Statins for the Prevention and Treatment of Infections

A Systematic Review and Meta-analysis

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Background: Emerging epidemiological evidence suggests that statin use may reduce the risk of infections and infection-related complications. Our objective was to examine the association between statin use and the risk of infections and related outcomes.

Methods: We searched several electronic databases from inception through December 2007 for randomized trials and cohort studies that examined the association between statin use and the risk or outcome of infections. Data on study characteristics, measurement of statin use, outcomes (adjusted for potential confounders), and quality assessment were extracted.

Results: Sixteen cohorts were eligible and differed in representativeness, outcome assessment, and comparability of exposed (statin) and unexposed (nonstatin) groups. Nine cohorts addressed the role of statins in treating infections: bacteremia (n = 3), pneumonia (n = 3), sepsis (n = 2), and bacterial infection (n = 1). The pooled adjusted effect estimate was 0.55 (95% confidence interval, 0.36-0.83; I² = 76.5%) in favor of statins. Seven cohorts addressed infection prevention in patients with vascular diseases (n = 3), chronic kidney disease (n = 1), diabetes (n = 1), intensive care unit–acquired infections (n = 1), and in general practice (n = 1). The pooled effect estimate was 0.57 (95% confidence interval, 0.43-0.75; I² = 82%) in favor of statin use; there was some evidence of publication bias for this analysis (Egger test; P = .07). Meta-regression did not identify potential effect modifiers that explain the between-study heterogeneity.

Conclusions: Results for our meta-analysis suggest that statin use may be associated with a beneficial effect in treating and preventing different infections. Given the presence of heterogeneity and publication bias, there is a need for randomized trials to confirm the benefit of statin use in this context.

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SEVERE SEPSIS IS VERY COMMON and poses a major challenge to health care systems. In a large population-based study, Angus et al1 estimated that there were 751,000 cases of severe sepsis in the United States in 1995 (3.0 cases per 1000 population), of which 51.1% required intensive care service, resulting in an estimated cost of $16.7 billion. This study also found that severe sepsis is frequently fatal, with a mortality rate approaching 30%; this death toll is equivalent to deaths due to acute myocardial infarction. It has also been shown that the incidence of severe sepsis is increasing over time.2 In a more recent study, rates of hospitalization for severe sepsis were found to have increased from 66.8 per 100,000 population to 132 per 100,000 population between 1993 and 2003.3 Furthermore, age-adjusted, population-based mortality rates within the same period increased from 30.3 to 49.7 per 100,000 population.

The hallmark of sepsis syndrome is an intense inflammatory response, which reflects a delicate interaction between the extensive activation of host defense mechanisms and direct and indirect effects of the invading microorganisms and their toxins. As a result, a number of important abnormalities occur during sepsis, including endothelial dysfunction and apoptosis, activation and increased production of cytokines and other proinflammatory mediators, activation and extravascular transmigration of leukocytes, and activation of platelets and coagulation and complement systems.4,5 Because of this multiple pathway involvement in the pathogenesis of sepsis, targeting a single component is likely to be insufficient to halt the septic process. In fact, a number of pharmacological agents have been tested in the setting of severe sepsis over the past 2 decades, and all failed except recombinant activated protein C, which showed encouraging results.6

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase,
were developed as lipid level-lowering agents, and have been studied extensively in relation to atherosclerosis. However, statins, not only reduce cholesterol level but also decrease the levels of intermediate products of cholesterol synthesis, mevalonate, farnesylpyrophosphate, and geranylgeranylpyrophosphate, which play a crucial role in several intracellular signaling pathways.7 Apparently, this effect is the major explanation for the observed pleiotropic effects of statins, which include the modulation of both innate and adaptive immune system and anti-inflammatory effects (reviewed by Kwak et al8), as well as their role in counteracting the deleterious effects of sepsis on the coagulation system by inhibiting tissue factor expression and reducing prothrombin fragment levels9 and by strongly increasing the expression of thrombomodulin.10 In addition, statins have been shown to have direct inhibitory effects on pathogenic microorganisms.11-17 Therefore, statins may be good candidates as novel therapeutic agents for the treatment and prevention of sepsis because they target a number of pathways that are dysregulated during the sepsis process and because of their direct antimicrobial effects. Indeed, in a murine model of sepsis, simvastatin was shown to profoundly improve survival.14 Similar effects were demonstrated with atorvastatin and pravastatin.5

