Statins for infection and sepsis: a systematic review of the clinical evidence

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Introduction: Statins are currently used for hyperlipidaemia control and considered useful for protection from cardiovascular events. In addition, there is increasing evidence for the potential use of statins in preventing and treating infections.

Methods: We performed a systematic review of the literature that compared the outcome between statin and non-statin users among patients suffering from sepsis or other infections. The relevant studies were identified from searches of PubMed, Scopus and the Cochrane Library databases.

Results: Twenty studies were identified (13 of them were retrospective), out of which 9 examined the use of statins in patients with sepsis, bacteraemia or multiorgan dysfunction syndrome, 4 community-acquired pneumonia (CAP), 1 ICU infections, 2 other bacterial infections and 4 viral infections. Eleven studies had data regarding mortality as the main outcome: 8 showed decreased mortality in statin users (3 of them reported on patients with bacteraemia), 2 showed no difference in mortality and 1 reported an increased mortality in patients who received statins. Seven studies examined the risk of sepsis as the main outcome; six of these studies showed a decreased risk of sepsis in patients receiving statins, whereas one study found no difference.

Conclusions: The majority of the studies suggest that statins may have a positive role in the treatment of patients with sepsis and infection. However, the majority of the reviewed studies have the inherent methodological limitations of retrospective studies. Conclusions regarding this important clinical question should wait for the results of ongoing relevant randomized controlled trials.

Keywords: atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin, HIV, intensive care

Introduction

Sepsis is considered one of the leading causes of mortality in the hospital setting. Although some advances have been made in treating patients with sepsis, the mortality of patients with sepsis remains extremely high.1

Sepsis is a process consisting of numerous inflammatory cascades and it is initiated by the presence of bacterial toxins and results in systematic inflammation and multiple organ and tissue damage. Cytokines have a prominent role in the defence mechanisms of the host. Their production is mediated by numerous metabolic pathways, which are independent one from another.2 In order to treat sepsis effectively, intervention should be made at multiple levels, as controlling just one or two pathways does not impede the process overall.

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, namely statins, are a class of drugs used for their ability to lower cholesterol levels. Their primary indication is the prevention of cardiovascular disease. Recently, however, statins have been attributed anti-inflammatory and immunomodulatory pleiotropic effects. They inhibit the synthesis of products of mevalonate pathway such as isoprenoids and geranyl-geranylpyrophosphate.3 In addition, they modify the intercellular interactions and the cellular chemotaxis of the immune system. Furthermore, statins reduce the release of cytokines and acute-phase proteins. They demonstrate antioxidant
Evidence for statin use in infections

properties, although they reduce ubiquinone (CoQ10) levels, which is an important endogenous antioxidant. They may also exert an anti-apoptotic action, contribute to the stabilization of the atheromatic plaque, modify cell activity by inhibiting the expression of certain genes and participate in various other mechanisms of the inflammatory response.

Having all these properties, statins have been suggested as an adjunct in the treatment of patients with sepsis. Although there have been reviews regarding various aspects of statin use in patients with sepsis, to our knowledge, there has been only one limited systematic review of the evidence about their use for this indication. Thus, we sought to critically examine the relevant data from studies regarding the use of statins for the treatment of patients with sepsis.

Methods

Search strategy

We performed an electronic search through Pubmed, Scopus and the Cochrane Library databases by using the following key terms: 'statins', 'infection', 'sepsis', 'bacteraemia', 'pneumonia', 'ICU infections', 'viral infections', 'HIV', 'CMV', 'HBV', 'HCV' and/or 'HAV'. Two independent reviewers (G. C. M. and D. K. M.) performed the literature search, study selection and data extraction. There was no time, language or publication limit in our literature search, and all references from identified articles were also searched for relevant information. An online search through http://clinicaltrials.gov was also performed for ongoing randomized control trials. The end date of the review was 30 June 2007.

