

# Systematic review of statins in sepsis: There is no evidence of dose response

Morgan Quinn<sup>1</sup>, Claire Moody<sup>1</sup>, Bill Tunnicliffe<sup>1</sup>, Zahid Khan<sup>1</sup>, Mav Manji<sup>1</sup>, Sandeep Gudibande<sup>1</sup>, Nick Murphy<sup>1</sup>, Tony Whitehouse<sup>1</sup>, Catherine Snelson<sup>1</sup>, Tonny Veenith<sup>1,2,3</sup>

## Abstract

**Objectives:** Sepsis is a common cause of morbidity and mortality and is associated with significant costs to the healthcare organizations. We performed a systematic review and meta-analysis to assess whether high or low-dose statin therapy improved mortality in patients with sepsis. **Methods:** The trials analyzed in this study were multicenter or single center randomized control studies using statins for sepsis in a hospital setting. The patients included were adults with suspected or confirmed infection. **Interventions:** This study found eight randomized controlled trials where participants were given either a statin or placebo daily for 14–28 days, the duration of their illness, or until their death or discharge, whichever occurred first. **Primary and Secondary Outcomes Measured:** This meta-analysis measured the effect of statin therapy on in-hospital and 28 days mortality. **Results:** In unselected patients, there was no demonstrable difference in the 28 days mortality (relative risk [RR] 0.88 95% confidence interval [CI], 0.70–1.12 and  $P = 0.16$ ). There was also no significant difference between statin versus placebo for in-hospital mortality (RR 0.98 95% CI, 0.85–1.14  $P = 0.36$ ). When the studies were divided into low-dose and high-dose groups, there were no statistically significant differences for in-hospital mortality between low-dose statin versus placebo for (RR 0.81 CI 0.44–1.49  $P = 0.27$ ) or high-dose statin versus placebo (RR 0.99 95% CI 0.85–1.16,  $P = 0.28$ ). There was no significant difference in adverse effects between the high- and low-dose groups. **Conclusions:** In this meta-analysis, we found that the use of statins did not significantly improve either in-hospital mortality or 28-day mortality in patients with sepsis. In the low-dose group, there were fewer quality multicenter studies; hence, conclusions based on the results of this subgroup are limited.

**Keywords:** High dose, mortality, low dose, sepsis, statin

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## Introduction

Sepsis is characterized by an exaggerated inflammatory response to infection, resulting in a multisystem physiological, cellular, and organ dysfunction. In a European study, a typical episode of severe sepsis costs the health care organization approximately €25,000.<sup>[1]</sup>

Assuming that we see 100,000 cases of severe sepsis per annum, this equates to a direct current cost to the national health services of England of over 2.5 billion every year. In the USA, the Centers for Disease Control and Prevention's National Center for Health Statistics estimates the number of hospital admissions attributed

## From:

<sup>1</sup>Department of Critical Care, Queen Elizabeth Medical Centre, Birmingham, B15 2TH, <sup>2</sup>Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, CB2 0QQ, <sup>3</sup>School of Immunity and Infection, University of Birmingham, B15 2TT, UK

## Correspondence:

Dr. Tonny Veenith, Department of Critical Care, Queen Elizabeth Medical Centre, Birmingham, B15 2TH, UK.  
E-mail: [tv227@cam.ac.uk](mailto:tv227@cam.ac.uk)

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to sepsis increased from 621,000 in the year 2000 to 1,141,000 in 2008.<sup>[2]</sup> In 2011, sepsis resulted in an aggregate healthcare cost of \$20.3 billion making it the most expensive condition treated in US hospitals.<sup>[3]</sup>

