A Multicenter Randomized Trial of Atorvastatin Therapy in Intensive Care Patients with Severe Sepsis

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Rationale: Observational studies link statin therapy with improved outcomes in patients with severe sepsis.

Objectives: To test whether atorvastatin therapy affects biologic and clinical outcomes in critically ill patients with severe sepsis.

Methods: Phase II, multicenter, prospective, randomized, double-blind, placebo-controlled trial stratified by site and prior statin use. A cohort of 250 critically ill patients (123 statins, 127 placebo) with severe sepsis were administered either atorvastatin (20 mg daily) or matched placebo.

Measurements and Main Results: There was no difference in IL-6 concentrations (primary end point) between the atorvastatin and placebo groups (P = 0.76) and no interaction between treatment group and time to suggest that the groups behaved differently over time (P = 0.26). Baseline plasma IL-6 was lower among previous statin users (129 [87–191] vs. 244 [187–317] pg/ml; P = 0.01). There was no difference in length of stay, change in Sequential Organ Failure Assessment scores or mortality at intensive care unit discharge, hospital discharge, 28- or 90-day (15% vs. 19%), or adverse effects between the two groups. Cholesterol was lower in patients treated with atorvastatin (2.4 [0.07] vs. 2.6 [0.06] mmol/L; P = 0.006). In the predefined group of 77 prior statin users, those randomized to placebo had a greater 28-day mortality (28% vs. 5%; P = 0.01) compared with those who received atorvastatin. The difference was not statistically significant at 90 days (28% vs. 11%; P = 0.06).

Conclusions: Atorvastatin therapy in severe sepsis did not affect IL-6 levels. Prior statin use was associated with a lower baseline IL-6 concentration and continuation of atorvastatin in this cohort was associated with improved survival.

Clinical trial registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12607000028404).

Keywords: statin; 3-hydroxy-3-methylglutaryl CoA reductase inhibitor; sepsis; critical illness; mortality

Severe sepsis is a common intensive care unit (ICU) admission diagnosis and consumes vast healthcare resources (1–3). Despite improvements in cardiovascular resuscitation, antibiotic therapy, and source control measures (4) mortality continues to remain high. The need for new effective adjunctive therapy, therefore, remains strong.

Severe sepsis is characterized by a marked inflammatory response to infection (5, 6) and efficacious new adjunctive therapies seem likely to involve immune-modulating properties (5). Animal studies and observational human studies suggest that statins possess antiinflammatory, antioxidant, and immune-modulating effects that may attenuate the inflammatory response to sepsis (7–9). Moreover, a retrospective study suggested that continued statin therapy was associated with fewer deaths in patients with bacteremia (10). However, continued statin therapy in observational studies may simply be a surrogate for decreased illness severity. Thus, better outcomes may reflect bias rather than a true beneficial effect. In addition, statin toxicity in the critically ill might be greater than that...
See in the general population (11). As a result, there is uncertainty about the balance of risks and benefits of administering statins de novo or continuing statin therapy in patients with sepsis.

These observations would support the need for a large phase III randomized controlled trial. However, given disappointing findings with interventions in critically ill not previously tested in phase II work (12–14), more robust double-blinded evidence of possible benefit is needed to justify the cost of such a trial. Accordingly, we conducted a prospective, randomized double-blind, placebo-controlled, phase II trial to assess the effects of 20 mg of atorvastatin on biologic and clinical outcomes in adult intensive care patients with severe sepsis.

METHODS

Study of Atorvastatin Therapy In Sepsis was a randomized double-blind, placebo-controlled, phase II trial designed to assess the biologic and clinical effects of atorvastatin therapy in critically ill patients with severe sepsis. The study was conducted in 21 ICUs across Australia and New Zealand between July 2007 and August 2010. It was registered with the Australian and New Zealand Clinical trials registry and endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group. The study was approved by the relevant human research ethics committee for each participating hospital and individual consent was obtained for all patients, either from the patient or the next of kin. The integrity of the data collection was independently verified by site visits from the project management monitoring team.

