Prior statin therapy and mortality among critically ill patients: a systemic review and meta-analysis of cohort studies

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Abstract: The effect of prior statin exposure in critically ill patients remains controversial and has not been established in previous cohort studies. We performed a systematic review of previous cohort studies to evaluate the association of prior statin therapy with mortality in critically ill patients and conducted a meta-analysis. The MEDLINE, EMBASE, and Cochrane CENTRAL databases, from their inception to January 7, 2020, were used for this study. Statin users were defined as patients prescribed statin regularly before intensive care unit admission or diagnosis of a specific disease, such as sepsis. The Cochran chi-square test and I statistics were used to determine heterogeneity between studies. In total, 199,985 critically ill patients from nine studies (44,582 statin users and 155,403 non-statin users) were included in the meta-analysis. According to the random effect model, the 30-day mortality of statin users was 31% lower than that of non-statin users (hazard ratio: 0.69, 95% confidence interval: 0.56 to 0.85). This association was similar in atorvastatin users and simvastatin users. However, hospital mortality in statin users was not significantly associated with that in non-statin users [odds ratios (ORs): 0.71, 95% CI: 0.42 to 1.21]. This study showed that there was a beneficial association of prior statin therapy with 30-day mortality in critically ill patients. However, there was no significant association with hospital mortality. Additional prospective cohort studies with a large sample size should be performed to confirm these findings.

Keywords: Critical care; critical illness; hospital mortality; intensive care unit; meta-analysis

Introduction

Statins are among the most commonly prescribed drugs for the treatment of dyslipidemia worldwide (1). They mainly lower the risk of acute cardiovascular events by lowering serum cholesterol levels (2). They also have anti-inflammatory, anti-thrombotic, and immuno-modulating effects (3,4). These effects are referred to as "pleiotropic effects" (5), which improve the outcomes of various diseases (6).

The effects of statin therapy in critically ill patients have

been evaluated in many studies. Previous meta-analyses have shown the benefit of statin therapy in terms of mortality among patients with severe infection or sepsis (7,8). In contrast, some randomized clinical trials (RCTs) have shown no benefit of statin therapy on mortality in patients with sepsis or septic shock (9-11), and this was supported by a recent meta-analysis (12). However, these RCTs focused on the effect of statin therapy after intensive care unit (ICU) admission or diagnosis of severe conditions such as sepsis or acute respiratory distress syndrome (ARDS). Although some cohort studies focused on the effect of statin therapy before

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ICU admission or diagnosis of a specific disease (e.g., sepsis or ARDS) on mortality in critically ill patients (13-21), their results remain controversial. Whereas some cohort studies reported a benefit of prior statin therapy on mortality among critically ill patients (13-19), others reported that there was no significant association in this regard (20,21).

Therefore, we performed a systematic review of previous cohort studies to evaluate the association of prior statin therapy with mortality and performed a meta-analysis with a larger sample size than that in previous cohort studies.

Methods

Search strategy

This systematic review was performed in compliance with the Meta-analysis of Observational Studies in Epidemiology guidelines (22) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [2009] (23). The MEDLINE, EMBASE, and Cochrane CENTRAL databases were searched for studies conducted on humans and published in English. The databases were searched, from their inception to January 7, 2020, for the following terms by TK Oh and IA Song: "Statin and Critically ill", "Statin and Intensive Care Units", "Statin and Sepsis", "Statin and ARDS", and "Preadmission Statin". The literature that included the search terms in the title, abstract, or keywords were initially searched, and articles that did not meet the eligibility criteria were excluded by TK Oh and IA Song after discussion. Any disagreement was resolved by S Choi after discussion.

Eligibility criteria

First, cohort studies were considered suitable for inclusion in this meta-analysis if they enrolled "critically ill patients" who required treatment or monitoring in the ICU. Therefore, mixed ICU patients, patients with sepsis or septic shock, ARDS patients, and patients with ventilator-associated pneumonia (VAP) were included in the category of critically ill patients in this meta-analysis. Second, cohort studies were mainly included if they investigated the association between prior or preadmission statin therapy and mortality among critically ill patients. The 30-day mortality and in-hospital mortality were considered outcomes. If a study focused on only statin treatment after ICU admission or hospitalization and not prior statin therapy, then it was excluded from the meta-analysis.

