European Review for Medical and Pharmacological Sciences 2021; 25: 2685-2695

The effect of statins on mortality among patients with infection: umbrella review of meta-analyses

R.A. GHAYDA[1,2], C.H. HAN[3], K.H. LEE[3], J.S. KIM[4], S.E. KIM[5], S.H. HONG[2,5], M. KIM[4], A. KRONBICHLER[6], K. TIZAOUI[7], H. LI[8], A. KOYANAGI[9,10], L. JACOB[9,11], M.S. KIM[12], D.K. YON[13], S.W. LEE[14], K. KOSTEV[15], J.I. SHIN[3], J.W. YANG[4], L. SMITH[16]

[1]Urology Institute, University Hospitals System, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[2]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[3]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea
[5]Yonsei University College of Medicine, Seoul, Republic of Korea
[6]Department of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria
[7]Laboratory Microorganismes and Active Biomolecules, Sciences Faculty of Tunis, University Tunis El Manar, Tunis, Tunisia
[8]College of Medicine, University of Florida, Gainesville, Florida, USA
[9]Research and development unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, Barcelona, Spain
[10]ICREA, Barcelona, Spain
[11]Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, France
[12]Korea University, College of Medicine, Seoul, Republic of Korea
[13]Department of Pediatrics, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
[14]Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea
[15]University Clinic of Marburg, Marburg, Germany
[16]The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge CB1 1PT, UK

Ramy Abou Ghayda, Chang Hoon Han, Keum Hwa Lee, Jae Seok Kim, Sung Eun Kim, Sung Hwi Hong, and Miryung Kim contributed equally to this work

Abstract. – OBJECTIVE: Although previous research has reported beneficial effects of statins on infectious diseases, these have yet to be concluded. Therefore, we conducted an umbrella review to provide a comprehensive understanding of the strength of evidence and validity of claimed associations between statins (hydroxymethyl glutaryl-CoA reductase inhibitors) and infectious diseases.

MATERIALS AND METHODS: We conducted an umbrella review and re-analyzed data from meta-analyses of randomized controlled trials and observational studies on associations between statin use and different infectious diseases such as bacteremia/sepsis and pneumonia. We also evaluated the level of evidence for each re-analyzed outcome based on the criteria using p-values of random and fixed-effects, 95% prediction intervals, small-study effects, between-study heterogeneity, and concordance between the effect estimate of the largest study and summary estimates of the

Corresponding Authors: Jae Il Shin, MD; e-mail: shinji@yuhs.ac
Jae Won Yang, MD; e-mail: kidney74@yonsei.ac.kr

meta-analysis. Moreover, publication bias was also examined.

RESULTS: Through a systematic literature search, we obtained 14 eligible articles including 25 meta-analyses. All 4 meta-analyses on overall infection, 3 out of 14 meta-analyses on bacteremia/sepsis, and 5 out of 7 meta-analyses on pneumonia demonstrated that statin use was associated with reduced mortality due to infections (caused by infections). Nonetheless, most significant results only showed a weak level of evidence, and one study with convincing evidence prior to adjustment also showed weak evidence after adjustment.

CONCLUSIONS: The present review identified a protective effect of statins on infection-related mortality, but all available studies had a weak level of evidence. Therefore, further studies with a strong level of evidence are needed, and it is also necessary to investigate the types of statins and to study clinical outcomes other than mortality to gain further insights.

Key Words:
Statin, HMG (hydroxymethyl glutaryl)-CoA reductase, Infectious disease, Pneumonia, bacteremia, Sepsis, mortality, Umbrella review.

Introduction

In modern medicine, several medications have brought significant changes to health care. Statins, which inhibit the HMG (hydroxymethyl glutaryl)-CoA reductase, are one such medication, and have contributed to a reduction in morbidity and mortality from cardio-cerebrovascular diseases[1,2]. In addition, a large number of studies have demonstrated the pleiotropic effects of statins beyond cholesterol lowering action[3]. For example, statins exert beneficial effects on the cardiovascular system through anti-oxidative[4] and anti-inflammatory actions[5], as well as an anti-tumor effect via inhibiting specific metabolic pathways[6]. Interestingly, statins also have an anti-infective potential. Although the anti-infective effect of statins may not be widely known, historically, the development of statins began as an attempt to find new antibiotics from fungi[7]. Therefore, it is justifiable to explore the potential anti-infective effect of statins.

Although the exact underlying mechanism has not yet been documented, many clinical studies including randomized controlled trials (RCTs) or observational studies have supported the protective effect of statins in patients suffering from different types of infection. However, comprehensive review studies to verify the clinical benefits of statins in infected patients are scarce. In this study, to discern and appraise the strength of the evidence of statin efficacy on reducing mortality in patients with infection, we carried out an umbrella review and thereby comprehensively re-analyzed the data of meta-analyses of RCTs and observational studies.

Materials and Methods

We performed an umbrella review of meta-analyses and systematic reviews studying the effects and associations between the use of statin and all-cause mortality in patients with different etiologies of infection. This umbrella review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8].

