Statin use does not affect the outcome of acute infection: a prospective cohort study

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Summary

Statins are used to prevent atherosclerosis because of their hypolipemic effects. In vitro testing and murine models suggest that statins may affect outcome in sepsis. Our meta-analysis of epidemiological studies in humans confirms that previous statin use appears to have a protective effect on infection rates and outcomes. The studies considered, however, were very different and heterogeneity was high, especially for mortality criteria.

Objective > To compare outcome for current statin users and nonusers hospitalized with fever, under pragmatic circumstances.
Design > Prospective cohort study.
Setting > University Hospital of Brest (France).
Participants > Febrile (>38 °C) patients older than 40 years, admitted to the hospital on an emergency basis in 2005. Patients’ outcome was compared according to their exposure to statins (current user or nonuser).
Main outcome measures > Mortality, length of hospitalization, admission to ICU and to convalescent homes
Results > Of 40 343 patients referred for admission by the emergency department in 2005, 964 patients older than 40 years had a fever higher than 38 °C and were included in the study. Statin-user status, however, was available for only 921. The ICU admission

Résumé

Absence d’impact de l’exposition aux statines lors d’une infection


Objectif > Comparer l’évolution des patients fébriles dans un service d’urgence en fonction de l’existence d’un traitement par statines en cours ou non.
Design > Cohorte observationnelle prospective.
Lieu > Service des urgences du Centre hospitalier universitaire de Brest.
Participants > patient de plus de 40 ans, fébrile (>38 °C) admis en hospitalisation en 2005.
Cas > patients sous traitement par statines à l’admission.
Contrôles > les autres.
Statin use does not affect the outcome of acute infection: a prospective cohort study

Statins are used to prevent atherosclerosis due to their hypolipemic effects. They also have several endothelial effects, which may play a role in sepsis settings. Murine models [1–4] have been used to study the potential impact of statins in outcomes of bacterial infection. We performed a meta-analysis (unpublished) of the epidemiological studies in humans that meet standard meta-analysis criteria [6–28]. This meta-analysis (figure 1) suggests that prior statin use has a protective effect:

- on the infection rate (relative risk (RR) and 95% confidence interval (CI), used as a criterion of global efficacy with an accepted alpha risk: 5% 0.85 (0.77-0.93)) but the heterogeneity, calculated by Cochran’s Q test (accepted alpha risk: 10%), between studies must be pointed out (p=10^-4 and a variability due to chance (I^2)=83%);
- on mortality (RR: 0.66 (0.59-0.74)), with the same heterogeneity (p=<10^-9 and I^2=94%);
- on mortality associated with infection (RR: 0.22 (0.17-0.30)), without heterogeneity (I^2= 0%; Q test: p=0.65), but with only four studies (12 188 patients) included in the analysis;
- on admission to intensive care units (ICU), although this rate did not reach statistical significance (RR: 0.88 (0.76-1.02); I^2=34%; Q test p=0.16).

Thus, statin use might induce a favorable infection outcome in humans. Nonetheless, these studies differed greatly in their design, population type and size, setting, infection, outcome criteria, assessment period and statin exposure. We therefore conducted a prospective study to examine the effect of statin use under pragmatic circumstances, by studying the outcome for febrile patients older than 40 years admitted through the emergency department.

**Methods**

This single-center prospective cohort was conducted at a tertiary health center (University Hospital of Brest, France) from January 2005 to December 2005. The study included all emergency department patients older than 40 years admitted to the hospital during the study period with a temperature of 38°C or more. We defined 2 groups: the current statin users (patients under statin treatment at admission) and the patients not receiving statin treatment at admission. We collected the following data: age, gender, statin status, corrected (+0.5°C) tympanic temperature at admission, and type and results of bacteriological

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**What was known?**

- Statins used to prevent atherosclerosis have several endothelial effects.
- In vitro studies and murine models have suggest that statins may affect sepsis outcome
- The results of epidemiological studies in humans are inconsistent