Selection of studies and data extraction

We extracted data regarding the name of the first author, year of publication, country in which the research was conducted, study design (i.e., single or multicenter cohort study), study period, diagnosis of the study population (e.g., sepsis or ARDS), number of patients in each group, main statistical method (multivariable adjustment or propensity score matching), and endpoints. The primary endpoints for this meta-analysis were 30-day mortality or hospital mortality after ICU admission or diagnosis of a specific disease (sepsis or ARDS). Adjusted hazard ratios (HRs) or odds ratios (ORs) for primary endpoints after propensity score matching were considered for this meta-analysis if the cohort study used both propensity score matching and multivariable adjustment. In addition, 28-day mortality was considered as 30-day mortality for the purpose of this meta-analysis. Whereas a study conducted at a single institution was considered a single-center cohort study, a study using a national health database was considered a multicenter cohort study.

Quality assessment of the studies

The risk of bias for each outcome in all included studies was evaluated using the Newcastle Ottawa Scale (24) by TK Oh and IA Song, and any disagreement was resolved by S Choi after discussion. Studies that scored 7–9 points on the Newcastle Ottawa Scale were considered as high-quality studies and were therefore included in the meta-analysis.

Statistical analysis

We chose the HRs and ORs of the primary endpoints as the effect size between the statin and non-statin groups. The risk of death was significantly higher in the statin group than in the non-statin group if the mean effect size was greater than 1 and if the calculated 95% CI did not include 1.

The selection of a fixed effects model or a random effects model for the calculation of the average effect size was decided assuming that the studies were derived from the same population and the analyses had the same purpose. These assumptions were considered according to the characteristics of the study, i.e., the study subjects, intervention methods, and study environment. The Cochrane chi-square test and I statistics were used to determine heterogeneity between the studies for meta-analysis. In particular, the fixed effects model was selected
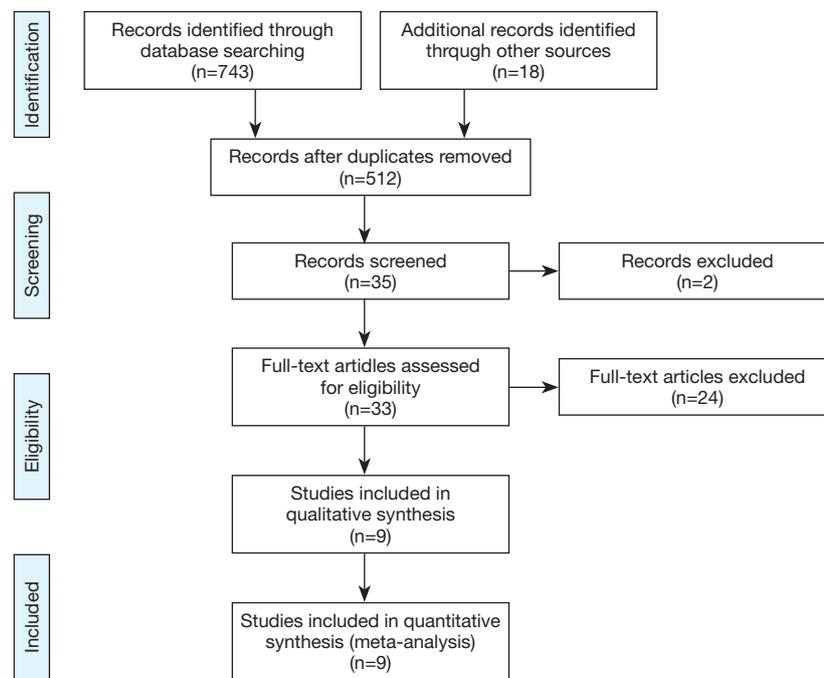
**Figure 1** Flow chart of study selection.

if the homogeneity statistic (I^2) was <50% or the P value of the Q statistic was >0.05. In all other cases, the random effects model was used. Begg's funnel plot and Egger's linear regression were used to assess for potential publication bias (25,26). The funnel plots were visually assessed for asymmetry. In addition, as the quality of data of prospective cohort studies is better than that of retrospective cohort studies, a 2-fold weight was applied for prospective cohort studies, as a sensitivity analysis. All statistical analyses were performed by a statistician (S Choi) using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with the meta package in this environment.