Literature Search

We performed our search using the following keywords: '(hydroxymethyl glutaryl-coa reductase inhibitor OR statin) AND (mortality OR infection) AND (meta-analysis OR systematic review)'. We limited our search to articles written in English. We performed the search in January 2020. Meta-analyses of either RCTs or observational studies were included in our search strategy. Each retrieved article was reviewed in detail including the title, abstract, and the full texts. Subsequently, inclusion and exclusion criteria were applied in the decision to include or exclude the articles. A supplementary EMBASE database search was also conducted for completion. Eligible meta-analyses that did not overlap with the PubMed search were included.

Eligibility Criteria and Data Extraction

Meta-analyses and systematic reviews of both RCTs and observational studies (cohort and case-control studies) investigating the association between statin use and mortality rates of patients with infection were included. Articles containing multiple meta-analyses were included, and each respective meta-analysis was assessed independently for inclusion. Review articles of *in vitro* studies and genetic studies were excluded.

Two of our investigators (G.H.J. and J.I.S) individually performed data search and extraction. Discrepancies were resolved via consensus. Information was gathered regarding the articles' first author, year of publication, infection etiol-

ogy, study design, number of included studies, mortality rates, total number of participants, and random effects with a 95% confidence interval (CI). Raw data of each individual study were analyzed considering all data on mortality rates of patients with infection, statins use and study design. Results of articles containing both RCTs and observational studies were reported separately.

Statistical Analysis

Each meta-analysis that satisfied the inclusion criteria was analyzed and the association between statin use and mortality among patients with infections was reported. In the case of overlapping meta-analyses, the individuals were combined according to mortality, infection type, and study design. In this case, a re-meta-analysis (to verify further this term) was conducted after eliminating overlapping individual studies. Summary effect size was reported with a 95% CI, and *p*-value with both random- and fixed-effects. All re-analyses in this study were performed using the Comprehensive Meta-Analysis software ver.3.3.070 (Borestein, NH, USA).

Estimation of Summary Effects and Estimation of Prediction Interval

All individual studies were re-examined for each meta-analysis. The summary effects and 95% CI using both random- and fixed-effects methods were assessed. We also reported the 95% prediction interval (PI), which addresses the dispersion of effects and also considers the in-between-study heterogeneity. Our CI reflected the accuracy of the mean.

Evaluation of Between-Study Heterogeneity and Small Study Effects

The I^2 metric of inconsistency and the *p*-value of the Cochrane Q test were used to assess heterogeneity across the studies. I^2 values of < 50% (low), 50-75% (moderate), and >75% (high) were used to describe heterogeneity. Egger's regression test was used to interpret publication biases. Small-study effects were used for detecting publication and reporting bias. An article was considered to have a small-study effect when Egger's test had *p*-value < 0.10 in random-effects meta-analyses.

Determination of the Level of Evidence

The evidence level of the association between statin uses and mortality among patients with infection was determined for each meta-analysis and re-analysis of the pooled meta-analysis. The criteria were based on a number of factors, including statistical significance by random and fixed-effects *p*-values, 95% PI, small-study effects, between-study heterogeneity, and concordance between the effect estimate of the largest study and summary estimate of the meta-analysis.

The criteria were stratified as follows:

Convincing evidence: (1) Statistical significance for the random- and fixed-effects at $p < 0.001$, (2) No small study effects or large between-study heterogeneity, (3) 95% PI rejected the null hypothesis, (4) Concordance between the effect estimate of the largest study and the summary effect of the random-effects meta-analyses.

Suggestive evidence: (1) Statistical significance of random effect at $p < 0.05$, (2) 95% PI included the null hypothesis, (3) No small study effects or large between-study heterogeneity.

Weak evidence: (1) Statistical significance of random effect at $p < 0.05$, (2) Small study effects or large between-study heterogeneity were found.

Non-significant association: There was no statistical significance for random effect of meta-analysis ($p > 0.05$).

In case of large heterogeneities, the results were reassessed to resolve whether it was secondary to differences in the direction of the effect or if it could be due to differences in the size of the association (level of evidence recalculated in the latter case).

Results

Study Characteristics

A total of 315 records were retrieved by the literature search. Among them, the full-text of 46 records was reviewed for eligibility, and 14 articles were considered eligible, corresponding to 25 meta-analyses (Figure 1)[9-22]. Six articles were meta-analysis of RCTs[10,13,17-19,21], 4 were of observational studies[9,11,15,20], and the other 4 were of both RCTs and observational studies[12,14,16,22]. We conducted re-analysis on all included meta-analyses and reported the outcome along with what was reported in each study. We classified the meta-analyses into 3 groups according to the types of diseases: (1) overall infection, (2) bacteremia/sepsis, and (3) pneu-