Mortality from sepsis has improved over the last decade but is still estimated to be 36% in Europe.<sup>[1]</sup> This warrants a search for novel therapeutic targets and preventative therapies in patient with sepsis. Statins are lipid-lowering drugs that inhibit 3-hydroxy-3 methylglutaryl coenzyme A reductase, with pleotropic mechanisms that may be beneficial in sepsis. They are hypothesized to possess a variety of benefits including anti-inflammatory, immunomodulatory, antioxidant, and antithrombotic effects.<sup>[4,5]</sup> In previous studies, statins have been shown to reduce the unregulated immune response, influence the gene transcription, and reduce the expression of mRNA to sepsis. The use of statins was associated with an improved mortality and morbidity following sepsis.<sup>[6,7]</sup> In animal studies, statins reduced the severity of sepsis.<sup>[8,9]</sup> It is also thought that statins exert a protective effect through down-regulation of toll-like receptor 4, inhibition of nuclear factor-kappa-B and protection against endothelial cell apoptosis.<sup>[10,11]</sup> Despite the initial promise from animal data and early clinical trials, these benefits have not been reproduced in the large, well-designed, randomized controlled trials (RCTs) published recently.<sup>[12,13]</sup>

This paper aims to assess the impact of both high and low dose statin therapy on in-hospital and 28-day mortality in patients with sepsis.

## Methods

### Search strategy for published studies with aggregate data

Electronic databases, including PubMed and EMBASE, were searched using a combination of keywords: "sepsis," "intensive care" "statin" "simvastatin," "atorvastatin," and "rosuvastatin" to create a list of articles published before October 2015. The search was limited to articles published in the English language.

### Study selection criteria

Articles were included if the study population was adult patients with a suspected or confirmed infection and reported 28 day or in-hospital mortality reported as a primary or secondary outcome. A total of 215 articles were identified. The following were excluded; 160 were not clinical trials, 2 *post hoc* analyses, 2 cell-based studies, 3 were not randomized control trials, and 31 were the wrong patient population. A total of 15 studies were fully assessed for eligibility. Of these, 3 were excluded

as mortality was not reported as a primary or secondary outcome, and 4 were excluded as they were the wrong patient populations: 3 were postcardiac surgery patient populations and 1 was neurosurgical patients. Eight studies were included in the meta-analysis [Figure 1].

### Data extraction and statistical analysis

Data were extracted independently by two authors and analyzed using Review Manager (RevMan) [Computer program]. Version 5.3.<sup>[14]</sup> Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. For each study, the characteristics of the study, number of participants, characteristics of included patients, selection criteria, drug and dose used, and outcomes observed in the study were extracted. Most studies reported in-hospital mortality and 28 days mortality outcomes. Some studies reported 28 days mortality only and others reporting in-hospital mortality only. To include all RCTs in this meta-analysis, the authors have performed a separate analyses on both 28 days mortality and in-hospital mortality for this reason. All studies had adequate randomization and blinding. The quality of the RCTs was evaluated using the method described in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>[15]</sup> In each study, patients were given either a dose of statin (simvastatin 20/40/80 mg, rosuvastatin 40 mg or atorvastatin 20 mg) or a placebo. Low-dose statin was defined as simvastatin 20 mg or atorvastatin 20 mg. High dose was defined as simvastatin 40 mg or 80 mg or rosuvastatin 40 mg.<sup>[16,17]</sup>

## Results

We examined a total of 8 RCTs with a total of 2275 patients. Figures 2 and 3 show forest plots of 28-day mortality and in-hospital mortality, respectively. Table 1 shows the 8 RCTs and the characteristics of each study. Table 2 shows assessment of bias for each