Although there are no data from randomized controlled trials of statins and sepsis, a number of observational studies were published over the last few years. These studies, including a systematic review as of June 2007,18 lend support to the potential role of statins in the prevention and treatment of sepsis. Therefore, we performed a systematic review and meta-analysis of the literature following the Meta-analysis of Observational Studies in Epidemiology guidelines to further elucidate the effect of statins in the treatment and prevention of infections.19

STUDY SELECTION
To be included, a study had to (1) be a randomized trial or a cohort study including more than 50 patients; (2) examine the association between statin use and (a) the outcome of infection (such as complications, severity, and mortality) and (b) the incidence of infections; and (3) report an adjusted effect estimate for 1 or more potential confounding variables for this association (for cohort studies). For cohort studies that did not report adjusted effect estimates, authors were contacted to obtain missing information.

DATA COLLECTION
A data collection form was developed and used to retrieve information on relevant features and results of pertinent studies. Two reviewers (T.K. and F.H.) independently extracted and recorded data on a predefined checklist. Disagreement among reviewers was discussed with 2 other reviewers (I.M.T. and V.A.Z.), and agreement was reached by consensus.

STUDY SEARCH STRATEGY
The search strategy and subsequent literature searches were performed by a medical reference librarian (P.J.E.) with 35 years of experience. The initial strategy was developed in Ovid MEDLINE (1990 through November 2007), using MeSH (Medical Subject Headings) controlled vocabulary, and then modified for Ovid EMBASE (1990 through December 2007). The primary terms were explode anticholesteremic agents or explode hydroxymethylglutarate-CoA Reductase Inhibitors, AND’d with explode infection, explode bacterial infections, or explode virus diseases, or explode respiratory tract infections, or explode sepsis. Subheadings (such as mortality, complication, prevention and control, drug therapy, and epidemiology) were attached to the subject heading to more fully focus the results on treatment and prevention. Articles were limited to clinical trials, meta-analyses, cohort studies, or case-control studies.

The strategy was again modified to text words for Ovid Cochrane Central Register of Controlled Trials (inception through December 2007), Thomson Scientific Web of Science (1993 through December 2007), and Elsevier Scopus (inception through December 2007). There was no restriction on language. All results were downloaded into EndNote 7.0 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania), a bibliographic database manager, and duplicate citations were identified and removed. Two authors (I.M.T. and F.H.) independently assessed the eligibility of identified studies.

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publication bias. The contour-enhanced funnel plot test of funnel plot asymmetry and vice versa. All analyses were conducted using Stata version 9.2 statistical software (StataCorp, College Station, Texas).

The search strategy yielded 246 publications, of which 229 were not eligible based on abstract and title review, including 8 studies with nonclinical outcomes,26-33 Seventeen articles were considered for full-text review, and identified 1 additional study from the reference list of all eligible articles. Two studies were later excluded because of small sample size (<100) and noninfection-related end points. A total of 9 studies addressing the role of statins in preventing infections were eligible. Outcome data on 2 studies were not reported; however, we were able to obtain them by contacting the primary authors. Figure 1 summarizes the study selection process.