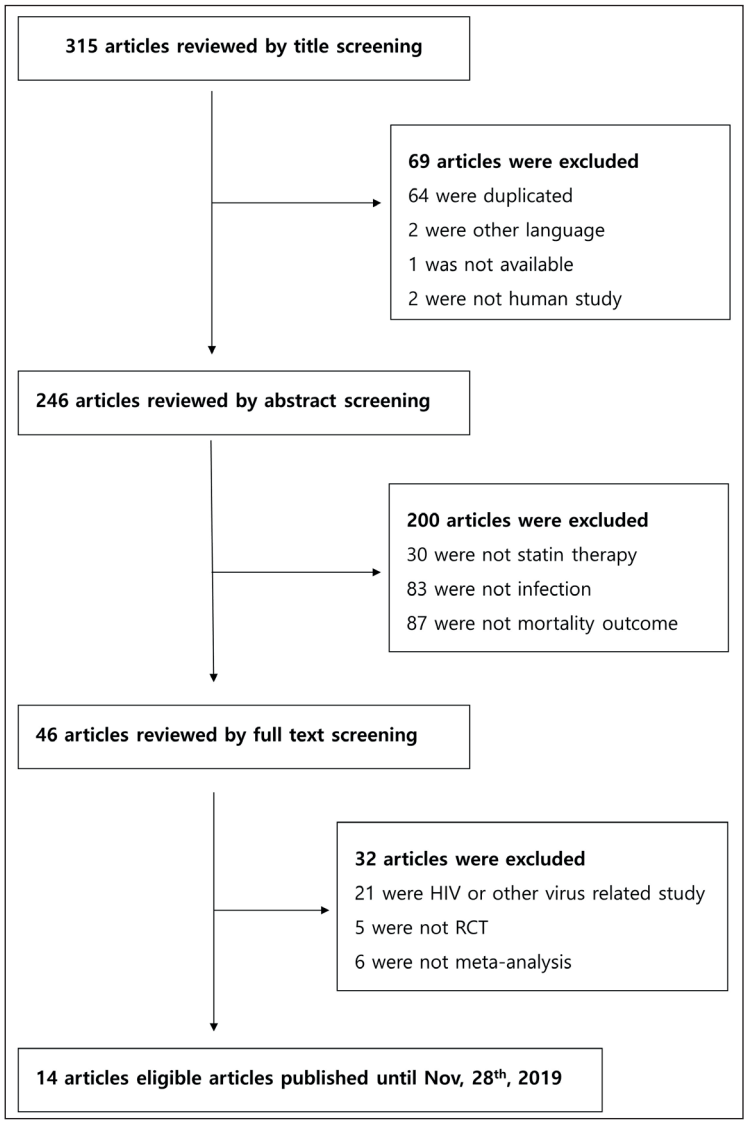

Figure 1. PRISMA flow chart of literature search.

monia. Four meta-analyses were classified into the overall infection group, corresponding to 102 individual studies and 3,346,104 patients. Fourteen meta-analyses were classified into the bacteremia/sepsis group, corresponding to 85 individual studies and 37,505 patients. Seven meta-analyses were classified into the pneumonia group, corresponding to 57 individual studies and 3,199,662 patients. Moreover, the meta-analyses of the pneumonia group were once again classified according to the inclusion of studies that reported adjusted OR.

Association of Statin Use and Overall Infection

Four articles and corresponding 4 meta-analyses including 2 RCTs and 4 observational studies investigated the relationship between statin use and overall infection (Table I). All the studies reported that statin use was associated with a reduced risk of all-cause mortality, and the same results were also found in our re-analysis. However, despite significant results, they only had a weak level of evidence.

Association of Statin Use and Bacteremia/Sepsis

There were 8 articles and corresponding 14 meta-analyses regarding bacteremia and sepsis, including 66 RCTs and 19 observational studies (Table II). The primary outcome was all-cause mortality and in-hospital mortality. Three studies reported that statin use is associated with reduced mortality, and similar results were carried out with our re-analysis as well. However, all the studies showed only weak level of evidence.

Table I. Statin therapy on overall infection.

Author et al, year	No of studies	Type of studies	Type of patients	Outcome	Intervention/ Total	Type of metrics	Model (reported)	Effect size (reported)	Random effect (re-analyzed)	Fixed effect (re-analyzed)	D/N/I*	Egger	I^2 (*p*-value)	*p*-value (random)	*p*-value (fixed)	95% PI	Small study effects	Evidence
Wan, 2014	26	OS	Infection/ Sepsis	All-cause mortality	55419/337648	RR	Random	0.65 (0.57-0.75)	0.66 (0.57-0.76)	0.76 (0.72-0.80)	17/9/0	0.016	73.4 (< 0.001)	< 0.001	< 0.001	0.39-1.12	Yes	Weak
Ma, 2012	41	RCT, OS (CC, Cohort)	Infection	All-cause mortality	1205169/2628988	OR	Random	0.70 (0.64-0.77)	0.71 (0.64-0.78)	0.85 (0.83-0.87)	22/18/1	0.00007	75.1 (< 0.001)	< 0.001	< 0.001	0.47-1.06	Yes	Weak
Björkhem-Bergman, 2010	15	OS	Bacterial infection	All-cause mortality	8611/113910	OR	Random	0.53 (0.42-0.66)	0.53 (0.42-0.66)	0.60 (0.54-0.67)	12/3/0	0.015	66.9 (< 0.001)	< 0.001	< 0.001	0.26-1.08	Yes	Weak
Janda, 2010	20	RCT, OS (CC, Cohort)	Infection	All-cause mortality	64229/265558	OR	Random	0.49 (0.37-0.61)	0.57 (0.47-0.69)	0.63 (0.58-0.69)	15/5/0	0.026	69.5 (< 0.001)	< 0.001	< 0.001	0.29-1.14	Yes	Weak