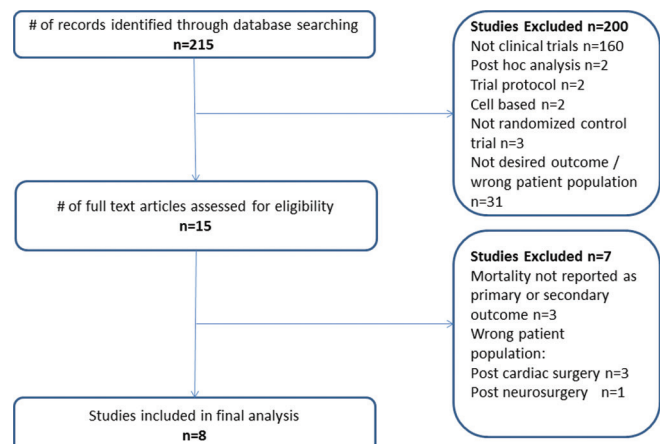
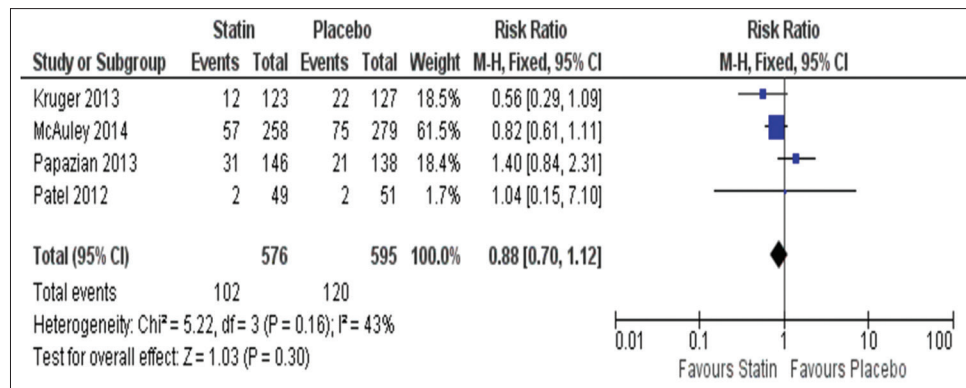
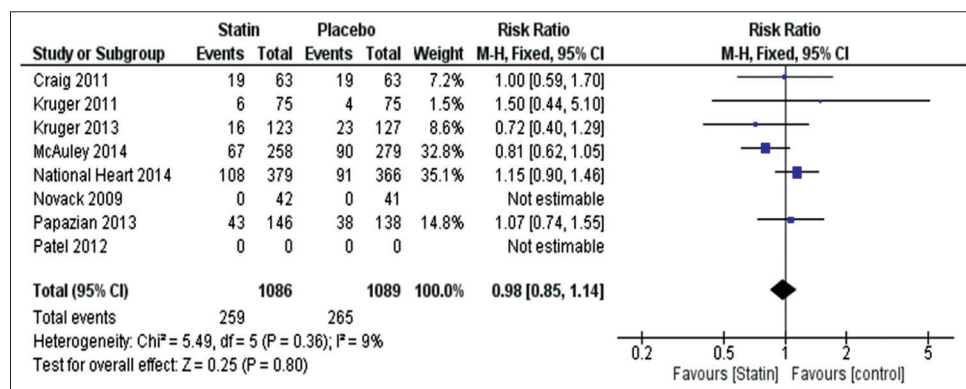


Figure 1: Studies included in this meta-analysis



**Figure 2:** Forest plot of proportional effect on 28-day mortality. Forest plot of proportional effect of all studies (low and high doses) on 28-day mortality (Diamonds = totals and subtotals [95% confidence interval]. Squares = individual studies [horizontal lines are 95% confidence intervals]. Area of square proportional to amount of statistical information in that category. Risk ratios are weighted to represent heterogeneity)



**Figure 3:** Forest plot of proportional effect for in-hospital mortality of individual studies. Forest plot of proportional effect on in-hospital mortality (Diamonds = totals and subtotals [95% confidence interval]. Squares = individual studies [horizontal lines are 95% confidence intervals]. Area of square proportional to amount of statistical information in that category. Risk ratios are weighted to represent heterogeneity)

study. All studies used in the meta-analysis are listed in Appendix 1.

### All dose statin, 28-day mortality

Results from 1171 patients demonstrated that there was no significant difference between statin (102/576) and placebo (120/595) for 28 day mortality (relative risk [RR] 0.88 95% confidence interval [CI], 0.70–1.12 and  $P = 0.16$ ), with a heterogeneity of the trials  $I^2 = 43\%$ ,  $P = 0.16$  [Figure 2].