CHARACTERISTICS OF THE INCLUDED STUDIES

Treatment Cohorts

Table 1 summarizes the characteristics of the 9 included treatment cohorts.36-41,43,44 Studies were conducted in several countries. Four were single-center studies, and the remaining were multicenter studies. Three studies were population based. Underlying infectious categories were bacteremia (n=3),38,39,45 pneumonia (n=3),37,40,41 sepsis (n=2),36,47 and bacterial infection (n=1).36 Statin use ascertainment was based on a review of medical records or prescription databases. All studies reported on short-term outcome (in-hospital up to 30 days after diagnosis) (Table 2). Relevant outcomes included all-cause mortality (n=5),36,38,45-47 infection-related mortality (n=2),37,44 severe sepsis (n=1),36, and a composite outcome of all-cause mortality or admission to intensive care unit (n=1).40

Prevention Cohorts

Table 3 summarizes the characteristics of the 7 included prevention cohorts.45-51 Studies were conducted in several countries. Three were single-center studies and the remaining were multicenter studies. Three studies were population based. Underlying conditions were cardiovascular diseases (n=3),45-47,49 chronic kidney diseases (n=1),49 diabetes (n=1),50 intensive care unit–acquired infections (n=1),47 and general practice (n=1).51 Statin use ascertainment was based on a review of medical records or prescription databases and was not available in one study (Coleman et al46). Relevant outcomes included sepsis (n=2),48,49 infection related mortality (n=1),45 pneumonia (n=2),50,51 and any infectious complication (n=1)46 (Table 4).

META-ANALYSIS

Treatment Cohorts

A random-effects model meta-analysis of treatment cohorts resulted in a pooled adjusted effect estimate of 0.55 (95% CI, 0.36-0.83; I²=76.5%), suggesting an improvement in the chance of survival in favor of statin use (Figure 2). Included studies adjusted for demographics (n=9), Charlson comorbidity index (n=3), individual comorbidity variables (n=6, with a range of 5-14 comorbidities), severity of illness (n=6: Pneumonia Severity Index [n=2], Acute Physiology And Chronic Health Evaluation [APACHE] II [n=3], and surrogate markers [n=1]). Of 9 studies, 7 adjusted for additional prognostic factors (range, 1-8 variables). Table 5 summarizes the variables considered in the multivariate model. There was some suggestion of asymmetry of the funnel plot (Figure 3), but this did not attain statistical significance by the Egger test (P=.15). None of the considered variables revealed statistically significant associations with meta-regression (data not shown). This is potentially explained by low power due to the small number of studies.

Prevention Cohorts

A random-effects model meta-analysis of 7 prevention cohorts resulted in a pooled effect estimate of 0.57 (95% CI, 0.43-0.75; I²=82%) in favor of statin use (Figure 2). Included studies adjusted for demographics (n=7), Charlson comorbidity index (n=2), individual comorbidity variables (n=5, with a range of 3-15 comorbidities), and health care use (n=4). Of 7 studies, 5 adjusted for additional prognostic factors (range, 2-10 variables). Table 6 summarizes the different variables considered in the multivariate model. There was some evidence of funnel plot asymmetry, which may be indicative of publication bias by visual inspection of the contoured funnel plot (Figure 4) and by the Egger test (P=.07). Since the perceived location of any missing studies is in
the area of $P > .05$ (ie, inside the defined triangle), this suggests that publication bias may be the cause of missing studies, which implies that the treatment effect may be overestimated. None of the considered variables revealed statistically significant associations with meta-regression (data not shown). This may be explained by low power due to the small number of studies.

**QUALITY ASSESSMENT OF THE INCLUDED COHORTS**

eTables 1 and 2 (http://www.archinternmed.com) summarize the different levels of study quality. Included studies differed in the representativeness of the cohorts (population-based studies vs others), outcome assessment (blinded vs not), and comparability of the exposed and nonexposed groups when exposure represents statin intake. Among the 9 treatment cohorts, 4 were population based or multicenter, 2 included blinded outcome assessment, and 8 adjusted for multiple confounders. Among the 7 prevention cohorts, 4 were population based or multicenter, 1 included blinded outcome assessment, and 6 adjusted for multiple confounders. All studies