Study selection

We identified studies that were relevant to statins and different kinds of infection (Figure 1). Studies included in our systematic review were observational cohort studies (prospective or retrospective) or case–control studies that compared the mortality and/or morbidity in patients with different infection profiles with and without use of statins. We identified no randomized control trials. Studies that were experimental or laboratory based were excluded.

Data extraction

We extracted data about the number of patients included, study design, type of infection (sepsis, bacteraemia, pneumonia, viral and others), co-morbidity (coronary artery disease, renal failure and diabetes), population settings, clinical outcomes and the protocol followed for statin administration before, during or after hospital admission. A quality score of the retrieved studies was performed with the use of the methodological index for non-randomized studies (MINORS).

Results

We identified 20 studies regarding the use of statins and their potential clinical application in patients with infectious diseases. We also identified six randomized control trials (RCTs) in the online registry of RCTs of US National Institutes of Health. Most of these trials were in recruiting state.

Fifteen out of 20 evaluable studies were cohort studies (10 retrospective and 5 prospective), 2 were retrospective case–control studies, 1 study included both cohort and case–control methodology in an overlapping patient population and 2 were prospective with small patient numbers (1 a pilot study and 1 a placebo–control crossover study).

The evaluable studies were divided into three groups according to the type of infection: studies regarding the use of statins in patients with sepsis, bacteraemia and multiorgan dysfunction syndrome (MODS) (Table 1); in patients with pneumonia, ICU infection, and other bacterial infections (Table 2); and in patients with viral infection (Table 3). In the first group, there are nine studies (four sepsis related, four bacteraemia related

Figure 1. Flow chart of the reviewed articles.
Table 1. Clinical evidence in the use of statins for sepsis, bacteraemia and MODS

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design (no. of patients)</th>
<th>Patients settings</th>
<th>Study groups</th>
<th>Outcome</th>
<th>Conclusion</th>
<th>MINORS score of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al.</td>
<td>prospective cohort study (1041)</td>
<td>patients in hemodialysis</td>
<td>statins group</td>
<td>rates of sepsis-related hospitalizations 41/1000 patient-years</td>
<td>statins were strongly and independently associated with a reduction in the risk of hospitalization for sepsis in patients who had chronic kidney disease and were receiving dialysis</td>
<td>20/24</td>
</tr>
<tr>
<td>Martin et al.</td>
<td>retrospective cohort study (53)</td>
<td>patients admitted with sepsis</td>
<td>-16 were receiving statins</td>
<td>rate of severe sepsis 56% in hospital mortality 38% rate of cardiovascular dysfunction 38%</td>
<td>statins appear to prevent sepsis from becoming severe, most notably through prevention of sepsis-induced hypotension</td>
<td>18/24</td>
</tr>
<tr>
<td>Yang et al.</td>
<td>retrospective cohort study (454)</td>
<td>oriental population with sepsis</td>
<td>-104 receive statins&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30-day sepsis-related mortality 19.2%</td>
<td>statin therapy has little effect on the survival of sepsis in oriental people, particularly in Taiwanese</td>
<td>18/24</td>
</tr>
<tr>
<td>Hackam et al.</td>
<td>propensity matched retrospective cohort analysis (69 168)</td>
<td>hospitalization for acute coronary syndrome, ischaemic stroke, or revascularization</td>
<td>-34 584 statin users&lt;sup&gt;b&lt;/sup&gt;</td>
<td>71.2 events of sepsis per 10 000 person-years</td>
<td>statins in patients with atherosclerosis is associated with a reduced risk of subsequent sepsis</td>
<td>20/24</td>
</tr>
<tr>
<td>Schmidt et al.</td>
<td>retrospective cohort study (120)</td>
<td>inclusion criterion was an APACHE II score 20 at admission to ICU</td>
<td>-40 patients with multi-organ dysfunction syndrome (MODS) receiving statin treatment</td>
<td>28-day mortality 33% hospital mortality 35%</td>
<td>patients under statin treatment developing MODS might have a better outcome than patients without statin therapy</td>
<td>18/24</td>
</tr>
<tr>
<td>Almog et al.</td>
<td>presumed or documented acute bacterial infection</td>
<td>-82 (22.7%) statins users before admission</td>
<td>severe sepsis developed in 2.4% required ICU admission 3.7%</td>
<td>prior therapy with statins may be associated with</td>
<td></td>
<td>24/24</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population</td>
<td>Statin Group (n)</td>
<td>Non-Statin Group (n)</td>
<td>30-Day Mortality</td>
<td>60-Day Mortality</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Thomsen et al.</td>
<td>Retrospective</td>
<td>Bacteraemia in patients with and without preadmission statin use</td>
<td>176</td>
<td>5177</td>
<td>20%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Kruger et al.</td>
<td>Retrospective</td>
<td>All patients requiring hospital care for an episode of bacteraemia</td>
<td>66</td>
<td>372</td>
<td>23.1% (P = 0.022)</td>
<td>18.3% (P = 0.014)</td>
</tr>
<tr>
<td>Liappis et al.</td>
<td>Retrospective</td>
<td>Bacteraemia infections due to aerobic Gram-negative bacilli and Staphylococcus aureus</td>
<td>35</td>
<td>353</td>
<td>6%</td>
<td>28% (P = 0.002)</td>
</tr>
</tbody>
</table>