Results

We initially identified 743 articles, of which 512 articles were selected after removing duplicated records. After screening by title and abstract, we identified 35 cohort studies that appeared to address issues potentially related to the primary study question. Next, after completely reading the 35 articles, 9 studies were included in the meta-analysis, as shown in *Figure 1* (13-21). Six of the nine studies were included in the meta-analysis of 30-day mortality (13,15-18,20), and 3 studies were included in the meta-analysis of in-hospital mortality (14,19,21). As the 30-day mortality

and hospital mortality were presented as HRs with 95% CIs in six studies (13,15-18,20) and as ORs with 95% CIs in three studies (14,19,21), HRs and ORs were used as endpoints for 30-day mortality and hospital mortality, respectively, in this meta-analysis. In addition, we had the full raw data for the study published by Oh *et al.* (15), which was conducted recently at our institution, and the HRs for 30-day mortality were re-analyzed to include the outcomes in this meta-analysis. The characteristics of the cohort studies are presented in *Table 1*, and the points allocated according to the Newcastle Ottawa Scale are presented in Supplementary *Table S1*. All nine studies scored relatively high scores of 8–9 points on the Newcastle Ottawa Scale, so the nine studies were not excluded. Finally, a total of 199,985 critically ill patients from nine studies (44,582 and 155,403 in the statin and non-statin groups, respectively) were included in the meta-analysis.

30-day mortality

Figure 2 shows the results of the meta-analysis of 30-day mortality among statin users compared with non-statin users before (A) and after (B) applying a 2-fold weight to prospective cohort studies. The analysis of heterogeneity among the six studies yielded an I^2 value of 94% (P<0.01),

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Table 1 Summary of identified cohort studies

Studies	Year of Publication	Study period	Multi-/single center	Country/region	Study design	Patients	Number of statin user	Number of non-statin user	Statistical adjustment	Included endpoint	Adjusted HR or OR (95% CI)
Bruyere	2014	2006–2013	Single	France	PC	VAP	93	256	MA	30-d mortality	1.23 (0.71, 2.14)
Lee	2017	1999–2011	Multi	Taiwan	RC	Sepsis	3,599	49,138	PSM	30-d mortality	0.86 (0.79, 0.93)
Christensen	2010	2001–2007	Multi	Denmark	PC	Mixed ICU	1,882	10,601	MA	30-d mortality	0.76 (0.70, 0.83)
Lee	2018	2000–2011	Multi	Taiwan	RC	Sepsis	3,503	49,234	PSM	30-d mortality	0.88 (0.79, 0.98)
Mansur	2015	2012–2014	Single	Germany	PC	ARDS	108	296	PSM	28-d mortality	0.18 (0.13, 0.25)
Oh	2019	2012–2017	Single	Korea	RC	Mixed ICU	7,396	17,532	PSM	30-d mortality*	0.76 (0.69, 0.84)
Dobesh	2009	2005–2006	Single	US	RC	Sepsis	60	128	MA	Hospital mortality	0.42 (0.31, 0.58)
Ou	2014	2000–2010	Multi	Taiwan	RC	Sepsis	27,792	27,792	PSM	Hospital mortality	0.86 (0.83, 0.89)
O'Neal	2011	2006–2008	Single	US	PC	Sepsis/ARDS	149	426	MA	Hospital mortality	1.06 (0.58, 1.94)

*, HR of 30-day mortality in statin users were not calculated in Oh *et al.*, and we calculated HR of 30-day mortality in statin users after PSM using same data set of our previous study to include it in meta-analysis. HR, hazard; OR, odds ratio; PC, prospective cohort; RC, retrospective cohort; VAP, ventilator-associated pneumonia; ICU, intensive care unit; MA, multivariable adjustment; PSM, propensity score matching; ARDS, acute respiratory distress syndrome.

indicating significant variations among the studies. The results of the random effects model showed that the 30-day mortality rate among statin users was 31% lower than that among non-statin users (HR =0.69, 95% CI: 0.56–0.85). After applying the 2-fold weight, the 30-day mortality rate among statin users was 34% lower than that among non-statin users (HR =0.66, 95% CI: 0.46–0.95). The funnel plot indicates that there was no publication bias (P value of Egger's test =0.338; *Figure S1*).