<table>
<thead>
<tr>
<th>Source, Study Period</th>
<th>Country</th>
<th>Centers</th>
<th>Setting</th>
<th>Condition</th>
<th>Inclusion Criteria</th>
<th>Study Design</th>
<th>Statin Type</th>
<th>Statin Use</th>
<th>Statin Use Ascertainment</th>
<th>Duration of Follow-up, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majumdar et al.2000-2002</td>
<td>Canada</td>
<td>6</td>
<td>Capital Health integrated health system, Edmonton, Alberta</td>
<td>CAP</td>
<td>Age $&gt;$ 17 y; inpatient; no TB, CF, PG; immunocompromized</td>
<td>Population-based prospective cohort</td>
<td>NR</td>
<td>$\geq$ 1 Week before and during hospitalization</td>
<td>Medical charts, patient/proxy interviews</td>
<td>In hospital</td>
</tr>
<tr>
<td>Liappis et al.1995-2000</td>
<td>United States</td>
<td>1</td>
<td>VA Medical Center Washington, DC</td>
<td>Aerobic bacilli or Staphylococcus aureus bacteremia</td>
<td>Inpatient</td>
<td>Retrospective cohort</td>
<td>A (2.8%), F (14%), L (2.8%), P (2.8%), S (7%), P (21%), S (70%), Other (9%)</td>
<td>At admission and during hospitalization</td>
<td>Computerized medical records</td>
<td>In hospital</td>
</tr>
<tr>
<td>Almqvist et al.2003</td>
<td>Israel</td>
<td>1</td>
<td>Sorroka University Medical Center</td>
<td>Bacterial infections (pneumonia, UTI, cellulitis)</td>
<td>Age $\geq$ 40 y</td>
<td>Prospective cohort</td>
<td>S (7%), P (21%), S (70%), Other (9%)</td>
<td>$\geq$ 1 Month before admission</td>
<td>Baseline assessment</td>
<td>28 or to death</td>
</tr>
<tr>
<td>Kruger et al.2000-2003</td>
<td>Australia</td>
<td>1</td>
<td>General hospital, 300 beds, Ipswich</td>
<td>Clinically significant bacteremia</td>
<td>Age $&gt;$ 18 y</td>
<td>Retrospective cohort</td>
<td>A (33.3%), P (12.1%), S (54.5%)</td>
<td>At admission and during hospitalization</td>
<td>Patient records, drug administration charts</td>
<td>In hospital</td>
</tr>
<tr>
<td>Frost et al.1992-2003</td>
<td>United States</td>
<td>Multi-center</td>
<td>Several moderately sized HMOs: Lovelace Patient Database</td>
<td>Influenza/pneumonia</td>
<td>Inpatient</td>
<td>Matched cohort</td>
<td>NR</td>
<td>$\geq$ 90 Days’ cumulative use before death or HMO disenrollment</td>
<td>Prescription filled, database record</td>
<td>30</td>
</tr>
<tr>
<td>Thomsen et al.1992-2002</td>
<td>Denmark</td>
<td>7</td>
<td>Hospitals, North Jutland County</td>
<td>Bacteremia</td>
<td>Age $&gt;$ 15 y; first hospitalization for bacteremia $\geq$ 1 y; county residency</td>
<td>Population-based prospective cohort</td>
<td>S (48%), P (28%), A (18%), Others (13%)</td>
<td>NR</td>
<td>At presentation</td>
<td>Medical record</td>
</tr>
<tr>
<td>Mortensen et al.1999-2002</td>
<td>United States</td>
<td>2</td>
<td>Tertiary teaching hospitals, San Antonio, TX</td>
<td>CAP</td>
<td>Age $&gt;$ 18 y; inpatient</td>
<td>Retrospective cohort</td>
<td>A</td>
<td>$\geq$ 1 Filled prescription</td>
<td>Prescription database</td>
<td>30</td>
</tr>
<tr>
<td>Mortensen et al.2000</td>
<td>United States</td>
<td>19</td>
<td>VA National Patient Care and Pharmacy Database</td>
<td>Sepsis</td>
<td>Age $&gt;$ 65 y; inpatient; first admission; no HIV</td>
<td>Retrospective national cohort</td>
<td>A, C, F, L, P, S</td>
<td>$\geq$ 90 Days’ before admission, sufficient quantity to last until admission</td>
<td>In hospital</td>
<td>30</td>
</tr>
<tr>
<td>Yang et al.2001-2002</td>
<td>Taiwan</td>
<td>1</td>
<td>National Taiwan University Hospital</td>
<td>Sepsis</td>
<td>Age $&gt;$ 18 y; baseline lipid profile at diagnosis; $\geq$ 1 positive blood culture result</td>
<td>Retrospective cohort</td>
<td>A (19.2%, 10-30 mg), F (9.6%, 20-40 mg), L (3.8%, 20-40 mg), P (17.3%, 10-30 mg), S (50.0%, 10-40 mg)</td>
<td>$\geq$ 30 Days before sepsis and during hospitalization</td>
<td>Medical records</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: A, atorvastatin; CAP, community-acquired pneumonia; C, cerivastatin; CF, cystic fibrosis; F, fluvastatin; HIV, human immunodeficiency virus; HMOs, health maintenance organizations; L, lovastatin; NR, not reported; P, pravastatin; PG, pregnancy; S, simvastatin; TB, tuberculosis; UTI, urinary tract infection; VA, Department of Veterans Affairs.