MODS, multiorgan distress syndrome; ICU, intensive care unit.

*Statin use for >30 days before and after admission.

Where prescribed a statin within 90 days of discharge.

*P* values where mentioned, refer to the comparison between the results of statin versus non-statin users, respectively.
### Table 2. Clinical evidence on the use of statins in pneumonia ICU infections and other bacterial infections

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design (no. of patients)</th>
<th>Patients settings</th>
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<th>MINORS score of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlienger et al.</td>
<td>population-based, retrospective, nested case–control analysis (134 262)</td>
<td>-55 118 patients receiving statins and/or fibrates, -29 144 patients with hyperlipidaemia not taking lipid-lowering agents, -50 000 randomly selected patients&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-1253 patients with CAP and 4838 controls</td>
<td>statin users: adjusted OR = 0.84 (95% CI: 0.61–1.17, P = 0.30) for uncomplicated pneumonia adjusted OR = 0.74 (95% CI: 0.50–1.08, P = 0.12) for pneumonia requiring hospitalization with survival death from pneumonia: statin use in 6.7% of cases versus 12.7% statin use in controls adjusted OR = 0.47 (95% CI: 0.25–0.88, P = 0.02) for fatal pneumonia</td>
<td>current use of statins was associated with a reduced risk of fatal pneumonia</td>
<td>20/24</td>
</tr>
<tr>
<td>van de Garde et al.</td>
<td>retrospective case–control study (142 175 patients with diabetes)</td>
<td>patients with a diagnosis of diabetes mellitus (type 1 and 2)</td>
<td>-4719 patients with CAP and 15 322 matched controls&lt;sup&gt;b&lt;/sup&gt;</td>
<td>statin users: crude odds ratio OR = 0.51, 95% CI: 0.37–0.68, adjusted OR = 0.49, 95% CI: 0.35–0.69 for risk of pneumonia</td>
<td>the use of statins is associated with a considerable reduction in the risk of pneumonia in diabetic patients</td>
<td>18/24</td>
</tr>
<tr>
<td>Majumdar et al.</td>
<td>population-based prospective cohort study (3415)</td>
<td>adults admitted to hospital with CAP</td>
<td>-325 statin users and 3090 non-statin users</td>
<td>statin users: mortality 8%, ICU admission 9% versus 10% mortality, 10% ICU admission for non-users adjusted OR = 1.10, 95% CI: 0.76–1.60 for risk of death or admission to ICU&lt;sup&gt;c&lt;/sup&gt;</td>
<td>statins are not associated with better outcome in patients with pneumonia</td>
<td>24/24</td>
</tr>
<tr>
<td>Mortensen et al.</td>
<td>retrospective cohort study (787)</td>
<td>patients admitted with CAP</td>
<td>receiving statins (110) not receiving statins (677)</td>
<td>statin users: 30-day mortality 0% for statin users versus 4% for non-users. adjusted OR = 0.36, 95% CI: 0.14–0.92 for risk of 30-day mortality</td>
<td>statin use was associated with decreased mortality in patients with CAP</td>
<td>18/24</td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients with hypotension or sepsis were excluded from the analysis.