Study Population

Patients were eligible for enrolment if they were critically ill; aged between 18 and 90 years; had strongly suspected or proved infection; fulfilled three or more of the features of systemic inflammatory response syndrome (15) within the 48 hours before randomization; and had an organ dysfunction of less than 24 hours duration (as defined in Appendix 1). Patients were excluded from the study if they were moribund or not expected to survive 28 days because of an underlying irreversible medical condition; were pregnant or breast feeding; had a known intolerance to statins or were unable to have enteral administration of study drug; had severe liver disease (acute liver failure, chronic liver disease Child-Pugh classification C); had a serum alanine amino transferase (ALT) level greater than five times the normal value or a serum creatinine kinase level (CK) level greater than 10 times the upper limit of normal; had commenced statin therapy less than 2 weeks before hospital admission; had drug-induced hepatitis; or if a serum CK level became greater than twice the initial value. For patients with a serum ALT concentration less than or equal to 110 IU/L on admission, therapy was discontinued if the level rose to more than five times the upper limit of normal.

Blood samples were collected at baseline and on study Days 1, 3, 5, 7, 10, and 14 for the measurement of C-reactive protein (CRP), lipid profile, ALT, CK, routine biochemistry, and hematology, all of which were measured at individual centers. A series of the samples (lithium heparin, ethylenediaminetetraacetic acid, citrate) were centrifuged and stored in aliquots frozen at −80°C for later analysis. Samples were collected for plasma drug concentrations on each of these days before dosing and then on two occasions after dosing on each of the study days. The first post-dose level was performed at 30 minutes after administration. A second post-dose sample was collected between 1 and 6 hours.

Serum lipid profiles and CRP were assessed using enzymatic methods and immunoturbidimetric assays, respectively. Frozen samples were transferred in batches to a central laboratory for batch assay. IL-6 was assayed by immunoassay (Jomar Bioscience Limited, Kingston, South Australia). The lower limit of quantification was 2 pg/ml. These assays were performed in duplicate by the same individual, in the same laboratory. For quality control, random samples were repeat assayed between batches. Plasma atorvastatin and its metabolites were assayed by a previously described technique (16).

Study Outcomes

The primary outcome was plasma IL-6 levels, which were compared over time between patients who did versus those who did not receive statin therapy. Secondary outcomes included CRP, lipid profile, plasma atorvastatin and its metabolites levels, and clinical outcomes including a modification (no Glasgow Coma Score component) of the Sequential Organ Failure Assessment (SOFA) Score (17); ICU and hospital mortality; and length of stay and both 28- and 90-day mortality.

Statistical Analysis

Sample size calculations were based on a previous study of severe sepsis (18), where the standard deviation for log (IL-6) was found to be approximately equal to 0.67 units. To remain conservative, this study was powered to detect an effect size that was 25% lower than previously observed. With 120 patients per group this study had more than 95% power to detect a difference between groups in log (IL-6) equal to 0.5 units with a two-sided P value of 0.05. A difference of this magnitude was perceived to be of biologic importance. To allow for loss to follow-up, a total of 250 subjects were recruited.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Data were initially assessed for normality and log-transformed where appropriate. Baseline comparisons were performed using chi-square tests for equal proportion or Fisher exact test where numbers were small with results presented as percentages (n). Continuously normally distributed variables were compared using Student t test and presented as means (standard deviations), whereas nonnormally distributed data were compared using Wilcoxon rank-sum test and reported as medians (interquartile range). IL-6 levels were found to be well approximated by a log-normal distribution. As such, the predefined longitudinal analysis of the primary outcome was performed using mixed linear modeling of log IL-6 with each patient treated as a random effect. To account for any baseline imbalances, additional analyses were performed with imbalanced variables included as covariates. Sensitivity analysis for secondary binomial outcomes (mortality) were also performed using logistic regression; however, because there were insufficient data to simultaneously adjust for all imbalanced variables, covariate adjustment was done on an individual basis. All analysis was performed on an intention-to-treat basis and a two-sided P value of 0.05 was considered to be statistically significant. Randomization was stratified by prior statin use and analysis was performed according to the presence or absence of preexisting statin therapy.

RESULTS

A total of 1,723 patients were screened and 250 randomized, 123 to atorvastatin and 127 to placebo (Figure 1). A total of 77 patients (30.8% of the cohort) were on prior statin therapy
(37 randomized to treatment, 40 to placebo), whereas 173 were allocated to receive de novo therapy (86 randomized to atorvastatin and 87 to placebo).

Baseline Characteristics

The demographic characteristics of the entire cohort and predefined subgroups are presented in Table 1. There was a statistically significant age difference at baseline between the treatment and placebo groups (58 [44–67] vs. 64 [50–75] yrs; P = 0.005). Statistically significant differences also existed at baseline for platelet count, use of unfractionated heparin, and occurrence of chronic obstructive airways disease. The source of infection was not different between the groups (Table 2).