a If more than 1 design was reported, only that providing results data in Table 3 is listed here.

b The percentages in the parentheses represent the percentage of the type of statin from all types used.
Table 2. Analytical Approach and Results of Included Treatment Cohorts

<table>
<thead>
<tr>
<th>Source</th>
<th>Sample Size (Statin Group)</th>
<th>Sample Size (Nonstatin Group)</th>
<th>Analytic Method</th>
<th>Outcome</th>
<th>Results: Adjusted Effect Estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majumdar et al40</td>
<td>325</td>
<td>3090</td>
<td>Logistic regression and propensity score</td>
<td>All-cause mortality or admission to ICU</td>
<td>Adjusted OR, 1.1 (0.76-1.6)</td>
</tr>
<tr>
<td>Liappis et al39</td>
<td>35</td>
<td>353</td>
<td>Logistic regression</td>
<td>All-cause in-hospital mortality</td>
<td>Adjusted OR, 0.13 (0.107-0.99)</td>
</tr>
<tr>
<td>Almog et al36</td>
<td>82</td>
<td>279</td>
<td>Logistic regression</td>
<td>Severe sepsis</td>
<td>Adjusted OR, 0.07 (0.01-0.51)</td>
</tr>
<tr>
<td>Kruger et al36</td>
<td>66</td>
<td>372</td>
<td>Cox regression and propensity score</td>
<td>All-cause in-hospital mortality</td>
<td>Adjusted OR, 0.059 (0.0008-0.43)</td>
</tr>
<tr>
<td>Frost et al42</td>
<td>19058</td>
<td>57174</td>
<td>Cox regression</td>
<td>Mortality due to influenza/pneumonia</td>
<td>Adjusted HR, 0.61 (0.41-0.92)</td>
</tr>
<tr>
<td>Thomsen et al43</td>
<td>176</td>
<td>5177</td>
<td>Cox regression</td>
<td>30-Day all-cause mortality</td>
<td>Adjusted MRR, HR 0.93 (0.66-1.30)</td>
</tr>
<tr>
<td>Mortensen et al42</td>
<td>110</td>
<td>677</td>
<td>Logistic regression</td>
<td>30-Day all-cause mortality</td>
<td>Adjusted OR, 0.36 (0.14-0.92)</td>
</tr>
<tr>
<td>Mortensen et al40</td>
<td>480</td>
<td>2471</td>
<td>Cox regression and propensity score</td>
<td>30-Day all-cause mortality</td>
<td>Adjusted OR, 0.48 (0.36-0.64)</td>
</tr>
<tr>
<td>Yang et al44</td>
<td>104</td>
<td>350</td>
<td>Cox regression</td>
<td>30-Day mortality due to sepsis</td>
<td>Adjusted OR, 0.98 (0.44-2.16)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; MMR, matched mortality rate; OR, odds ratio.