<sup>b</sup> Patients with a history of statin use were excluded from the analysis.

<sup>c</sup> Patients with a history of statin use were excluded from the analysis.
### Fernandez et al.\(^{19}\) retrospective cohort study (438)

<table>
<thead>
<tr>
<th>Patients entering ICU at high risk of ICU-acquired infections</th>
<th>-38 treated with statins</th>
<th>ICU-acquired infection rate 29%</th>
<th>statin therapy is associated with worse outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>-400 not treated with statins</td>
<td></td>
<td>ICU-acquired infection rate 38% ((P = 0.3))^*</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality 61%</td>
<td></td>
<td>ICU-acquired infection rate 38% ((P = 0.03) in favour of patients not receiving statins)</td>
<td></td>
</tr>
</tbody>
</table>

### Other bacterial infection

#### Almog et al.\(^{20}\) prospective cohort study (11362)

<table>
<thead>
<tr>
<th>Patients with atherosclerotic diseases were identified and followed for up to 3 years</th>
<th>-5698 statin users and 5664 non-statin users</th>
<th>for statin users: adjusted HR = 0.37, 95% CI: 0.27–0.52 ((P &lt; 0.001)) for infection-related mortality</th>
<th>therapy with statins may reduce the risk of infection-related mortality</th>
</tr>
</thead>
</table>

#### Hauer-Jensen et al.\(^{21}\) retrospective cohort study (10782)

<table>
<thead>
<tr>
<th>Patients who underwent inguinal or ventral hernia repair</th>
<th>-1242 receiving statins and 9540 not receiving statins</th>
<th>for statin users: adjusted OR = 1.6, 95% CI: 1.03–2.44 ((P = 0.04)) for postoperative hemorrhage and hematoma</th>
<th>statins after hernia repair have an increased risk of postoperative wound haematoma/haemorrhage</th>
</tr>
</thead>
</table>

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CAP, community-acquired pneumonia; OR, odds ratio; ICU, intensive care unit; HR, hazard ratio.

*Patients without hyperlipidaemia and without lipid-lowering agents.

*Controls were randomly selected from the baseline cohort of diabetic patients without a record of pneumonia, so as to control for potential prognostic factors.

*OR after complete adjustment for confounding factors and propensity score.