CAP: community-acquired pneumonia, CC: case-control, NA: not assessed, No: number, OS: observational study, OR: odds ratio, PI: prediction interval, RCT: randomized controlled trial, RR: relative risk, *Number of individual studies reporting; D: statistically significant decrease in mortality by statin therapy, N: not statistically significant effect of statin on mortality, I: statistically significant increase in mortality by statin therapy.

Table II. Statin therapy on bacteremia/sepsis.

Author et al, year	No of studies	Type of studies	Type of patients	Outcome	Intervention/ Total	Type of metrics	Model (reported)	Effect size (reported)	Random effect (re-analyzed)	Fixed effect (re-analyzed)	D/N/I*	Egger	I^2 (*p*-value)	*p*-value (random)	*p*-value (fixed)	95% PI	Small study effects	Evidence
Chen, 2018	7	RCT	Sepsis	All-cause mortality In-hospital	1078/2159	RR	Fixed	0.96 (0.83-1.11)	0.95 (0.80-1.13)	0.96 (0.83-1.11)	0/7/0	0.778	20 (0.28)	0.572	0.595	0.70-1.28	No	No
Chen, 2018	5	RCT	Sepsis	All-cause mortality 28-day	613/1246	RR	Fixed	0.90 (0.73-1.11)	0.93 (0.71-1.21)	0.92 (0.75-1.12)	0/5/0	0.947	29 (0.23)	0.585	0.424	0.55-1.56	No	No
Pertzov, 2018	13	RCT	Sepsis	All-cause mortality 30-day	1201/2430	RR	Fixed	0.96 (0.83-1.10)	0.94 (0.82-1.09)	0.95 (0.83-1.09)	0/13/0	0.237	4 (0.40)	0.420	0.462	0.78-1.14	No	No
Pertzov, 2018	9	RCT	Severe sepsis	All-cause mortality 30-day	1006/2040	RR	Fixed	0.97 (0.84-1.12)	0.94 (0.80-1.11)	0.96 (0.84-1.11)	0/9/0	0.347	19 (0.27)	0.493	0.594	0.70-1.28	No	No
Shrestha, 2016	6	OS	Bacteremia	All-cause mortalit In-hospital	905/7553	OR	Random	0.49 (0.30-0.81)	0.50 (0.31-0.81)	0.67 (0.54-0.83)	3/3/0	0.003	67.6 (0.009)	0.004	<0.001	0.12-2.03	Yes	Weak
Quinn, 2016	4	RCT	Sepsis	All-cause mortality 28-day	576/1171	RR	Fixed	0.88 (0.70-1.12)	0.89 (0.61-1.31)	0.88 (0.70-1.12)	0/4/0	0.471	42.6 (0.156)	0.565	0.310	0.23-3.46	No	No
Quinn, 2016	6	RCT	Sepsis	All-cause mortality In-hospital	1086/2175	RR	Fixed	0.98 (0.85-1.14)	0.98 (0.83-1.15)	0.98 (0.85-1.14)	0/6/0	0.492	8.9 (0.359)	0.795	0.807	0.73-1.31	No	No
Deshpande, 2015	5	RCT	Sepsis	All-cause mortality In-hospital	819/1620	RR	Random	1.04 (0.87-1.24)	1.04 (0.87-1.24)	1.04 (0.87-1.24)	0/5/0	0.246	0.0 (0.429)	0.680	0.680	0.78-1.38	No	No
Deshpande, 2015	3	RCT	Sepsis	All-cause mortality 28-day	318/634	RR	Random	0.93 (0.46-1.89)	0.93 (0.46-1.89)	1.00 (0.68-1.48)	0/3/0	0.422	56.6 (0.100)	0.845	0.998	0.00-1457.16	No	No
Thomas, 2015	4	RCT	Severe sepsis	All-cause mortality 28-day	903/1802	RR	Random	0.93 (0.72-1.20)	0.93 (0.72-1.20)	0.96 (0.82-1.12)	0/4/0	0.274	52.1 (0.099)	0.573	0.584	0.17-4.51	No	No
Thomas, 2015	4	RCT	Severe sepsis	All-cause mortality 60-day	907/1818	RR	Random	0.95 (0.72-1.27)	0.88 (0.60-1.29)	0.88 (0.74-1.05)	1/3/0	0.483	74.9 (0.008)	0.504	0.146	0.36-2.43	No	No
Pasin, 2013	6	RCT	Sepsis	All-cause mortality	423/862	RR	Fixed	0.95 (0.74-1.21)	0.92 (0.64-1.33)	0.92 (0.64-1.33)	0/6/0	0.110	0.0 (0.947)	0.664	0.664	0.55-1.54	No	No
Ma, 2012	6	OS (Cohort)	Bacteremia	All-cause mortality	900/7571	OR	Random	0.40 (0.20-0.78)	0.39 (0.20-0.76)	0.77 (0.63-0.94)	5/1/0	0.0004	78.1 (< 0.001)	0.006	0.012	0.05-3.08	Yes	Weak
Ma, 2012	7	OS (Cohort)	Sepsis	All-cause mortality	899/4424	OR	Random	0.61 (0.41-0.90)	0.61 (0.41-0.90)	0.59 (0.47-0.72)	3/4/0	0.477	55.0 (0.038)	0.012	< 0.001	0.21-1.74	No	Weak