Table 3. Characteristics of Included Prevention Cohorts

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period (Country)</th>
<th>Underlying Condition</th>
<th>Centers, No.</th>
<th>Setting</th>
<th>Inclusion Criteria</th>
<th>Study Design</th>
<th>Statin Type</th>
<th>Statin Use</th>
<th>Statin Use Ascertainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hackam et al43</td>
<td>1997-2002 (Canada)</td>
<td>Cardiovascular disease</td>
<td>Multiple</td>
<td>All province hospitals, province of Ontario linkage of multiple databases</td>
<td>Age &gt;65 y; posthospitalization for specific atherosclerotic event or revascularization procedure; alive ≥3 months after discharge</td>
<td>Population-based retrospective review of a multiple-linked database</td>
<td>A (37%) C (2%) F (3%) L (10%) P (21%) S (28%)</td>
<td>≥1 Prescription during 3 months after discharge</td>
<td>Prescription database</td>
</tr>
<tr>
<td>Gupta et al49</td>
<td>1995-2005 (United States)</td>
<td>Chronic kidney disease</td>
<td>81</td>
<td>OP dialysis clinics (national collaboration), 19 states</td>
<td>Age &gt;17 y; long-term OP dialysis ≥3 months’ duration</td>
<td>Prospective cohort</td>
<td>A F L P S</td>
<td>At baseline</td>
<td>Dialysis clinic notes; hospital discharge summaries; computerized order entry records; withdrawing statins from pharmacy</td>
</tr>
<tr>
<td>Almog et al36</td>
<td>2001-2003 (Israel)</td>
<td>Atherosclerotic disease</td>
<td>1 University medical center, Sorroka</td>
<td>Age 20-80 y; background atherosclerotic disease; hospitalized for any cause</td>
<td>Population-based prospective cohort</td>
<td>At least in final month before follow-up termination or hospitalization leading to death</td>
<td>At baseline</td>
<td>Prescription records</td>
<td></td>
</tr>
<tr>
<td>Van de Garde et al42</td>
<td>1987-2001 (United Kingdom)</td>
<td>Diabetes</td>
<td>Multicenter</td>
<td>650 General practices, GPRD</td>
<td>Age ≥18 y; diabetes; first CAP episode</td>
<td>Case-control</td>
<td>A C F P S</td>
<td>Before pneumonia Dx</td>
<td>Prescription records</td>
</tr>
<tr>
<td>Coleman et al44</td>
<td>2004-2006 (United States)</td>
<td>Cardiovascular disease</td>
<td>1 Urban teaching hospital, Hartford, CT</td>
<td>Cardiac surgery (CABG, valve replacement, or both)</td>
<td>Retrospective cohort</td>
<td>NR</td>
<td>For any period before surgery</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Schlienger et al37</td>
<td>1995-2003 (United Kingdom)</td>
<td>NA: general practice</td>
<td>Multicenter</td>
<td>General practice, GPRD</td>
<td>Population-based nested case-control</td>
<td>≥1 Statin and/or fibrate prescription &lt;30 days before Dx</td>
<td>Prescription database</td>
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<td></td>
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<tr>
<td>Fernandez et al41</td>
<td>2002-2004 (Spain)</td>
<td>High risk for ICU-acquired infection</td>
<td>1 University affiliated, Hospital de Sabadell, Barcelona</td>
<td>Admitted to ICU; requiring &gt;96 hours of mechanical ventilation</td>
<td>Retrospective cohort</td>
<td>S (40 mg daily)</td>
<td>Before admission and during hospitalization</td>
<td>Medical chart review</td>
<td></td>
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</tbody>
</table>

Abbreviations: A, atorvastatin; C, cerivastatin, CABC, coronary artery bypass surgery; CAP, community-acquired pneumonia; Dx, diagnosis; F, fluvastatin; GPRD, general practice research database; HIV, human immunodeficiency virus; ICU, intensive care unit; L, lovastatin; NA, not applicable; NR, not reported; OP, outpatient; P, pravastatin; S, simvastatin.