*\(^P\) values where mentioned, refer to the comparison between the results of statin versus non-statin users, respectively.
<table>
<thead>
<tr>
<th>First author</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Frost et al.</td>
<td>retrospective matched cohort study (76 232) and two separate case–control studies (397 influenza and 207 chronic obstructive pulmonary disease deaths)</td>
<td>matched cohort study</td>
<td>non-statin users (57 174) statin use &lt; 4 mg/d (7 475)</td>
<td>0.73 (0.47–1.13)² 0.76 (0.51–1.13)² 0.89 (0.32–1.39)² 0.83 (0.28–1.54)²</td>
<td>this study found greatly reduced risk of mortality due to pneumonia and significantly reduced risk of influenza mortality among moderate-dose statin users</td>
<td>18/24</td>
</tr>
<tr>
<td>Horne et al.</td>
<td>prospective observational study (2315)</td>
<td>monitored patients with angiographically significant coronary arterial disease (stenosis &gt;70%) for an average of 2.4 years</td>
<td>use of statins (651) 76% CMV seropositive CRP = 2.05 mg/dL not use of statins (1664) 77% CMV seropositive CRP = 2.03 mg/dL</td>
<td>0.62 (0.43–0.91) (P &lt; 0.05) -CMV (−)/low CRP (mortality rate, 5% with statin versus 4% without statin P = 0.44; HR: 1.7; 95% CI: 0.44–6.5) -CMV (+)/low CRP (mortality rate, 2% versus 7%; HR: 0.44; 95% CI: 0.16–1.3) -CMV (−)/high CRP (mortality rate, 1% versus 8%; HR: 0.16; 95% CI: 0.02–1.2) -CMV (+)/high CRP (mortality rate, 6% versus 17%; HR: 0.42; 95% CI: 0.23–0.70)</td>
<td>there was a reduction in mortality of patients with CAD, CMV seropositivity and high CRP who were using statins</td>
<td>18/24</td>
</tr>
<tr>
<td>Moncunill et al.</td>
<td>prospective pilot study (12)</td>
<td>HIV-positive individuals treated for 8 weeks with simvastatin in the absence of antiretroviral treatment</td>
<td>-4 weeks of treatment with simvastatin</td>
<td>no significant (P = 0.56) change in the mean viral load after 4 weeks a drop in the CD4 T-cell counts was observed in five out of 10 subjects the mean CD4 T-cell count increased slightly but did not reach statistical significance no significant change (P = 0.43) in the mean viral load only one patient out of 11 had a relevant decrease (−0.55 log copies/mL), whereas three patients had an increase in their viral load</td>
<td>no anti-HIV activity was detected at subtoxic concentrations and simvastatin did not induce a significant change in the mean viral load or CD4 cell count in study patients</td>
<td>10/16</td>
</tr>
</tbody>
</table>
Evidence for statin use in infections

Studies examining the use of statins in patients with sepsis, bacteraemia or MODS (Table 1)

The maximum numbers in the study populations was 69,168 patients and 5,353, whereas the minimum number was 53 patients. Seven studies showed statistical significance in favour of the use of statins in patients with sepsis, bacteraemia or MODS regarding the rate of sepis, the rate of hospital-acquired bacteraemia and mortality, and overall hospital mortality. In the study by Yang et al., no such statistical significance was observed, and in the study by Thomsen et al., it was shown that long-term mortality was reduced in statin users and short-term survival was not significantly altered.

Clinical evidence for the use of statins in patients with pneumonia, ICU infection and other infections (Table 2)

The largest patient sample was 11,362 and the minimum 438. Three of the studies were based on patients with certain pathological backgrounds such as diabetes, atherosclerotic disease and patients with a high risk of ICU infection. Clinical evidence for patients with pneumonia. We identified four studies where the role of statins was examined in patients with pneumonia. The patients in these studies were admitted with the diagnosis of community-acquired pneumonia; in the study by van de Garde et al., the patients were also suffering from diabetes mellitus type 1 or 2. Three of these studies reported beneficial effects from the use of statins in the reduction of mortality and the risk of developing pneumonia. However, in the study by Majumdar et al., there was no difference between the two groups regarding the outcome of pneumonia or the need for admission to an ICU. In the same study, documented bacteraemia was more common in patients who did not receive statins in comparison to those who did (6% versus 3%, P = 0.03). In multivariate analysis, documented bacteraemia was an independent risk factor for mortality on admission, whereas the use of statins was not.

Clinical evidence for patients with ICU-related infections. We identified one study regarding the use of statins in patients entering the ICU at high risk for ICU-acquired infections. This study showed a statistical significance in favour of patients not receiving statins regarding the outcome and suggested that this happened probably due to underlying clinical conditions that are insufficiently considered in mortality predictors.

Clinical evidence for patients with other bacterial infections. In the study by Almog et al., the population consisted of atherosclerotic patients with various types of infections, namely lung, urinary tract, soft tissue, biliary and gastrointestinal infections. There was a statistically significant reduction in the infection-related mortality in patients who received statins before admission.
Falagas et al.