CC: case-control, No: number, OS: observational study, OR: odds ratio, PI: prediction interval, RCT: randomized controlled trial, RR: relative risk, *Number of individual studies reporting; D: statistically significant decrease in mortality by statin therapy, N: not statistically significant effect of statin on mortality, I: statistically significant increase in mortality by statin therapy.

None of the studies, including individual studies, showed a positive association between statin use and mortality.

Association of Statin Use and Pneumonia

Four articles and corresponding 7 meta-analyses investigated the relationship between statin use and pneumonia. The meta-analyses included 57 individual studies, of which 4 were RCTs and 53 were observational studies (Table III). Of the 7 meta-analyses of studies with unadjusted OR, 5 reported that statin therapy lowered the mortality of patients with pneumonia. Our re-analysis confirmed published results. Interestingly, one article reported different effects of statin use on mortality according to the severity of pneumonia. The article demonstrated a negative association in non-severe pneumonia (OR: 0.64; 95% CI: 0.57-0.73), but not in severe pneumonia (OR: 1.03; 95% CI 0.77-1.38).

We analyzed the studies with adjusted OR separately, and there were 6 meta-analyses from 3 articles including 45 observational studies (Table IV). None of the meta-analyses included RCTs. Among the 6 meta-analyses, 5 reported decrease in mortality with statin therapy, while our re-analysis showed that 4 meta-analyses had significant results.

In particular, while most meta-analyses that showed significant results had only weak level of evidence as in bacteremia and sepsis, one meta-analysis had a convincing level of evidence. Nevertheless, the convincing level of evidence was not found in the analysis of studies with adjusted OR.

Discussion

Statins are one of the most prescribed drugs in the world. Its pleiotropic effects are variable ranging from anti-lipid to anti-inflammatory actions[23]. Thus, many researchers have tried to find the novel role of statin beyond anti-lipid effects for several decades. Among them, an anti-bacterial effect is one of the important properties of statins. Many *in vitro* and *in vivo* studies have demonstrated the anti-bacterial and anti-viral effects of statins[24,25]. According to those studies, certain types of statins have a bacteriostatic effect and synergies with antibiotics through multiple mechanisms. The mechanisms of action have not been clearly elucidated, but it seems that inhibiting infectious organisms do not depend on reducing HMG-CoA reductase. Instead, many studies have indicated that the anti-infective effect of statins is due to the multifaceted action[26], including interaction with bacterial cell walls[24], synergy with antibiotics[27,28], attenuating virulence factors[25], immune enhancements[29] and anti-inflammatory actions[30,31]. However, despite many experimental studies demonstrating the antibiotic effects of statins, the clinical effects on infectious diseases in humans have yet to be concluded. In addition, the results of many clinical trials are conflicting, and systemic reviews and meta-analyses of those studies do not give a clear answer as well[32,33].

In this study, we investigated the relationship between statin treatment and mortality in patients with infectious diseases by analyzing 25 meta-analyses from 14 articles. As a result, we were able to identify clinical benefits of statins on serious infections such as sepsis and pneumonia. Nonetheless, the evidence for significant results was mostly weak. One study showed convincing evidence in pneumonia patients, but this was no longer the case after adjustment. Our analyses demonstrated that most weak levels of evidence were primarily due to large between-study heterogeneity. In addition, small-study effects and 95% PI including the null hypothesis were also thought to contribute to the lack of evidence. Therefore, despite positive effects of statins on infections, our study suggests that further studies should be required to obtain more convincing evidence.

Importantly, when analyzing according to the type of infectious disease, relatively more meta-analyses showed significant results in the pneumonia group. Five out of 7 meta-analyses had significant results in the analysis of studies with unadjusted OR, and 4 out of 6 were significant with adjusted OR. In contrast, only 3 out of 14 meta-analyses had significant results in the bacteremia and sepsis group. In this regard, we could understand such results based on the fact that pneumonia usually has a less severe clinical course and a lower mortality rate than bacteremia and sepsis. Actually, although many studies have reported the clinical effects of statins on infections, it seems unlikely that such effects are also significantly related to serious infections. In particular, as the outcome of sepsis is the result of a variety of complex clinical situations and treatments, it is not easy to prove that only one factor, such as statin use, could lower mortality[34-36]. We believe that the results of our research

Table III. Statin therapy on pneumonia (studies reporting unadjusted OR data).