The percentages in the parentheses represent the percentage of the type of statin from all types used.
had adequate selection of the nonexposed (nonstatin) cohort, ascertainment of statin exposure, and follow-up of all patients.

**COMMENT**

**KEY FINDINGS**

Findings from our systematic review and meta-analysis suggest that statin use may be associated with a beneficial effect in treating and preventing different infections. Our pooled adjusted estimate from observational studies suggests that patients who have infections and are taking statins have a better outcome, including chance of survival. Moreover, the pooled adjusted estimate from both prevention and treatment studies suggests that statin use is associated with a lower risk of infections despite the potential quality deficiencies and publication bias.

Analysis of the prevention and treatment studies displayed large heterogeneity. This is not uncommon for epidemiological studies. Between large studies, heterogeneity can be large due to highly precise effect sizes.25

**MECHANISMS**

Although the exact mechanism(s) behind the observed association remains unknown, it could be attributed to several factors, including the immunomodulatory and anti-inflammatory effect of statins and their impact on endothelial function. First, a number of clinical studies in different settings including atherosclerosis, organ transplantation, osteoporosis, dementia, multiple sclerosis, and rheumatoid arthritis provide evidence for the immunomodulatory effects of statin use independent of lipid level lowering.7,53; they reduce interferon-γ-induced major histocompatibility complex class II expression, which is involved in controlling immune responses such as T-cell activation.7 Statins also affect leukocyte-endothelial interaction and trans-
migration of leukocytes through the endothelial layer as they decrease a number of molecules involved in this process including interleukin 8, RANTES (regulated on activation, normal T cell expressed and secreted), P-selectin, monocyte chemoattractant protein 1, and membrane attack complex type 1 and directly block leukocyte function–associated antigen 1.8 This may explain the observed protective effect of statins in the context of sepsis, a process that is well known to be associated with maladaptive dysregulated immune response. Second, statins also exert an anti-inflammatory response independent of their lipid level–lowering properties.53 For example, it has been shown that simvastatin inhibits the inflammatory response to Staphylococcus aureus alpha toxin in rats,54 and cerivastatin pretreatment in mice reduces tumor necrosis factor and interleukin 1/H9252 levels after lipopolysaccharide treatment.55 Third, clinical trials in the context of atherosclerosis have shown that statins improve endothelial function (reviewed by Jain and Ridker53). In fact, sepsis is associated with endothelial dysfunction and apoptosis, which is associated with deranged homeostasis.56 It has also been shown that statins upregulate endothelial nitric oxide synthase, which is well known to have a number of favorable effects.57 Finally, statins exert direct effects on pathogenic microorganisms; for example, lovastatin reduces the intracellular growth of Salmonella typhimurium in cultured macrophages11 and also reduces human immunodeficiency virus type 1 viral load and increases CD4+ cell counts in acute infection models and patients with chronic infection.12 In human umbilical vein endothelial cells infected with cytomegalovirus, fluvastatin significantly reduces cytomegalovirus DNA and viral particles.13 Similarly, a number of studies found that statins exhibit direct antifungal activity.15-17 The direct antimicrobial effects and the immunomodulatory properties of statins may explain the observed preventive effects against infection in a number of observational studies.

**STRENGTHS AND LIMITATIONS**

Two systematic reviews addressing somewhat similar questions raised by our study were published recently.18,58 However, our review is unique. First, we identified more eli-
gible studies (2 more studies\textsuperscript{42,46} with clinical end points than the review by Falagas et al\textsuperscript{18} and 8 more studies than the review by Chua et al\textsuperscript{38}). Second, we obtained data from 2 studies with missing adjusted effect estimates. Third, we differentiated between treatment and prevention cohorts. Fourth, we limited our review to relevant clinical outcomes. Fifth, we used a different approach to summarize, critically appraise, and present the data. We provided the reader with a detailed list of relevant variables about the characteristics and analytical methods of included studies. We also used the validated Newcastle-Ottawa Quality Assessment Scale for cohort studies. Sixth, we performed a meta-analysis and assessed for publication bias. Our observation of the potential effect of publication bias weakened the conclusion about the benefit of statins that was strongly inferred from individual studies and previous systematic reviews.