Bacteremia was proved in 31% of patients with no difference between the groups (35% [43] atorvastatin vs. 28% [35] placebo; P = 0.22). Patients that were prior statin users were older and had more coexisting disease at baseline compared with nonusers.

Intervention

After trial drug administration, there was a significant difference in plasma atorvastatin concentration between the groups (P < 0.0001). A plasma level of greater than 10 ng/ml (an accepted plasma level after 20 mg dosing for cholesterol lowering [19]) was seen in 87% of the samples from the atorvastatin group compared with 1.6% from the placebo group (P < 0.0001). Post-dose plasma levels were consistently greater than 20 ng/ml on all study days as opposed to generally unrecordable levels in the placebo group and this was statistically significant (P < 0.0001). All recordable plasma levels in the placebo group were from prior statin users.

Study duration was similar for both groups (atorvastatin 6 [4–10] vs. placebo 6 [3–13] d; P = 0.5). Patients in both groups received the same number of doses of study medication (atorvastatin 4 [2–8] vs. placebo 4 [2–10]; P = 0.84). The protocol criteria for administration or withholding of study drug was correctly followed on 97% of occasions, with most missed doses reflecting withheld medication as dictated by protocol caused by increased ALT or CK levels.
TABLE 1 DEMOGRAPHICS FOR THE ENTIRE COHORT AND PRESPECIFIED SUBGROUPS STRATIFIED AT RANDOMIZATION

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire Cohort</th>
<th></th>
<th>De Novo = No Prior Statin Use</th>
<th></th>
<th>Prior Statin Use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>P Value</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>(n = 123)</td>
<td>(n = 127)</td>
<td></td>
<td>(n = 86)</td>
<td>(n = 87)</td>
<td></td>
</tr>
<tr>
<td>Male sex, % (n)</td>
<td>59 (73)</td>
<td>65 (82)</td>
<td>0.40</td>
<td>60 (52)</td>
<td>66 (57)</td>
<td>0.49</td>
</tr>
<tr>
<td>Age, yrs median (IQR)</td>
<td>58 (44–67)</td>
<td>64 (50–75)</td>
<td>0.005</td>
<td>56 (43–66)</td>
<td>60 (47–75)</td>
<td>0.10</td>
</tr>
<tr>
<td>Admission source: emergency department, % (n)</td>
<td>50 (61)</td>
<td>49 (62)</td>
<td>0.99</td>
<td>44 (38)</td>
<td>49 (43)</td>
<td>0.49</td>
</tr>
<tr>
<td>Bloodstream infection, % (n)</td>
<td>35 (43)</td>
<td>28 (35)</td>
<td>0.74</td>
<td>35 (30)</td>
<td>27 (24)</td>
<td>0.62</td>
</tr>
<tr>
<td>Preexisting conditions, % (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Coexisting disease</td>
<td>76 (93)</td>
<td>77 (98)</td>
<td>0.77</td>
<td>66 (57)</td>
<td>69 (60)</td>
<td>0.70</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26 (32)</td>
<td>28 (35)</td>
<td>0.78</td>
<td>14 (12)</td>
<td>16 (14)</td>
<td>0.70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (43)</td>
<td>38 (48)</td>
<td>0.78</td>
<td>23 (20)</td>
<td>24 (21)</td>
<td>0.90</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>19 (23)</td>
<td>15 (19)</td>
<td>0.43</td>
<td>5 (4)</td>
<td>3 (3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>12 (15)</td>
<td>13 (17)</td>
<td>0.78</td>
<td>10 (9)</td>
<td>10 (9)</td>
<td>0.98</td>
</tr>
<tr>
<td>Renal failure</td>
<td>11 (14)</td>
<td>16 (20)</td>
<td>0.31</td>
<td>8 (7)</td>
<td>10 (9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>9 (11)</td>
<td>20 (26)</td>
<td>0.01</td>
<td>7 (6)</td>
<td>20 (17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Indicators of disease severity, % (n)</td>
<td>13 (18)</td>
<td>8 (10)</td>
<td>0.08</td>
<td>15 (13)</td>
<td>7 (6)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Definition of abbreviations: APACHE – Acute Physiology and Chronic Health Evaluation; GCS – Glasgow Coma Score; IQR – interquartile range; SOFA – Sequential Organ Failure Assessment.