Author et al, year	No of studies	Type of studies	Type of patients	Outcome	Intervention/ Total	Type of metrics	Model (reported)	Effect size (reported)	Random effect (re-analyzed)	Fixed effect (re-analyzed)	D/N/I*	Egger	I^2 (*p*-value)	*p*-value (random)	*p*-value (fixed)	95% PI	Small study effects	Evidence
Jia, 2015	11	OS (CC, Cohort)	Non-severe pneumonia	All-cause mortality	NA/195466	OR	NA	0.70 (0.67-0.73)	0.64 (0.57-0.73)	0.69 (0.66-0.73)	7/4/0	0.114	78.2 (< 0.001)	< 0.001	< 0.001	0.43-0.95	No	Weak
Jia, 2015	8	RCT, OS (Cohort)	Severe pneumonia	All-cause mortality	901/2755	OR	NA	1.05 (0.86-1.28)	1.03 (0.77-1.38)	1.05 (0.86-1.28)	0/7/1	0.338	41.3 (0.103)	0.835	0.626	0.50-2.11	No	No
Cheng, 2014	3	OS) (CC, Cohort	Pneumonia	All-cause mortality In-hospital	26750/178764	OR	Random	0.86 (0.56-1.34)	0.86 (0.55-1.35)	0.69 (0.64-0.74)	1/2/0	0.216	85.4 (0.001)	0.517	< 0.001	0.00-186.57	No	No
Cheng, 2014	5	OS (CC, Cohort)	Pneumonia	All-cause mortality 30-day	1899/35716	OR	Random	0.44 (0.29-0.67)	0.44 (0.29-0.67)	0.55 (0.47-0.64)	3/2/0	0.110	67.3 (0.016)	< 0.001	< 0.001	0.11-1.70	No	Weak
Cheng, 2014	4	OS (Cohort)	Pneumonia	All-cause mortality long-term	3230/39550	OR	Random	0.49 (0.29-0.84)	0.49 (0.29-0.84)	0.54 (0.48-0.59)	4/0/0	0.333	95.5 (< 0.001)	0.010	< 0.001	0.04-6.35	No	Weak
Chopra, 2012	10	RCT, OS (CC, Cohort)	CAP	All-cause mortality	26825/167151	OR	Random	0.62 (0.54-0.71)	0.61 (0.53-0.70)	0.64 (0.61-0.68)	6/4/0	0.125	49.2 (0.039)	< 0.001	< 0.001	0.44-0.85	No	Convincing
Ma, 2012	16	OS (CC, cohort)	Pneumonia	All-cause mortality	1186015/2580260	OR	Random	0.69 (0.62-0.78)	0.70 (0.62-0.78)	0.86 (0.83-0.88)	12/4/0	0.001	83.0 (<0.001)	< 0.001	< 0.001	0.47-1.02	Yes	Weak

CAP: community-acquired pneumonia, CC: case-control, NA: not assessed, No: number, OS: observational study, OR: odds ratio, PI: prediction interval, RCT: randomized controlled trial, RR: relative risk, * Number of individual studies reporting; D: statistically significant decrease in mortality by statin therapy, N: not statistically significant effect of statin on mortality, I: statistically significant increase in mortality by statin therapy.

Table IV. Statin therapy on pneumonia (studies reporting adjusted OR data).

Author et al, year	No of studies	Type of studies	Type of patients	Outcome	Intervention/ Total	Type of metrics	Model (reported)	Effect size (reported)	Random effect (re-analyzed)	Fixed effect (re-analyzed)	D/N/I*	Egger	I^2 (*p*-value)	*p*-value (random)	*p*-value (fixed)	95% PI	Small study effects	Evidence
Jia, 2015	15	OS (CC, cohort)	Non-severe pneumonia	All-cause mortality	NA/309307	OR	NA	0.78 (0.75-0.82)	0.71 (0.64-0.79)	0.78 (0.75-0.82)	12/3/0	0.010	74.3 (< 0.001)	< 0.001	< 0.001	0.50-1.02	Yes	Weak
Jia, 2015	3	OS (Cohort)	Severe pneumonia	All-cause mortality	144/1104	OR	NA	0.92 (0.53-1.60)	0.86 (0.37-1.99)	0.92 (0.53-1.60)	0/3/0	0.377	41.0 (0.184)	0.719	0.762	0.00-3356.59	No	No
Cheng, 2014	3	OS (CC, cohort)	Pneumonia	All-cause mortality In-hospital	26750/178764	OR	Fixed	0.89 (0.81-0.97)	0.84 (0.66-1.07)	0.89 (0.81-0.97)	2/1/0	0.359	50.9 (0.130)	0.156	0.007	0.07-10.65	No	No
Cheng, 2014	9	OS (CC, cohort)	Pneumonia	All-cause mortality 30-day	NA/79499	OR	Random	0.59 (0.48-0.73)	0.59 (0.48-0.73)	0.76 (0.71-0.81)	9/0/0	0.002	81.1 (< 0.001)	< 0.001	< 0.001	0.32-1.10	Yes	Weak
Cheng, 2014	4	OS (Cohort)	Pneumonia	All-cause mortality long-term	3230/39550	OR	Random	0.65 (0.51-0.82)	0.65 (0.51-0.82)	0.69 (0.62-0.78)	3/1/0	0.206	61.9 (0.049)	< 0.001	< 0.001	0.25-1.65	No	Weak
Chopra, 2012	11	OS (CC, cohort)	CAP	All-cause mortality	26825/167151	OR	Random	0.66 (0.55-0.79)	0.66 (0.55-0.79)	0.79 (0.73-.084)	8/3/0	0.006	72. (<0.001)	< 0.001	< 0.001	0.38-1.13	Yes	Weak