Our inferences from this meta-analysis are, however, weakened by limitations inherent to the meta-analysis and the individual studies. First, the pooled estimates of the meta-analyses are limited by the suggestion of potential publication bias, particularly among the prevention studies, and by the statistically significant heterogeneity in the pooled estimates for both treatment and prevention studies. Although we pooled heterogeneous trials regarding patients, setting, and treatment regimens, we believe there was a valid biological justification to perform a broad meta-analysis, which considerably increases generalizability and usefulness. Furthermore, a broad meta-analysis increases power, reduces the risk of erroneous conclusions, and facilitates exploratory analyses, which can generate hypotheses for future research. Although we identified no source for heterogeneity in the results of the meta-regression analyses, the small number of participating studies meant that statistical power was low.

Second, given the observational design of included studies and retrospective data collection in several studies, the possibility that the observed association between statin use and outcome was associated with bias or confounding should be considered. For example, comorbidities and severity of illness are known confounders that are associated with statin intake and mortality. The healthy user effect could theoretically explain a potential role for statins in infection prevention; however, the opposite could also be the case where the sicker patients have more exposure to statins.\textsuperscript{47} Nevertheless, the combined effect estimate from the studies that used regression models to adjust for possible confounders including age, comorbidities, and severity of illness—although the models were not uniform—supports our conclusions. As with any observational study, residual confounding cannot be fully excluded, particularly when the observed association is not very strong.

We expect that more studies will be published addressing the same question as our review, and thus an updated meta-analysis may be warranted in the future. We are aware of one recently published prevention study.\textsuperscript{39} A sensitivity analysis including this study\textsuperscript{59} shows a pooled effect estimate of 0.62 (95% CI, 0.50-0.76), which is consistent with our overall findings.

**RECOMMENDATION AND FUTURE DIRECTIONS**

Although this study suggests that there may be an association between statin intake and the prevention or treatment of infectious diseases, several issues need resolution or clarification before adopting the use of statins to treat or prevent infections.\textsuperscript{50} First, there is a need for properly conducted, randomized, placebo-controlled trials in this context. There are several such trials under way (see examples in Table 7). Unfortunately, all of these trials are single center studies that do not have mortality as the primary outcome variable. Moreover, there are no such ongoing trials in the context of prevention of infections.

Second, the safety of statins in the setting of sepsis should be examined. Statins have proven to be extremely safe in most patients\textsuperscript{61}; however, 2 common adverse effects are particularly relevant in sepsis: liver dysfunction and myositis. Many changes in liver function occur during the course of sepsis. Statins can adversely affect hepatic function, and elevated hepatic transaminases occur in 0.5% to 2.0% of patients.\textsuperscript{60} In the context of severe sepsis, in which hepatic dysfunction is common, the use of statins may be contraindicated in some patients.\textsuperscript{60} Abnormal creatine kinase levels are also commonly encountered in patients with sepsis, and it is not known whether patients with sepsis are more prone to the muscle adverse effects of statins such as myositis and rhabdomyolysis.
Third, the lack of an intravenous formulation or a clear pharmacokinetic profile for statins in patients with sepsis would need to be addressed before their use could become widespread. The current drugs in the “statin” class are only available as oral preparations. All statins are absorbed rapidly from the gastrointestinal tract after administration, reaching peak plasma concentration within 4 hours. As statins are highly protein bound, it is particularly important to define the influence of hypoalbuminemia on statin bioavailability and toxicity.

CONCLUSIONS

Our systematic review and meta-analysis of observational studies suggest that statin use is associated with a beneficial effect in treating and preventing different infections. Although our findings are consistent for both prevention and treatment studies, they are weakened by the presence of heterogeneity and potential publication bias. Moreover, our meta-analysis of observational studies cannot prove causality. Given the biological plausibility of our observation, there is a need for properly conducted, randomized, placebo-controlled trials to confirm or refute its benefit before the use of statins could become widespread in this context.

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