Primary Outcome

As shown in Figure 2, there was no overall difference in plasma IL-6 between groups (P = 0.76) and no significant interaction between group and time (P = 0.26). Results remained similar after adjustment for baseline imbalance was performed (see Figure E1 in the online supplement). IL-6 levels were strongly related to ICU mortality, 28- and 90-day mortality, and SOFA score (P < 0.0001 for each).

There was a statistically significant difference in IL-6 at baseline between prior statin users and nonusers (prior users 129 [87–191] vs. nonusers 244 [187–317] pg/mL; P = 0.01) (Figure 3). After multivariate adjustment for baseline differences in age, weight, coexisting disease, and Acute Physiology and Chronic Health Evaluation II score (see Table E2), baseline IL-6 levels still remained significantly lower in prior statin users (geometric mean [95% confidence interval (CI)], 110 [66–185] vs. 208 [149–291] pg/mL; P = 0.046). However, for prior statin users, there was no significant difference in IL-6 during treatment between atorvastatin and placebo groups (overall geometric mean [95% CI] 32.1 [18.9–54.6] vs. 37.4 [22.2–63] pg/mL; P = 0.68), with no significant interaction between group and time (P = 0.46). For patients receiving de novo statin therapy, there was also no significant difference in IL-6 between treatment groups (overall geometric mean [95% CI] 38.6 [27.0–55.0] vs. 39.4 [28.5–54.6]; P = 0.91) and no significant interaction between group and time (P = 0.37). These findings remained similar after adjustment for baseline imbalances.

Secondary Outcomes

Clinical outcomes. Between group comparisons for mortality and length of stay are presented in Table 3. For the cohort as a whole there was no statistically significant difference in ICU, hospital, 28- or 90-day mortality, or length of stay between the groups. Results remained similar after adjustment for baseline imbalances (Table 3, see Table E1).

Continued atorvastatin therapy in prior statin users was associated with a statistically significant improvement in 28-day mortality (5% [2 of 37] vs. 28% [11 of 40]; P = 0.01). The difference was not statistically significant at 90 days (28 vs. 11%; P = 0.06). These results remained similar after adjustment for baseline characteristics (Table 3, see Table E1).

TABLE 2 SUSPECTED SOURCE OF INFECTION AT TIME OF RANDOMIZATION (MORE THAN ONE POSSIBLE)

<table>
<thead>
<tr>
<th>Suspected source of sepsis</th>
<th>Entire Cohort</th>
<th></th>
<th>De Novo = No Prior Statin Use</th>
<th></th>
<th>Prior Statin Use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>P Value</td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>P Value</td>
</tr>
<tr>
<td></td>
<td>(n = 123)</td>
<td>(n = 127)</td>
<td></td>
<td>(n = 86)</td>
<td>(n = 87)</td>
<td></td>
</tr>
<tr>
<td>Lung, % (n)</td>
<td>46 (56)</td>
<td>49 (62)</td>
<td>0.6</td>
<td>45 (39)</td>
<td>52 (45)</td>
<td>0.4</td>
</tr>
<tr>
<td>Urine, % (n)</td>
<td>24 (30)</td>
<td>28 (36)</td>
<td>0.48</td>
<td>28 (24)</td>
<td>26 (23)</td>
<td>0.84</td>
</tr>
<tr>
<td>Soft issue, % (n)</td>
<td>8 (10)</td>
<td>8 (10)</td>
<td>0.94</td>
<td>5 (4)</td>
<td>9 (8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Central nervous system, % (n)</td>
<td>6 (7)</td>
<td>4 (5)</td>
<td>0.52</td>
<td>5 (5)</td>
<td>3 (3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Intraabdominal, % (n)</td>
<td>12 (15)</td>
<td>16 (20)</td>
<td>0.42</td>
<td>13 (11)</td>
<td>14 (12)</td>
<td>0.85</td>
</tr>
<tr>
<td>Wound, % (n)</td>
<td>16 (20)</td>
<td>9 (12)</td>
<td>0.11</td>
<td>13 (11)</td>
<td>6 (5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other, % (n)</td>
<td>11 (13)</td>
<td>8 (10)</td>
<td>0.46</td>
<td>14 (12)</td>
<td>7 (6)</td>
<td>0.13</td>
</tr>
</tbody>
</table>
De novo therapy was not associated with a significant difference in mortality (Table 3). However, it was associated with a small reduction in ICU length of stay (5.7 [3.1–9.0] vs. 8.5 [3.0–14.1] d; P = 0.03) but not in hospital length of stay (17.8 [9.9–38.7] vs. 23 [12.6–37.9] d; P = 0.37). There was no difference in SOFA Score between the groups either for prior statin users (P = 0.88) or those with de novo therapy (P = 0.70) (Figure 4).