CAP: community-acquired pneumonia, CC: case-control, NA: not assessed, No: number, OS: observational study, OR: odds ratio, PI: prediction interval, RCT: randomized controlled trial, RR: relative risk, *Number of individual studies reporting; D: statistically significant decrease in mortality by statin therapy, N: not statistically significant effect of statin on mortality, I: statistically significant increase in mortality by statin therapy.

can be interpreted in that context. Furthermore, even in the case of pneumonia, one study showed a significant inverse association between statin and mortality in non-severe pneumonia, whereas this was not the case in severe pneumonia. Therefore, in order to obtain the exact effect of statins on infections, the type and severity of infectious diseases should be considered.

Our study has some limitations. First, we could not identify the effects of individual statins on infection. Previous studies[28,37] showed that simvastatin, atorvastatin, and rosuvastatin have anti-bacterial activity, while other statins do not. Therefore, studies conducted without distinguishing the type of statins are expected to fundamentally underestimate the anti-infective effect of statins. Second, since our goal was to identify the benefits of the respective statin on infection-related mortality, we could not examine other clinical outcomes such as the duration of antibiotics or intensive care unit stay. If we focus only on mortality and judge the clinical effects of statins, we may miss out on a number of other clinical effects in infectious diseases. Finally, we could not be sure that the beneficial effect of statin on survival through anti-lipid action was properly excluded in the analysis. It was believed that RCTs generally controlled such confounding factor, while it was uncertain whether the factor was properly adjusted in observational studies.

Conclusions

Our umbrella review study comprehensively reanalyzed the existing meta-analyses that investigated the beneficial effects of statins on sepsis or pneumonia. We could identify the beneficial effects of statins on infection-related mortality, but the effects have only weak evidence. Therefore, further research is needed to verify the protective effect of statins on infections. In addition, it is necessary to distinguish the type of statin and to assess clinical outcomes other than mortality.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding Information

Neither financial support nor any sort of sponsorship was received for this study.

References

1) Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Smith GD, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 2013: CD004816.
2) Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular Disease. JAMA 2013; 310: 2451-2452.
3) Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. Circ Res 2017; 120: 229-243.
4) Shishehbor MH, Brennan M, Aviles RJ, Fu X, Penn MS, Sprecher DL, Hazen SL. Statins promote potent systemic antioxidant effects through specific inflammatory pathways. Circulation 2003; 108: 426-431.
5) Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov 2005; 4: 977-987.
6) Bello ED, Zwergel C, Mai A, Valente S. The innovative potential of statins in cancer: new targets for new therapies. Front Chem 2020; 8: 516.
7) Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci 2010; 86: 484-493.
8) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
9) Bjorkhem-Bergman L, Bergman P, Andersson J, Lindh JD. Statin treatment and mortality in bacterial infections--a systematic review and meta-analysis. PLoS One 2010; 5: e10702.
10) Chen M, Ji M, Si X. The effects of statin therapy on mortality in patients with sepsis: A meta-analysis of randomized trials. Medicine 2018; 97: e11578.
11) Cheng HH, Tang TT, He Q, Huang LJ, Lin XL, Chen M, Yang C, Geng DF, Jiang SP. Beneficial effects of statins on outcomes in pneumonia: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2014; 18: 2294-2305.
12) Chopra V, Rogers MA, Buist M, Govindan S, Lindenauer PK, Saint S, Flanders SA. Is statin use associated with reduced mortality after pneumonia? A systematic review and meta-analysis. Am J Med 2012; 125: 1111-1123.
13) Deshpande A, Pasupuleti V, Rothberg MB. Statin therapy and mortality from sepsis: a meta-analysis of randomized trials. Am J Med 2015; 128: 410-417.
14) Janda S, Young A, Fitzgerald JM, Etminan M, Swiston J. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care 2010; 25: 656.

