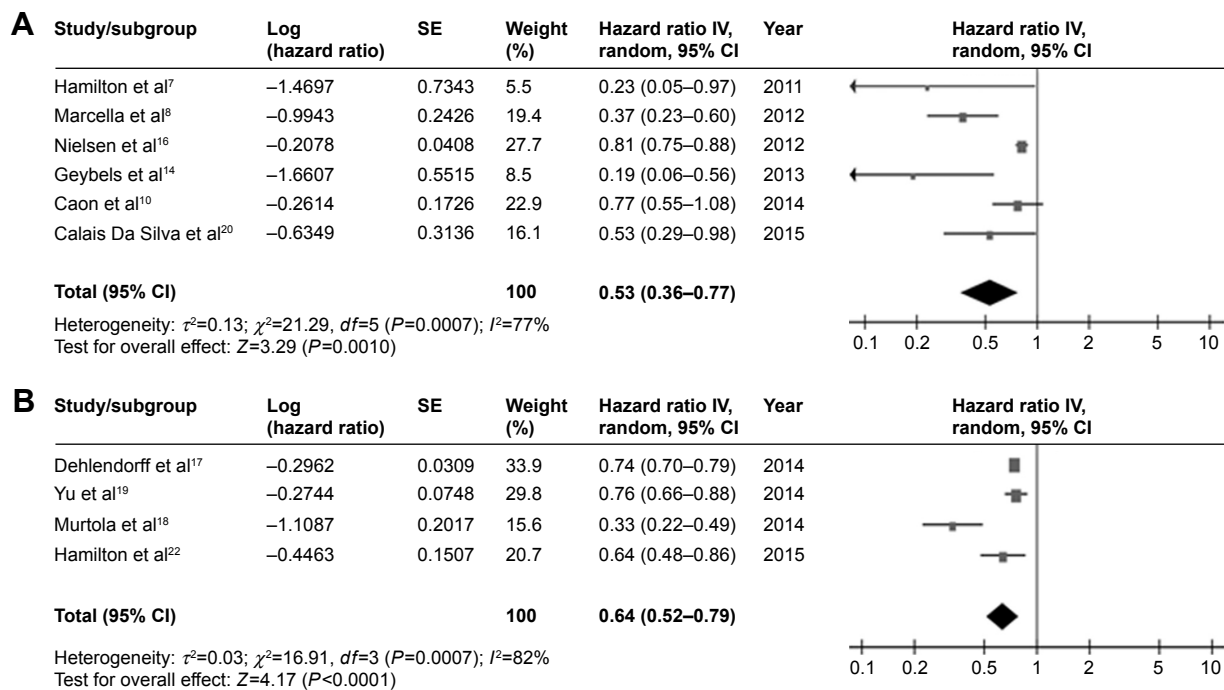statins had a 0.4-fold lower risk of ACM in patients with PCa who were treated with local therapy, and 3) both pre- and postdiagnostic use of statins was correlated with a significantly lower risk of PCSM in patients who were treated with androgen deprivation therapy.

Statins are commonly used to reduce cholesterol levels and are associated with a decrease in the prevalence of cardiovascular events, but the impact of statins on the prognosis of patients with PCa is still controversial.
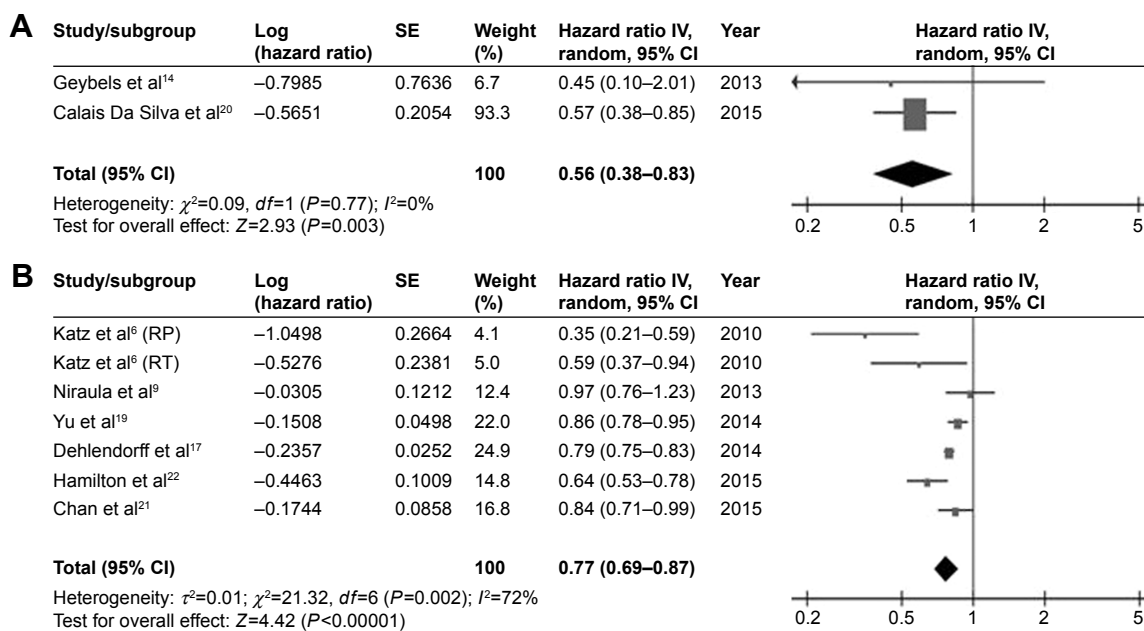
Figure 2 Pooled analyses for the effect of prediagnostic (**A**) and postdiagnostic (**B**) statin use on all-cause mortality of prostate cancer.
Abbreviations: CI, confidence interval; df, degrees of freedom; RP, radical prostatectomy; RT, radiotherapy; SE, standard error.

