CLINICAL RESEARCH STUDY

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Statin Therapy and Mortality from Sepsis: A Meta-analysis of Randomized Trials

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ABSTRACT

BACKGROUND: Statin therapy for sepsis has been suggested by observational studies. However, randomized controlled trials have not demonstrated this benefit. We conducted a systematic review and meta-analysis of randomized trials to evaluate the effect of statin therapy on mortality in patients with sepsis.

METHODS: We searched 6 electronic databases for articles published before August 2014. Randomized trials reporting the effect of statin therapy on mortality in patients with sepsis were included. The primary outcome of interest was in-hospital or 28-day mortality. Two independent reviewers searched and identified studies and extracted data. Risk ratios (RRs) were pooled across studies using random-effects models and were verified using fixed-effects models.

RESULTS: Seven randomized trials were included in the analyses, comprising 1720 patients. Statin therapy did not significantly decrease in-hospital mortality (RR, 1.04; 95% confidence interval, 0.87-1.24; $I^2 = 0\%$; $P = .68$) or 28-day mortality (RR, 0.93; 95% confidence interval, 0.46-1.89; $I^2 = 57\%$; $P = .85$) in patients with sepsis. Study quality of the included trials was high; the median Jadad score was 4.5 (range, 4-5).

CONCLUSIONS: This systematic review and meta-analysis of randomized trials suggests that statin therapy does not improve mortality outcomes in patients with sepsis compared with placebo.

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KEYWORDS: Meta-analysis; Mortality; Sepsis; Statins

Sepsis is characterized by a systemic inflammatory response to microbial toxins leading to tissue damage and multiple organ dysfunction.[1] Severe sepsis is defined as an infection associated with new organ dysfunction, hypoperfusion, or hypotension and is a leading cause of hospitalizations and mortality in the United States.[2,3] In addition to their cholesterol-lowering effects, statins (hydroxymethyl glutaryl coenzyme A reductase inhibitors) have been shown to have anti-inflammatory and immunomodulatory properties.[4-6] Therefore, it has been hypothesized that statins may have a role in the prevention and treatment of sepsis.[7] Several observational studies have suggested that statins may dramatically improve mortality outcomes in patients with sepsis.[8-10] Previous systematic reviews and meta-analyses of observational studies also have shown a significant protective and therapeutic effect of statins in patients with sepsis.[11-13] However, since 2009, several small published randomized controlled trials failed to demonstrate statistically significant beneficial effects of statins on mortality rates in patients with sepsis.[14-16] Therefore, whether statins are beneficial for the treatment of sepsis remains controversial. It is likely that observational studies are associated with biased estimations and unmeasured confounding variables. For example, healthier patients are more likely to be prescribed statins and statin users may have less severe comorbidities in these studies.[17] Two previous meta-analyses on this topic were limited by their study design[18] and smaller number of randomized trials included.[19] We conducted a systematic review and meta-analysis of all published placebo-controlled randomized trials with the primary objective of summarizing and critically evaluating the effect of statin therapy on mortality in sepsis.

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Conflict of Interest: None.

Authorship: AD and VP contributed equally to this study. All authors had access to the data and played a role in writing this manuscript.

The PubMed search strategy and Jadad scoring of randomized controlled trials are available in an **Online Supplement**.

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MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement in conducting this systematic review and meta-analysis.[20]

Data Sources and Searches

A comprehensive literature search was performed. The databases searched included PubMed-Medline, EMBASE, the Cochrane Library, Web of Science, clinicaltrials.gov, and Scopus. The dates searched were from the inception of each database to August 2014. The search was conducted independently by 2 investigators (AD and VP). The search terms included the following keywords: statin, hydroxymethylglutaryl coenzyme A reductase inhibitor, anticholesteremic agent, simvastatin, rosuvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, pitavastatin, lovastatin, sepsis, bacteremia, and randomized controlled trial. The search was extended by review of bibliographies from articles included in the final selection. The search strategy of PubMed is available in an **Online Supplement**.

CLINICAL SIGNIFICANCE

- Meta-analysis of randomized trials suggests that there is no evidence to support that statin therapy decreases mortality in patients with sepsis.
- Neither atorvastatin nor rosuvastatin provided any benefit with respect to mortality.
- Further randomized controlled trials on the topic would seem to offer little value.

Study Selection and Data Extraction

The following predetermined inclusion criteria were used: (1) randomized controlled trials, (2) studies evaluating the efficacy of statin treatment for sepsis in comparison with a control group without statin treatment, (3) data available on the mortality, and (4) study in any language. Unpublished trials and data presented in short reports or letters to the editor were also not eligible. Abstracts and conference proceedings were excluded because detailed methodology is not clear, and they provide insufficient information to adequately judge quality. A list of retrieved articles was reviewed independently by 2 investigators (AD and VP) to choose potentially relevant articles, and disagreements about particular studies were discussed and resolved by consensus.

Two reviewers (AD and VP) independently extracted data from studies using standardized coding forms. The following information was extracted: study design, study population/setting, mean age, blinding, type of statin, and dosage at baseline. The primary outcome of interest was mortality (in-hospital and 28-day mortality). The Cohen's inter-rater kappa statistic for inclusion agreement and data abstraction was 0.90 and 0.92, respectively, indicative of excellent inter-rater agreement.

Evaluation of Study Quality

Jadad Score. The quality of all included trials was assessed using a 5-item instrument developed and validated by Jadad.[21] The 5 items in this scale include (1) description of randomization, (2) appropriateness of randomization, (3) description of blinding, (4) adequacy and appropriateness of blinding, and (5) description of withdrawals and dropouts. Study quality was assessed independently by 2 investigators (VP and AD). Disagreements were resolved by consensus. A score of 0 to 2 was considered low quality, and a score of 3 to 5 was considered high quality.

Risk of Bias Assessment. We assessed the risk of bias of the included studies according to the Cochrane Collaboration's tool.[22] Seven items were considered (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) blinding of data analyst, (6) incomplete outcome data, and (7) selective reporting. For each randomized controlled trial, each item was described as low risk of bias, high risk of bias, and unclear risk of bias by 2 independent investigators (AD and VP). The Cohen's inter-rater kappa statistic for study quality assessment (Jadad score and Cochrane risk of bias tool) was 1.0 and 0.94, respectively, indicative of excellent inter-rater agreement.

Publication Bias. To examine bias in the results of the meta-analyses, Egger's test was used to evaluate asymmetry of the funnel plots.[23]

Data Synthesis and Analysis. Some degree of heterogeneity was expected; therefore, to take into account the sources of heterogeneity, 3 subgroup meta-analyses were prespecified: (1) type of statin, (2) dose of statin (high vs low), and (3) observed mortality rates. Also, sensitivity analyses were performed by sequentially removing each study and reanalyzing the remaining dataset.

A random-effects meta-analysis was performed by default because of expected between-study heterogeneity. DerSimonian and Laird random effects models were used for meta-analyses.[24] We used the Mantel-Haenszel method to calculate pooled relative risk ratios (RRs) and their 95% confidence intervals (CIs). Statistical heterogeneity was evaluated with the Cochran chi-square test and the I^2 statistics. I^2 values of 30% to 60% represented a moderate level of heterogeneity. A P value of $<.1$ for chi-square was defined as indicating the presence of heterogeneity. We used Review Manager (RevMan 5.0, Oxford, UK; The Cochrane Collaboration, 2008) for our statistical analyses.

RESULTS

Eligible Studies

Our search identified 1114 publications. After removing duplicates and screening titles of the studies, 651 articles