**What this study adds?**

- Our meta-analysis of human studies confirms that prior statin use has a protective effect on infection rates and outcomes.
- Our prospective study does not confirm this effect.
- It suggests that the favorable effect of statins may be due to extremely cautious care or to nonspecific cardiovascular prevention.
<table>
<thead>
<tr>
<th>Ref</th>
<th>Years</th>
<th>n</th>
<th>Design</th>
<th>Statins exposed, %</th>
<th>Age mean, y</th>
<th>Population</th>
<th>Male gender, %</th>
</tr>
</thead>
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<tr>
<td>[17]</td>
<td>1997-2001</td>
<td>141487</td>
<td>R</td>
<td>33</td>
<td>74.1</td>
<td>Pneumonia</td>
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<td>[8]</td>
<td>438</td>
<td>R</td>
<td>8.7</td>
<td>62.4</td>
<td>Mechanical ventilation&gt;96h</td>
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<td>[19]</td>
<td>2000-2002</td>
<td>3360</td>
<td>R</td>
<td>15%</td>
<td>77</td>
<td>Pneumonia</td>
<td>50.8</td>
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<td>[21]</td>
<td>2003-2004</td>
<td>2036</td>
<td>P</td>
<td>23.3</td>
<td>61</td>
<td>Infection Hospital admission</td>
<td>51.7</td>
</tr>
<tr>
<td>[26]</td>
<td>2000</td>
<td>3018</td>
<td>R</td>
<td>15.9</td>
<td>74.4</td>
<td>Sepsis with hospital admission</td>
<td>98.6</td>
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<tr>
<td>[27]</td>
<td>2000</td>
<td>8652</td>
<td>R</td>
<td>18.1</td>
<td>75</td>
<td>Pneumonia with hospital admission</td>
<td>98.6</td>
</tr>
</tbody>
</table>

- **Exposed / non exposed studies**

<table>
<thead>
<tr>
<th>Ref</th>
<th>Years</th>
<th>n</th>
<th>Design</th>
<th>Statins exposed, %</th>
<th>Age mean, y</th>
<th>Population</th>
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<tr>
<td>[10]</td>
<td>1997-2002</td>
<td>5353</td>
<td>R</td>
<td>3.2</td>
<td>72</td>
<td>Bacteremia</td>
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<td>[12]</td>
<td>2000-2001</td>
<td>454</td>
<td>R</td>
<td>22.9</td>
<td>64</td>
<td>Sepsis</td>
<td>54.6</td>
</tr>
<tr>
<td>[14]</td>
<td>2003</td>
<td>361</td>
<td>P</td>
<td>22.7</td>
<td>69.7</td>
<td>Skin, Lung or Urinary infection</td>
<td>48.5</td>
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<tr>
<td>[16]</td>
<td>2000-2002</td>
<td>3415</td>
<td>P</td>
<td>10</td>
<td>69.6</td>
<td>Pneumonia</td>
<td>52.7</td>
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<tr>
<td>[18]</td>
<td>1987-2001</td>
<td>20041</td>
<td>R</td>
<td>23.5</td>
<td></td>
<td>Diabetes</td>
<td></td>
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<tr>
<td>[19]</td>
<td>1986</td>
<td>447</td>
<td>P</td>
<td>10.2</td>
<td>50</td>
<td>Hajj pilgrims</td>
<td>56.9</td>
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<tr>
<td>[22]</td>
<td>2001-2002</td>
<td>22174</td>
<td>P</td>
<td>9.3</td>
<td>70.2</td>
<td>General population</td>
<td>46.1</td>
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<tr>
<td>[23]</td>
<td>1997-2005</td>
<td>7733</td>
<td>R</td>
<td>34</td>
<td>64.9</td>
<td>Cardiac surgery</td>
<td>77</td>
</tr>
<tr>
<td>[28]</td>
<td>2004-2006</td>
<td>1934</td>
<td>P</td>
<td>64.5</td>
<td>66.3</td>
<td>Cardiac bypass graft</td>
<td>71.3</td>
</tr>
</tbody>
</table>

- **Mortality**

- **Infection related mortality**

- **ICU admission**

- **Infection**

RR: 0.66 (0.59-0.74) 0.22 (0.17-0.30) 0.88 (0.76-1.02) 0.85 (0.77-0.93)
testing. The team providing patient care was unaware of the study objectives.

Our outcome criteria, used in most previous studies, included the rates of mortality (defined as death during the course of hospitalization) and ICU admission. We decided not to use infection-associated mortality due to infection because of its subjective nature. We also included two indirect criteria of severity: length of hospitalization and convalescent home admission rate.

The statistical analysis used logistic regression to compare the continuous variables and a two-tailed Fisher’s exact test for binary variables. The sample was also divided into binary strata for separate analysis according to median age, median temperature at admission, gender, and bacteriological results.

The results showed that ICU admission was significantly higher among the patients using statin at admission (relative risk: 4.69; 95% CI: 2.42; 9.08), but statin use was not associated with hospital mortality (relative risk: 0.98; 95% CI: 0.47; 2.03), with length of hospital stay (effect size: -0.13; 95% CI: -0.3; 0.1), or with convalescent home admission (relative risk: 0.79; 95% CI: 0.53; 1.18).