### All dose statin, in-hospital mortality

Results from 2175 patients demonstrated that there was no significant difference between statin (259/1086) versus placebo (265/1089) for in-hospital mortality (RR 0.98 95% CI, 0.85–1.14  $P = 0.36$ ) with low heterogeneity between the studies  $I^2 = 9\%$   $P = 0.36$ . The authors excluded 83 patients from the Novack 2009 study from the analysis, as both arms of the trial had zero events [Figure 3].<sup>[18]</sup>

### Low dose statin, in-hospital mortality

Results from 400 patients demonstrated no statistically significant difference between low-dosage statin use (22/198) versus placebo (27/202) for in-hospital mortality [RR 0.81 CI (0.44–1.49)  $P = 0.27$ ,  $I^2 = 16\%$  Figure 4].

### High dose statin, in-hospital mortality

Results from 1692 patients demonstrated that there was no significance between high-dose statin usage (237/846) versus placebo (239/846) for in-hospital mortality [RR 0.99 95% CI 0.85–1.16  $P = 0.28$ ,  $I^2 = 21\%$ , Figure 5].

### Adverse effects in high dose and low dose groups

From all reported trials, patients with sepsis who received statins did not have a significantly higher incidence of adverse effects compared to placebo. In patients who were treated with high-dose statins, the incidence of adverse effects was higher (11.6% vs. 8.5%,  $P > 0.05$ ), but this failed to reach statistical significance.

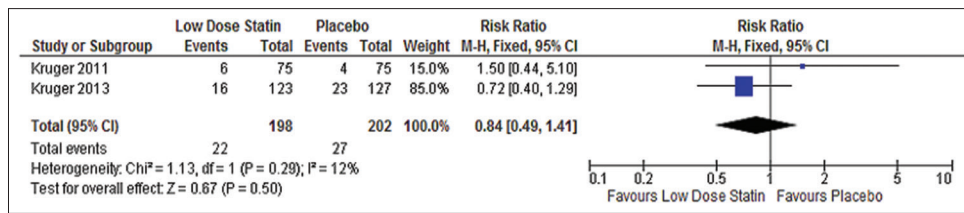
**Table 1: Characteristics of included studies**