15) Jia M, Huang W, Li L, Xu Z, Wu L. Statins Reduce Mortality After Non-severe but Not After Severe Pneumonia: A Systematic Review and Meta-Analysis. J Pharm Pharm Sci 2015; 18: 286-302.

16) Ma Y, Wen X, Peng J, Lu Y, Guo Z, Lu J. Systematic review and meta-analysis on the association between outpatient statins use and infectious disease-related mortality. PLoS One 2012; 7: e51548.

17) Pasin L, Landoni G, Castro ML, Cabrini L, Belletti A, Feltracco P, Finco G, Carozzo A, Chiesa R, Zangrillo A. The effect of statins on mortality in septic patients: a meta-analysis of randomized controlled trials. PLoS One 2013; 8: e82775.

18) Pertzov B, Eliakim-Raz N, Atamna H, Trestioreanu AZ, Yahav D, Leibovici L. Hydroxymethylglutaryl-CoA reductase inhibitors (statins) for the treatment of sepsis in adults - A systematic review and meta-analysis. Clin Microbiol Infect 2019; 25: 280-289.

19) Quinn M, Moody C, Tunnicliffe B, Khan Z, Manji M, Gudibande S, Murphy N, Whitehouse T, Snelson C, Veenith T. Systematic review of statins in sepsis: There is no evidence of dose response. Indian J Crit Care Med 2016; 20: 534-541.

20) Shrestha P, Poudel DR, Pathak R, Ghimire S, Dhital R, Aryal MR, Mahmood M, Karmacharya P. Effect of Statins on the Mortality of Bacteremic Patients: A Systematic Review and Meta-analysis of Clinical Trials. N Am J Med Sci 2016; 8: 250-251.

21) Thomas G, Hraiech S, Loundou A, Truwit J, Kruger P, McAuley DF, Papazian L, Roch A. Statin therapy in critically-ill patients with severe sepsis: a review and meta-analysis of randomized clinical trials. Minerva Anestesiol 2015; 81: 921-930.

22) Wan YD, Sun TW, Kan QC, Guan FX, Zhang SG. Effect of statin therapy on mortality from infection and sepsis: a meta-analysis of randomized and observational studies. Crit Care 2014; 18: R71.

23) Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis 2009; 203: 325-330.

24) Bergman P, Linde C, Pütsep K, Pohanka A, Normark S, Henriques-Normark B, Andersson J, Björkhem-Bergman L. Studies on the antibacterial effects of statins--in vitro and in vivo. PLoS One 2011; 6: e24394.

25) Graziano TS, Cuzzullin MC, Franco GC, Schwartz-Filho HO, de Andrade ED, Groppo FC, Cogo-Müller K. Statins and Antimicrobial Effects: Simvastatin as a Potential Drug against Staphylococcus aureus Biofilm. PLoS One 2015; 10: e0128098.

26) Ko HHT, Lareu RR, Dix BR, Hughes JD. Statins: antimicrobial resistance breakers or makers? PeerJ 2017; 5: e3952.

27) Brown D. Antibiotic resistance breakers: can repurposed drugs fill the antibiotic discovery void? Nat Rev Drug Discov 2015; 14: 821-832.

28) Thangamani S, Mohammad H, Abushahba MF, Hamed MI, Sobreira TJ, Hedrick VE, Paul LN, Seleem MN. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. Sci Rep 2015; 5: 16407.

29) Chow OA, von Köckritz-Blickwede M, Bright AT, Hensler ME, Zinkernagel AS, Cogen AL, Gallo RL, Monestier M, Wang Y, Glass CK, Nizet V. Statins enhance formation of phagocyte extracellular traps. Cell Host Microbe 2010; 8: 445-454.

30) Terblanche M, Almog Y, Rosenson RS, Smith TS, Hackam DG. Statins and sepsis: multiple modifications at multiple levels. Lancet Infect Dis 2007; 7: 358-368.

31) Millar PJ, Floras JS. Statins and the autonomic nervous system. Clin Sci (Lond) 2014; 126: 401-415.

32) van den Hoek HL, Bos WJ, de Boer A, van de Garde EM. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. BMJ 2011; 343: d7281.

33) Nassaji M, Ghorbani R, Afshar RK. The Effect of statins use on the risk and outcome of acute bacterial Infections in adult patients. J Clin Diagn Res 2015; 9: OC09-12.

34) Patel JM, Snaith C, Thickett DR, Linhartova L, Melody T, Hawkey P, Barnett AH, Jones A, Hong T, Cooke MW, Perkins GD, Gao F. Randomized double-blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). Crit Care 2012; 16: R231.

35) Kruger PS, Terblanche M. Statins in patients with sepsis and ARDS: is it over? No. Intensive Care Med 2017; 43: 675-676.

36) Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, Howe B, Jones D, Joyce C, Kostner K, McNeil J, Nichol A, Roberts MS, Syres G, Venkatesh B. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med 2013; 187: 743-750.

37) Masadeh M, Mhaidat N, Alzoubi K, Al-Azzam S, Alnasser Z. Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin. Ann Clin Microbiol Antimicrob 2012; 11: 13.