In the strata defined by age, gender, temperature and bacteriological findings, only hospital mortality and convalescent home admission were significantly lower among the patients with negative bacteriological findings or with fever lower than 38.5 °C. The impact of statin use on ICU admission disappeared in the stratum of patients older than 74 years.

**Results**

Of the 40 343 patients referred for admission from the emergency department in 2005, 964 patients were older than 40 years and had fever higher than 38 °C and were thus eligible for inclusion. Statin use status, however, was available for only 921. The 43 patients for whom statin status was missing accounted for less than 5% of the population, and their principal characteristics did not differ from the patients who were included (data not shown).

The statin group included 139 patients and the unexposed group 782. The groups did not differ significantly for age, temperature, gender, or bacteriological findings.

**Figure 2**

Design and results of our prospective cohort study that compared the following outcome criteria (mortality rate, length of hospitalization, admission to the intensive care unit and to a convalescent home) between statin users and nonusers under pragmatic circumstances: Patients older than 40 referred for admission from the emergency department with a fever (>38 °C). The analysis (alpha risk: 5%) used Fisher’s exact test (binary variables) or logistic regression (continuous variables) before and after stratification according to age (median), temperature (median), gender and bacteriological results.
Discussion

This prospective cohort study did not confirm any effect of statin use on outcome in patients with sepsis. The higher rate of ICU admission, unaccompanied by any increase in mortality or length of hospitalization, may be explained by more cautious care for patients treated with statins. In open studies, even if the staff is unaware of the study purpose, as here, one cannot ensure that cases and controls receive the same care. Thus, mortality during the ICU stay could be higher in the statin group at the same time as it is lower during the overall hospitalization [8]. Some authors [7] suggest comparing prescribed antibiotic therapy (dose and regimen), but we do not think that this step is sufficient to avoid this bias and did not collect these data. This more cautious care for statin users probably existed before hospitalization and includes the prescription of other treatments against atherosclerosis [22,26]. Some of these can affect the outcome of infection [27]. Two studies, with cases and controls who had the same estimated cardiovascular risk [7,17], could not rule out the hypothesis that the reduction in hospitalization among statin users might be due to better primary care, even though outpatient antibiotic therapy was similar. It should be noted that in France, 81.9% of statin users receive at least one other cardiovascular treatment [29]. None of the cardiovascular treatments, alone or included in regression models, have showed any interaction in the relation between statin use and infection outcome [7,9,11,14]. On the other hand, most of the studies have shown that statin users have a higher level of cardiovascular risk factors, including age [16] and diabetes [6-8,10,13,14,22]. At the same time, however, nonusers had a higher prevalence of non-cardiovascular diseases (pneumonia/soft tissue infection [9], cirrhosis, hyperbilirubinemia or alcohol abuse [6,13], hypoalbuminemia [7,11], trauma [8], hemodialysis modality [6], hypercreatinemia [14], etc.). That is a common bias linked to this incidence-based design even though the study results did not change after adjustment [7,9,10,14,17] or propensity-matched analysis [6,17]. Our results were not consistent with most previous studies. Nonetheless, inclusion of our data in our meta-analysis did not change the primary results (data not shown). As pointed out above, however, the studies differed greatly in their designs, populations and outcome criteria (figure 1). Hence, when considering death within the first 30 days after inclusion, rather than afterwards, the impact of statin use is reported to be favorable [10]. The type of infection acquired in the hospital or community may directly affect the results: the survival rate in the statin group is significantly higher in the first case but not in the second [8,9]. Furthermore, maintenance of prior statin therapy during infection appears to play a central role [11], unlike dose or regimen [17]. We did not verify whether statin treatment was interrupted after admission, this could account for our negative results.

Finally, the impact of statin use on mortality has not been proved to be due solely to infectious circumstances. During sepsis, patients not receiving statins might be exposed to unrecognized, cardiovascular risk situations. A meta-analysis [30] has confirmed the protective effect of statin use on mortality after cardiovascular surgery (2.2 vs 3.2%, p=0.0001); this effect is due above all to a decrease in cardiovascular disease and not in infectious disease. This finding indicates the need to continue statin therapy during physiological aggression including infection, even if the favorable impact of prior statin therapy might be explained by the application of especially cautious care, before and during the hospital stay, and not by a specific protection effect against infection. The possible relevance of initiating statin therapy in patients at high cardiovascular risk during infection requires interventional studies designed with this objective in mind.

Conflict of interest: none

References

[11] Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G. Statins therapy is associated with...