Figure 3 shows the results of meta-analysis of 30-day mortality among atorvastatin (A) and simvastatin (B) users compared with non-statin users. In the fixed effects models, the 30-day mortality rate among both atorvastatin users (HR =0.78, 95% CI: 0.72–0.84) and simvastatin users (HR =0.84, 95% CI: 0.78–0.91) was lower than that among non-statin users.

In-hospital mortality

Figure 4 shows the results of the meta-analysis of in-hospital mortality among statin users compared with non-statin users. The analysis of heterogeneity among the three studies yielded an I^2 value of 90% (P<0.01), indicating significant variations among the studies. Therefore, the results of the random effects model revealed that compared with no statin use, statin use was not significantly associated with in-hospital mortality (OR =0.71, 95% CI: 0.42–1.21).

Discussion

In this systemic review and meta-analysis of cohort studies, we showed that there was a significant association of prior statin therapy with 30-day mortality rate among critically ill patients, whereas there was no significant association of prior statin therapy with in-hospital mortality. In addition to the results of a previous meta-analysis of RCTs **(12)**, which focused on the effect of statin therapy after ICU admission or diagnosis of a specific disease (sepsis or ARDS), our results suggest that statin therapy before ICU admission might have a potential benefit in terms of 30-day mortality among critically ill patients.

The most important characteristic of our study is that we only included cohort studies that focused on the effect of prior statin therapy in critically ill patients. Long-term statin exposure is known to cause immuno-modulation by a pleiotropic effect (27), and it suggested that prior statin therapy before ICU admission or diagnosis of a specific disease, such as sepsis or ARDS, might affect patient
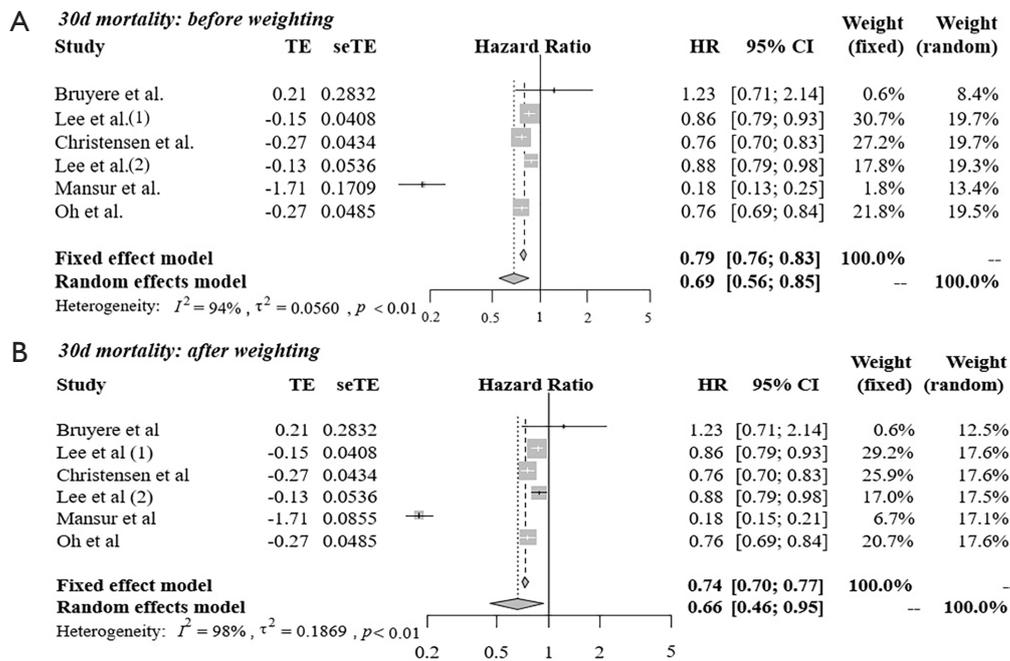
Figure 2 Meta-analysis of 30-day mortality among statin users compared with non-statin users before (A) and after (B) applying a 2-fold weight to prospective cohort studies.
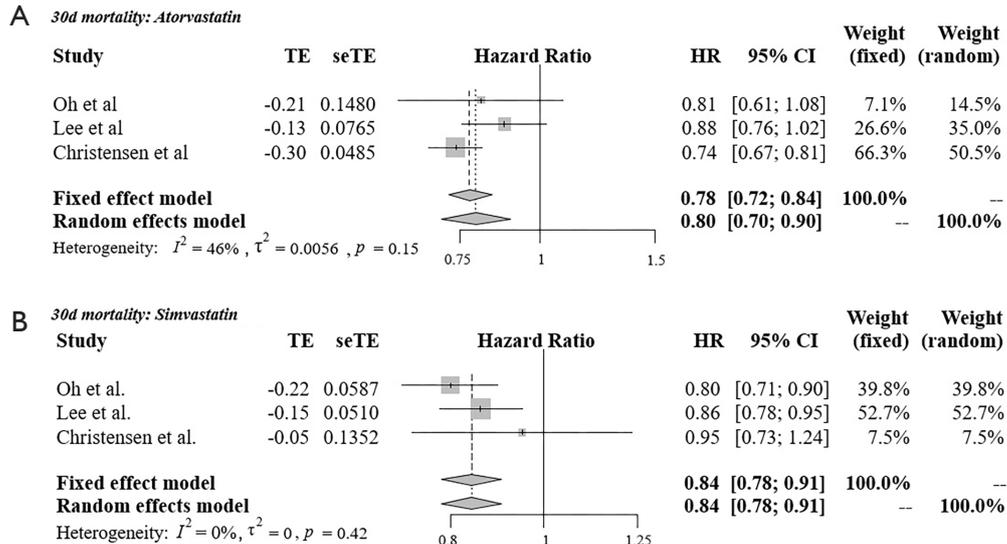
Figure 3 Meta-analysis of 30-day mortality among atorvastatin users (A) and simvastatin users (B) compared with non-statin users.