In the study by Hauer-Jensen et al., the population consisted of patients having undergone inguinal or ventral hernia repair. There was no difference between patients receiving statins and those not receiving statins as regards the risk of wound infection and delayed wound healing. Furthermore, there was a statistically significant increase in the risk of post-operative haemorrhage and haematoma for patients receiving statins.

Clinical evidence for the use of statins in patients with viral infection (Table 3)

The evaluable studies comprised patients with influenza, coronary artery disease (CAD) and cytomegalovirus (CMV) seropositivity, and patients with human immunodeficiency virus (HIV) seropositivity. In the study by Frost et al., there was a statistically significant reduction in mortality due to influenza/pneumonia in favour of the patients receiving statins in moderate doses. In the study by Horne et al., there was a statistically significant reduction regarding mortality in patients with CAD, CMV seropositivity and high C-reactive protein who were receiving statins. Two studies with small study populations showed a non-favourable effect (in one of them mortality was increased in statin users). Among the studies, decreased mortality was noted in patients with bacteraemia (2 of 2 studies). Two out of the 11 studies showed no difference in mortality and in one there was increased mortality in patients who received statins. Seven studies examined the risk of sepsis as the main outcome; six of these studies showed a decreased risk of sepsis in patients receiving statins (compared with those patients that did not receive them), whereas one study found no difference. The two studies that examined the effect of statin therapy on HIV viral load found no difference between statin and non-statin users. There is no relationship between the quality of MINORS scoring of the studies and the obtained results (regarding a favourable or non-favourable effect of statins). Specifically among the three studies that achieved a maximum MINORS score (24 out of 24), two studies showed a favourable outcome, whereas one showed a non-favourable outcome. Six studies had a MINORS score of 20 out of 24; four of them showed a favourable outcome, whereas two studies showed a non-favourable outcome. Two studies scored above the cut-off (7 with a favourable and 2 with a non-favourable effect) and 11 studies scored below the cut-off (7 with a favourable and 2 with a non-favourable effect); Spearman’s correlation was −0.06 and non-significant (0.7).

Another potential source of bias is publication bias. Since we did not perform any quantitative synthesis of the extracted data due to considerable clinical heterogeneity between the included studies regarding the use of statins for the treatment of patients with sepsis. We identified 20 studies including various population settings. The majority of the reviewed studies suggested a clinically significant superiority of statins in patients with sepsis and infection as shown by decreased mortality (8/11 studies) or decreased risk of infection (6/7 studies), while no effect was observed regarding HIV load (2/2 studies). In the reviewed studies, decreased mortality was noted in patients with bacteraemia as well as in patients with community-acquired pneumonia; the decreased risk for infection referred to decreases in the events of sepsis and risk of pneumonia. These positive effects of statins cannot be ignored. However, no definitive conclusions could be drawn from the pooled data of the available studies for several reasons. The included studies are rather heterogeneous in certain aspects such as the population setting, the number of patients included, the dosage and duration of statin administration and the type of infection of the patients. Also, the majority of the studies are either retrospective studies or case series with different methodologies, which may not allow a formal meta-analysis. Ideally, an RCT would give more insight in the role of statins in infection; prospective cohort studies would probably also allow for more accurate evaluation than retrospective cohort studies.