Study	Method	Participants	Interventions	Low or high dose	Outcomes	Number of patients
Kruger 2011 <sup>[27]</sup>	Prospective double-blind placebo-controlled RCT	Patients with 2/4 SIRS criteria present and known or suspected infection, preexisting statin therapy, and the treating physician prepared to either continue or discontinue this therapy	20 mg atorvastatin or placebo administered for the duration of hospital admission up to a maximum of 28 days	Low	Progression of sepsis (SOFA score), 28-day mortality, requirement of ICU admission, changes in inflammatory markers, changes in lipid profile	150 (75/75)
Kruger 2013 <sup>[28]</sup>	Prospective double-blind placebo-controlled RCT	Patients 2/4 SIRS criteria + known/suspected infection, preexisting statin therapy, and the treating physician prepared to either continue or discontinue this therapy	20 mg atorvastatin or placebo administered for the duration of hospital admission up to a maximum of 28 days	Low	Progression of sepsis (SOFA score), 28-day mortality, requirement of ICU admission, changes in inflammatory markers, changes in lipid profile	150 (75/75)
Craig 2011 <sup>[29]</sup>	Single-center, prospective, double-blind, placebo-controlled RCT	Patients undergoing mechanical ventilation in ITU within 48 h of the diagnosis of ALI and ARDS	80 mg simvastatin or placebo was administered daily for up to 14 days if the CK < 10 × reference range and transaminases < 3 × upper normal range. Treatment was continued until death, discontinuation of mechanical ventilation, request by patient/relative or on day 14	High	Extravascular lung water, ventilator-free days, duration of mechanical ventilation, ICU-free days, ICU survival, hospital length of stay, hospital survival	540 (270/270)
National Heart Lung and Blood Institute 2014 <sup>[13]</sup>	Multicenter, double blind, placebo controlled RCT	Patients who were undergoing mechanical ventilation with the presence of bilateral pulmonary infiltrates on chest X-ray, and a known or suspected source of infection (WCC > 12 or < 4, > 10% WCC differential, or temperature > 38 or < 36)	40mg loading dose of either rosuvastatin or placebo given orally, then 20 mg thereafter until the 3 <sup>rd</sup> day from discharge from ITU, day 28, hospital discharge or death, which-ever came first	High	In-hospital mortality before discharge, day-60 mortality, ventilator-free days, organ failure free days to day 14, ICU free days to day 28	745 (379/366)
McAuley 2014 <sup>[23]</sup>	Multicenter, double blind, placebo controlled RCT	Patients > 16 years requiring mechanical ventilation with ARDS within 48 h of onset of ARDS. ARDS defined as the ration of partial pressure of oxygen to the FiO <sub>2</sub> , with bilateral pulmonary infiltrates on chest X-ray	80 mg of simvastatin via nasogastric tube daily or placebo for until day 28 or discharge from critical care	High	Ventilator-free days, days free of nonpulmonary organ failure, 28 days mortality, in-hospital mortality, in critical care mortality	540 (259/281)
Novack 2009 <sup>[18]</sup>	Single-center, double-blinded, placebo controlled RCT	Patients > 18 years, not receiving statin therapy during the 3 months prior to admission, within 12 h of admission to general medical ward, have a documented bacterial infection and have intravenous antibiotics prescribed (independent of study team)	40 mg simvastatin or placebo given orally immediately postenrollment followed by 20 mg daily until hospital discharge or the development of severe sepsis	High	Development of severe sepsis (defined by PROWESS investigators), change in level of cytokines, death, length of stay, need for mechanical ventilation	83 (42/41)
Papazian 2013 <sup>[12]</sup>	Multicenter trial placebo-controlled, double-blind, parallel-group RCT	Patients who required mechanical ventilation for more than 2 days and who had a suspected ventilator acquired pneumonia, defined as a modified clinical pulmonary infection score of 5 or greater	60 mg statin or placebo given orally from study inclusion to ICU discharge, death, or day 28, whichever occurred first	High	28-day mortality, day-14 mortality, ICU mortality, ICU-free days, ventilator-free days	284 (146/136)
Patel 2012 <sup>[19]</sup>	A single-center phase II, double-blind placebo-controlled RCT	Patients age > 18 years with documented new or suspected infection with 2 or more SIRS criteria for < 24 h	40 mg atorvastatin or placebo administered within 24 h of randomization and continued until discharge or day 28, whichever occurred first	High	Progression of sepsis to severe sepsis (identified using the SSCG screening tool), ITU admission rate, hospital readmission rate at 28 days and 1 year, length of stay, and 28-day mortality and 1-year mortality	100 (49/51)

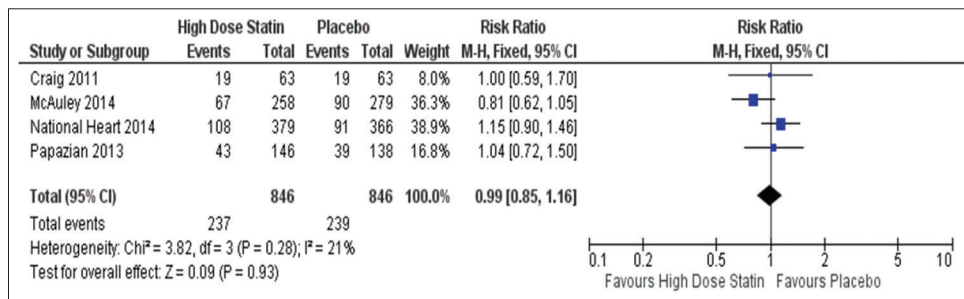
RCT: Randomized controlled trial; SIRS: Systemic inflammatory response syndrome; SSCG: Surviving Sepsis Campaign Guidelines; ICU: Intensive Care Unit; WCC: White cell count; ARDS: Acute respiratory distress syndrome; ALI: Acute lung injury; CK: Creatinine kinase; SOFA: Sequential organ failure assessment; ITU: Intensive treatment unit