prognosis. However, it might be impossible to demonstrate this in a RCT because the development of sepsis or ARDS and ICU admission are not usually predictable and thus statin exposure before the events cannot be evaluated in a retrospective cohort design. Our meta-analysis included a prospective cohort study (18) that prospectively included patients with sepsis-associated ARDS, but it evaluated the history of prior statin therapy retrospectively, in addition to the effect of statin therapy after the diagnosis of sepsis-associated ARDS. A recent meta-analysis of five

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Hospital mortality

Study	TE	seTE	Odds Ratio	OR	95% CI	Weight (fixed)	Weight (random)
Dobesh et al.	-0.87	0.1607		0.42	[0.31; 0.58]	0.9%	34.6%
Shu-Yu et al.	-0.15	0.0153		0.86	[0.83; 0.89]	98.9%	39.3%
O'Neal et al.	0.06	0.3087		1.06	[0.58; 1.94]	0.2%	26.1%
Fixed effect model				0.85	[0.83; 0.88]	100.0%	--
Random effects model				0.71	[0.42; 1.21]	--	100.0%

Heterogeneity: $I^2 = 90\%$, $\tau^2 = 0.1866$, $p < 0.01$
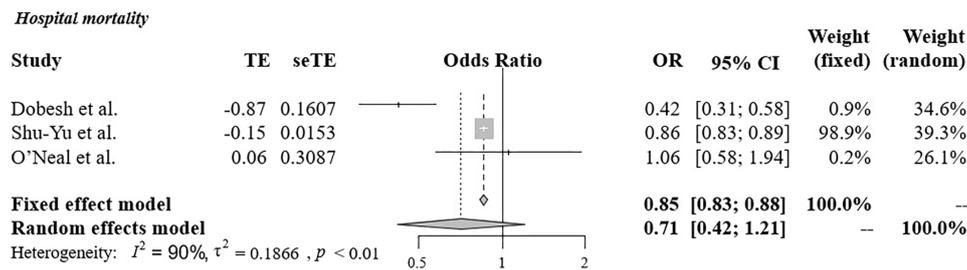
Figure 4 Meta-analysis of in-hospital mortality among statin users compared with non-statin users.

retrospective cohort studies, with a similar design to our meta-analysis, reported that metformin exposure before ICU admission was associated with a lower mortality in adult patients with diabetes mellitus diagnosed with sepsis (28). Therefore, our rationale behind inclusion of cohort studies should be interpreted in consideration of these perspectives.