In our study, we sought to critically examine the data from studies regarding the use of statins for the treatment of patients with sepsis. It is suggested that patients receiving statins belong to higher socioeconomic classes than patients who do not. This means that they may have a higher education, better awareness regarding their health, they may pay more visits to GPs and be more compliant with the treatments they are administered, thus increasing the possibility for a better outcome in case of infection. Additionally, in a study by Brookhart et al., statin users were more likely to have been vaccinated against influenza virus [hazard ratio (HR): 1.21, 95% CI: 1.12–1.31] and Streptococcus pneumoniae (HR: 1.46, 95% CI: 1.17–1.83) and hence a decreased incidence of pneumonia. On the other hand, these patients usually demonstrate higher co-morbidity, which, in many cases, was the cause for the prescription of statins in the first place. In the majority of the reviewed studies that adjusted for the healthy user effect in the multivariate analysis, a favourable outcome was associated with the use of statins (Table 4). Thus, the beneficial effects of statin therapy cannot be explained by the healthy user effect alone. For example, in the study by Thomsen et al., 75% of the cost of statins was reimbursed by the respective national health service and all patients had access to the county’s seven hospitals, suggesting that the benefit observed was possibly due to the medication itself. Another potential source of bias is publication bias. Since we did not perform any quantitative synthesis of the extracted data due to considerable clinical heterogeneity between the included
Table 4. Impact of the healthy user effect on the effect of statins in sepsis

<table>
<thead>
<tr>
<th>First author</th>
<th>Potential confounders related to healthy user effect assessed</th>
<th>N of statin users (%) in the group with the potential confounder or mean of potential confounder in statin users</th>
<th>N of non-statin users (%) in the group with the potential confounder or mean of potential confounder in non statin users</th>
<th>Univariate analysis</th>
<th>Multivariate analysis (MVA) regarding the respective outcome of the study with adjustment for potential confounders</th>
<th>Propensity analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta et al.</td>
<td>Late referral to a nephrologist Dialysis sit-down rounds</td>
<td>16 (18.6) 90 (42.9)</td>
<td>41 (23.4) 47 (44.8)</td>
<td>$P = 0.14$</td>
<td>did not adjust for confounders (NS on univariate)</td>
<td>yes</td>
</tr>
<tr>
<td>Hackam et al.</td>
<td>N of outpatient clinic visits (mean)</td>
<td>35.8</td>
<td>35.7</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>yes</td>
</tr>
<tr>
<td>Schlienger et al.</td>
<td>APACHE II score</td>
<td>10.8</td>
<td>11.1</td>
<td>$P = 0.72$</td>
<td>adjusted for GP visits OR: 0.45 (0.25–0.88)</td>
<td>no</td>
</tr>
<tr>
<td>Almog et al.</td>
<td>Pre-admission antibiotic therapy</td>
<td>70 (8.5)</td>
<td>35 (12.6)</td>
<td>$P = 0.32$</td>
<td>did not adjust for confounders (NS on univariate)</td>
<td>no</td>
</tr>
<tr>
<td>van de Garde et al.</td>
<td>N of admissions (mean)</td>
<td>1.7</td>
<td>1.1</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>no</td>
</tr>
<tr>
<td>Majumdar et al.</td>
<td>N of medications (mean)</td>
<td>11.5</td>
<td>11.5</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>no</td>
</tr>
<tr>
<td>Mortensen et al.</td>
<td>N of medications (mean)</td>
<td>12 134 (35)</td>
<td>12 107 (35)</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>no</td>
</tr>
<tr>
<td>Almog et al.</td>
<td>N of medications (mean)</td>
<td>8.0</td>
<td>7.9</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>no</td>
</tr>
<tr>
<td>Frost et al.</td>
<td>N of medications (mean)</td>
<td>1086 (1.9)</td>
<td>ND</td>
<td>ND</td>
<td>adjusted for confounders HR: 0.81 (0.72–0.91)</td>
<td>no</td>
</tr>
</tbody>
</table>

$N$, number; MVA, multivariate analysis; NS, non-significant; GP, general practitioner; ND, no data; OR, odds ratio; d, days; ARB, angiotensin receptor antagonists; aConfounders were included in the calculation of the propensity score.
Falagas et al.

trials, it is not possible to assess the possibility of publication bias in mathematical terms. Although the literature search has been done in a systematic way, we cannot exclude the possibility of publication bias; this should be taken under consideration when interpreting the findings of our review.