**Table 2: Assessment of risk of bias**

Study	Type of bias					
	Randomization	Allocation concealment	Blinding of participants and personnel	Blinding of outcome	Incomplete outcome data	Reporting bias
Craig 2011 <sup>[29]</sup>	Low risk Randomization performed by independent statistician	Low risk Independent clinical trial pharmacist performed treatment randomization	Low risk Study drugs were encapsulated by independent pharmacist	Low risk Double-blind	Low risk None lost to follow-up	Low risk Study protocol published prior to commencement of trial and all outcomes reported
Kruger 2011 <sup>[27]</sup>	Low risk Computer-generated randomization	Low risk Placed in sealed opaque envelopes	Low risk Study drugs were encapsulated by independent pharmacist	Low risk Double-blind	Low risk 2/75 missing from treatment group. Reasons for withdrawal acceptable and documented	
Kruger 2013 <sup>[28]</sup>	Randomization was performed using a computer-generated list	Low risk Allocation concealed using computer	Low risk Placebo/study drug identical. Both prepared by central pharmacy under controlled conditions	Low risk Double-blind	Low risk 32 patients (15 treatment/17 placebo) dropped out from study due to adverse effects of drug	
National Heart Lung and Blood Institute 2014 <sup>[13]</sup>	Patients were randomly assigned in permuted blocks of 8	Unclear risk Insufficient information to permit judgment	Unclear risk Reported as double blind but no method described	Low risk Blinding of outcome assessment to all participants except pharmacist, lab technicians and leaders of coordinating center	Low risk No missing outcome data. Study stopped early due to futility	Low risk Study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported
McAuley 2014 <sup>[23]</sup>	Low risk Centralized computer-generated randomization available 24 h/day	Low risk Computer-assigned centralized block randomization 1:1 ratio	Low risk Double-blind and study drugs reported as identical	Low risk Double-blind	Low risk 3/540 lost to follow-up 8/540 did not receive study drug	Low risk Study protocol published before clinical trial and all outcomes have been reported
Novack 2009 <sup>[18]</sup>	Low risk Computer-generated randomization	Low risk Allocation concealment was ensured through use of sequentially numbered envelopes	Low risk Study drugs or placebo encapsulated and prepared by pharmacy	Low risk Double-blind	Low risk No losses to follow-up	
Papazian 2013 <sup>[12]</sup>	Low risk Computer-generated randomization using table in blocks of 4	Low risk Block size unknown to investigators, telephone-based randomization	Low risk Study drug identical to placebo, investigators and patients blinded	Low risk Double-blind	Low risk 16 patients excluded from analysis (7 treatment/9 placebo), reasons for withdrawal appropriate and well documented	Low risk Primary and secondary outcomes reported in full
Patel 2012 <sup>[19]</sup>	Low risk Computer-generated randomization sequence in blocks of 4	Low risk Sequentially numbered identical drug containers	Low risk Study drugs prepared by independent pharmacy and investigators blinded	Low risk Double-blind	Low risk No patients lost to follow-up	Low risk The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way



**Figure 4:** Forest plot of proportional effect for low dose statin, in-hospital mortality. Forest plot of proportional effect on in-hospital mortality (Diamonds = totals and subtotals [95% confidence interval]. Squares = individual studies [horizontal lines are 95% confidence intervals]. Area of square proportional to amount of statistical information in that category. Risk ratios are weighted to represent heterogeneity)



**Figure 5:** Forest plot of proportional effect for high dose statin, in-hospital mortality. Forest plot of proportional effect on in-hospital mortality (Diamonds = totals and subtotals [95% confidence interval]. Squares = individual studies [horizontal lines are 95% confidence intervals]. Area of square proportional to amount of statistical information in that category. Risk ratios are weighted to represent heterogeneity)

### Discussion

This meta-analysis demonstrated that statin therapy does not reduce in-hospital or 28 days mortality in sepsis when compared to placebo. This meta-analysis also failed to show any significant difference in outcome of treating patients with low or high dose statins.