While a previous meta-analysis of RCTs concluded that there was no significant effect of statin therapy in sepsis patients (12), we found a significant association of prior statin therapy with mortality among critically ill patients. Our results should be interpreted carefully considering the characteristics of the cohort studies. RCTs and population-based cohort studies have different strengths and limitations (29) and might arrive at different conclusions for several reasons (30). First, cohort studies may have a more pronounced selection bias or more confounders because of the absence of randomization. Second, the generalizability of the results of RCTs and cohort studies might be different because many RCTs have specific inclusion and exclusion criteria that are often restrictive, whereas cohort studies usually include much broader populations (31). Third, as RCTs may sometimes be underpowered for detecting important differences in outcomes, they can lead to erroneous conclusions (generally false negatives). The total sample size of this meta-analysis was sufficiently large (with 199,985 patients from nine studies); therefore, it was possible to detect a beneficial association of prior statin therapy with mortality with adequate statistical power rather than to perform a meta-analysis of RCTs.

The diverse characteristics in this meta-analysis should also be considered when interpreting the results of this study. In this meta-analysis, we defined and included "critically ill patients" as those who required treatment or monitoring in the ICU. Therefore, the mixed ICU population, sepsis patients, ARDS patients, and patients with VAP were all included in this study. The World Federation of Societies of Intensive and Critical Care Medicine convened a task force to define ICU. They defined ICU as a health care resource that provides intensive and specialized medical and nursing care to critically ill patients (32). From this perspective, our broader inclusion criteria of critically ill patients in this meta-analysis can be understood.

This study has some limitations. First, the nine studies included in the meta-analysis did not use identical statistical methods to adjust for confounders. Also, the number of confounders, diseases, and types of confounders considered in each study were not identical. This is a common limitation of all meta-analyses; a random effects model had to be used to adjust for the differences. Third, five retrospective cohort studies were included in this meta-analysis. Compared with prospective cohort studies, the quality of data in retrospective cohort studies is not guaranteed, which might in turn affect the results of the meta-analysis. Fourth, only three studies were included to evaluate the effect of prior statin therapy on in-hospital mortality among critically ill patients; thus, the results regarding in-hospital mortality should be interpreted carefully. Fifth, we did not evaluate the effect of dosage among prior statin users in this meta-analysis because of the lack of data. Finally, as mentioned above, our study broadly included critically ill patients; therefore, our results might not be generalizable to specific disease groups, such as patients with sepsis or ARDS.

In conclusion, this study showed that there was a beneficial association of prior statin therapy with 30-day mortality among critically ill patients. However, there was no significant association of prior statin therapy with in-hospital mortality. Future prospective cohort studies with large sample sizes are required to confirm our findings.

Footnote

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Table S1 The Newcastle-Ottawa quality assessment scale of including studies

| Studies	Selection			Comparability			Assessment of outcome			Total quality score
	Represent-activeness of exposure arm	Selection of the comparative arm	Origin of exposure source	Demonstration that outcome of interest was not present at start of study	Studies controlling the most important factors	Studies controlling the other main factors	Assessment of outcome with independency	Adequacy of follow-up length (to assess outcome)	Lost to follow-up acceptable (less than 10% and reported)	
Bruyere	*	*	*	*	*	*	*	*	*	9
Lee	*	*	*	*	*	*	*	*	*	9
Christensen	*	*	*	*	*	*	*	*	*	9
Lee	*	*	*	*	*	*	*	*	*	9
Mansur	*	*	*	*	*	*	*	*	*	9
Oh	*	*	*	*	*	*	*	*	*	9
Dobesh	*	*	*	*	*	*	*	*	*	9
Ou	*	*	*	*	*	*	*	*	*	9
O'Neal	*	*	*	*	*	*	*	*		8

*. 1 point.

Figure S1 Begg's funnel plot.