Although statins seem to pose a useful complement in the treatment of sepsis, to draw a safe conclusion, more prospective and randomized controlled trials should be conducted. The absolute effect size of the use of statins in infections varies extensively in some of the studies; for example, the number needed to treat (NNT) to avoid one episode of sepsis is 588 in one study\textsuperscript{9} compared with six in another.\textsuperscript{11} This 100-fold difference in the NNT patients receiving statins has to be kept in mind when interpreting the results. Especially because, in the past, there have been examples of medications that seemed innovative and have been regarded for decades as useful complementary treatments for certain diseases, but evidence has shown that this is not true. A well-known example is the use of hormone therapy not only for the amelioration of menopausal symptoms but also for its cardioprotective effects in women of post-partum age. Although such drugs were administered regularly as post-menopausal supportive treatment for several years in most countries, recent data suggest that this treatment carries an excess risk of breast cancer while concurrently it does not offer cardioprotection.\textsuperscript{33,34}

The key question regarding the effect of statins in patients with sepsis remains, and a recommendation based on current clinical evidence cannot be given. It has to be acknowledged that statins did not result in a decreased rate of non-vascular death in a recent meta-analysis of RCTs involving 90,056 patients, while their positive effect on reducing vascular death was indisputable.\textsuperscript{35} In the mentioned meta-analysis, no difference regarding non-vascular causes of death was detected between statin users and non-statin users; mortality was 3.8% and 4.0% [relative risk (RR): 0.95, 95% CI: 0.91–1.12] respectively, in the comparators. In contrast, mortality due to any vascular cause was 4.7% versus 5.7% in statin and non-statin users, respectively [RR: 0.83, 95% CI: 0.79–0.87]. In addition, other pleiotropic effects of statins (e.g. on cancer) have not been verified in RCTs.\textsuperscript{36}

Future RCTs and prospective cohort studies aiming to elucidate the issue should address whether statins influence the frequency and mortality of sepsis. Specifically, the dose and duration of administration of statins for this purpose need to be clarified. The question of whether statins have to be given continuously as prophylaxis against sepsis (as is the case in primary and secondary prevention of cardiovascular disease) or whether the initiation of statin administration should occur when the infection begins has to be examined. Of even more importance, the possible adverse effects of statins in the septic patient, if any, have to be examined as well, to detect whether the frequency of muscle involvement or liver involvement due to sepsis per se and due to a variety of factors in the ICU setting are augmented.

Currently there are six clinical trials recruiting patients in order to examine the potential clinical benefit from the use of statins in infection. Three of them examine the use of statins in patients with sepsis; two studies are in Phase II\textsuperscript{26,27} and one in Phase IV.\textsuperscript{28} Furthermore, three studies examine the potential benefit of statin use in patients with viral infections. One of them examines patients with HIV (Phase II)\textsuperscript{29} and two examine patients with hepatitis C infection (Phase II).\textsuperscript{30,31} It is obvious that there is a substantial effort from the scientific community to find evidence concerning this issue.

Conclusion

There is an increasing interest about the use of statins for other purposes apart from their original one. Part of this trend is the hypothesis that statins might play a role in the prophylaxis and treatment of infections. The majority of the existing evidence seems to support this hypothesis in different kind of infections. However, these studies are mainly retrospective and have several limitations. There is a need for prospective studies and randomized controlled trials in order to draw a safe conclusion regarding the consideration of statins as useful complementary agents in the treatment of sepsis and infection.

Summary points

- Statins are the treatment of choice in the majority of patients with hyperlipidaemia. Basic science studies show that there is a rationale for their clinical use in sepsis.
- In the majority of the reviewed studies, statins had a beneficial effect in sepsis (mortality or risk of infection is decreased in statin users in comparison to non-users).
- However, there are several methodological issues that limit the interpretation of the reviewed studies.
- Clinical decision-making should wait for the results of the ongoing RCTs.

Transparency declarations

None to declare.

References

Evidence for statin use in infections


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