Statins were shown to be beneficial in animal model studies,<sup>[6]</sup> and early RCTs demonstrated benefits in critically ill patients with sepsis, however these studies were single center RCTs with a relatively small sample size.<sup>[19]</sup> In this study, we investigated whether the dose of statin was associated with adverse events. Statin therapy is associated with musculoskeletal side effects including myopathy, myositis, and rhabdomyolysis. Myalgia and arthralgia are reported in up to 5% of participants in clinical trials.<sup>[20-22]</sup> Reported incidence of dose dependent adverse events such as deranged hepatic transaminases was 0.5–2%.<sup>[16,20]</sup> In one study, there were a significant number of adverse events related to the intervention arm when using 80 mg of simvastatin.<sup>[23]</sup> However, across all studies in this analysis, the total incidence of adverse events in patients who were treated with high dose statins was not significantly different compared to placebo or to low dose statins.

In this up to date meta-analysis, we focused only on eligible RCTs to eliminate the risk of confounding

variables often seen in observation studies. Compared to previous meta-analyses, we have not only included up to date RCTs but also tried to delineate the role of high and low-dose statins.<sup>[24]</sup> These findings are in contradiction to previous literature reviews and observational studies.<sup>[7,25]</sup> As our meta-analysis relies purely on RCTs, this limits the study to a relatively small sample size. This is particularly true for the low-dose statin subgroup of patients.

While preclinical and observational studies hypothesized the potential benefits of statin usage in sepsis, our meta-analysis contradicts this presumption. Although the beneficial effects *in vitro* and animal models have been well documented in literature,<sup>[6,11]</sup> these effects do not confer a detectable benefit in large human model RCTs. This could be due to the heterogeneity of the populations being studied; there is an inter subject variability in the host response due to age, existing comorbidities and genetic profile. Genes involved in sepsis have been analyzed for links between single-nucleoside polymorphisms and sepsis susceptibility, organ dysfunction and mortality.<sup>[26]</sup> Despite the heterogeneity of the populations being studied, there are no suggestions from this study that a specific population group would benefit from statin therapy.

## Conclusions

This meta-analysis found no beneficial effect of statin therapy in the context of sepsis and the mortality of critically ill patients. Our findings are in contradiction to previous reviews of the literature and also to those of observational studies.<sup>[7,19,25]</sup>

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## Conflicts of interest

There are no conflicts of interest.

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## Appendix

### Appendix 1: Studies included in this meta-analysis

1. Papazian L, Roch A, Charles PE, Penot-Ragon C, Perrin G, Roullet P, *et al.* Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: A randomized clinical trial. *JAMA* 2013;310:1692-700.
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### Search criteria

((“sepsis”[MeSH Terms] OR “sepsis”[All Fields]) AND (((“atorvastatin”[Supplementary Concept] OR “atorvastatin”[All Fields]) OR (“rosuvastatin”[Supplementary Concept] OR “rosuvastatin”[All Fields])) OR (“simvastatin”[MeSH Terms] OR “simvastatin”[All Fields])) OR ((“intensive care”[MeSH Terms] OR (“intensive”[All Fields] AND “care”[All Fields]) OR “intensive care”[All Fields]) AND (((“atorvastatin”[Supplementary Concept] OR “atorvastatin”[All Fields]) OR (“rosuvastatin”[Supplementary Concept] OR “rosuvastatin”[All Fields])) OR (“simvastatin”[MeSH Terms] OR “simvastatin”[All Fields]))))