A

Study/subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Year
Hamilton et al[7]	−1.4697	0.7343	5.5	0.23 (0.05–0.97)	2011
Marcella et al[8]	−0.9943	0.2426	19.4	0.37 (0.23–0.60)	2012
Nielsen et al[16]	−0.2078	0.0408	27.7	0.81 (0.75–0.88)	2012
Geybels et al[14]	−1.6607	0.5515	8.5	0.19 (0.06–0.56)	2013
Caon et al[10]	−0.2614	0.1726	22.9	0.77 (0.55–1.08)	2014
Calais Da Silva et al[20]	−0.6349	0.3136	16.1	0.53 (0.29–0.98)	2015
Total (95% CI)			100	**0.53 (0.36–0.77)**	

Heterogeneity: $\tau^2=0.13$; $\chi^2=21.29$, $df=5$ ($P=0.0007$); $I^2=77\%$
Test for overall effect: $Z=3.29$ ($P=0.0010$)

B

Study/subgroup	Log (hazard ratio)	SE	Weight (%)	Hazard ratio IV, random, 95% CI	Year
Dehlendorff et al[17]	−0.2962	0.0309	33.9	0.74 (0.70–0.79)	2014
Yu et al[19]	−0.2744	0.0748	29.8	0.76 (0.66–0.88)	2014
Murtola et al[18]	−1.1087	0.2017	15.6	0.33 (0.22–0.49)	2014
Hamilton et al[22]	−0.4463	0.1507	20.7	0.64 (0.48–0.86)	2015
Total (95% CI)			100	**0.64 (0.52–0.79)**	

Heterogeneity: $\tau^2=0.03$; $\chi^2=16.91$, $df=3$ ($P=0.0007$); $I^2=82\%$
Test for overall effect: $Z=4.17$ ($P<0.0001$)

Figure 3 Pooled analyses for the effect of prediagnostic (**A**) and postdiagnostic (**B**) statin use on prostate-cancer-specific mortality of prostate cancer.
Abbreviations: CI, confidence interval; df, degrees of freedom; SE, standard error.

However, in this study, we demonstrated that statins were associated with a decreased risk of both ACM and PCSM in patients with PCa, and this finding is supported by an observational study of 295,925 patients, which reported a decreased rate of cancer-related mortality among patients who took statins.[16]

Several factors may account for the beneficial impact of statins on ACM and PCSM. 1) Cholesterol is required for basic cellular functions, including maintenance of membrane integrity and involvement of signaling pathways, which are critical for cancer cell proliferation,[23–25] thus a decrease in cholesterol level might reduce PCa growth. 2) Previous experimental studies have demonstrated that statins may have anti-inflammatory, proapoptotic, and antiangiogenic effects, which may reduce metastasis and invasiveness.[26,27] A recent meta-analysis demonstrated that statins were associated with a lower risk of PCa recurrence in patients who were treated with radiotherapy. 3) Cholesterol is a precursor of androgens; thus, a reduction in cholesterol level leads to a decrease in testosterone and dihydrotestosterone, which are crucial to androgen receptor,[28,29] and a reduction in androgen receptor may predict PCa outcome.[30] In line with this, the study suggests that both pre- and postdiagnostic use of statins is correlated with a significantly lower risk of PCSM in patients who were treated with androgen deprivation therapy. This phenomenon has also been seen in patients with breast cancer.[31]

Additionally, Nielsen et al[16] revealed the absence of a dose-dependent effect of statins, while Yu et al[19] found that long-term treatment with statins provided greater benefit than short-term treatment. Therefore, randomized trials are needed to investigate the effect of statins on ACM and PCSM, especially with regard to dose and time dependency.

Several limitations should be taken into consideration when interpreting our results. First, we found between-study heterogeneity in the meta-analysis, which might affect the strength of the results in the study. However, we performed subgroup analyses to explore the source of heterogeneity when we could not find it. Second, we did not evaluate the effect of postdiagnostic statin use on the association between prediagnostic statin use and patient survival because of limited data from included studies. We therefore evaluated postdiagnostic statin use, without taking into account the effect of prediagnostic statin use.

Conclusion

Both pre- and postdiagnostic use of statins is associated with better overall survival and cancer-specific survival. Randomized controlled trials are needed to further assess

the effect of statin use on the mortality of patients with PCa in the future.

Disclosure

The authors report no conflicts of interest in this work.

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