Biologic outcomes. There was no difference in CRP between the groups (P = 0.17) and no significant difference in the pattern of change over time (P = 0.17). The cholesterol concentration was lower in the treatment group during the study period (2.4 [0.07] vs. 2.6 [0.06] mmol/L; P = 0.006) (Figure 5). This pattern persisted after adjustment for baseline differences. High-density lipoprotein was much lower than normal reference values in both groups with a mean (SD) concentration of 0.53 (0.03) mmol/L in the atorvastatin group and 0.51 (0.02) mmol/L in the placebo group. No difference in high-density lipoprotein was seen between groups (P = 0.46) and the pattern of change over time was similar between treatment and placebo (P = 0.50).

For patients with no prior statin use cholesterol was significantly lower in the atorvastatin patients (P = 0.001) with no difference in the pattern of change over time (P = 0.30) (see Figure E2). No such difference was seen for the prior use group (between groups [P = 0.57] and over time [P = 0.51]).

Adverse effects. Study drug was ceased for adverse effects in 12.2% (95% CI, 6.42–17.98%) of patients (15 of 123) in the atorvastatin group and 13.4% (95% CI, 7.48–19.32%) of patients (17 of 127) in the placebo group (P = 0.85). No adverse events or serious adverse events were reported as definitely related to study medication. One rise in ALT was reported as probably related to study medication (placebo). A total of 44 adverse events or serious adverse events were reported as possibly related to study medication (20 treatments, 24 placebos).

There was no significant difference between groups overall in ALT and CK levels during the study period (P = 0.74 and P = 0.85, respectively) and no significant interaction between group and time (P = 0.21 and P = 0.17, respectively). CK levels greater than 10,000 were only recorded on two occasions during the study (both patients received placebo).

DISCUSSION

Key Findings

We conducted a phase II placebo-controlled multicenter double-blind randomized trial to investigate the effects of enteral atorvastatin on biologic and clinical end points in critically ill patients with severe sepsis. We found that despite adequate blood levels, atorvastatin therapy did not affect IL-6 levels but that prior statin use was associated with lower baseline IL-6 levels. Additionally, continued use of atorvastatin therapy in prior statin users was associated with improved 28-day survival. Finally, during the episode of sepsis, de novo atorvastatin therapy and atorvastatin therapy in prior statin users were not associated with an increase number of adverse events.

Relationship to Previous Studies

Thousands of patients develop severe sepsis every day (4) and millions of patients receive statins every day (20). Statin therapy may improve the outcome of sepsis (9, 21). Because of the numbers involved this issue is of major public health significance. Statins have been shown in human and animal in vitro and in vivo studies to have immunomodulating properties (pleiotropic effects) (22, 23). This suggests a potential benefit of continued administration or de novo use in sepsis. Several observational studies involving continued administration of the drug in prior users have linked statin therapy with improved outcomes (24, 25). However, in a previous randomized trial there was no difference in the regression of severe sepsis or changes in IL-6 with continued atorvastatin use in prior statin users (26). Only a minority of these patients was critically ill and the observational data have limited information on baseline
illness severity. Furthermore, de novo therapy with statins in septic patients has not been studied. Finally, several observations justify concerns about the safety of statin therapy in critically ill patients (11, 27–29).

**Study Significance**

Our study suggests no biologic effect of de novo statin use on a major marker of inflammation (IL-6) in sepsis. However, it also raises the possibility that established statin therapy may attenuate this biologic response. This observation is consistent with studies in human volunteers injected with LPS and pretreated with statins (30) and was not explained by lower illness severity at randomization in prior statin users.

We hypothesized that continuing or stopping established statin therapy might have different effects to de novo use, hence the stratification at randomization. In keeping with this hypothesis and in contrast with de novo users, atorvastatin therapy in prior statin users was associated with improved survival. Our data also provide some preliminary evidence of safety regarding continuing statins in critically ill patients, because the side effect profile was similar between the two groups. Our findings suggest that atorvastatin therapy in prior statin users is safe and potentially beneficial.

The presence of a baseline imbalance in age despite randomization was a limitation. Accordingly, we adjusted for such confounders in our statistical analysis and the overall results remained unchanged. IL-6 levels in this study were found to be higher and exhibited more variability than previously reported in patients with sepsis (18). Although a retrospective review of the sample size might suggest this study was underpowered, the lack of any discernible biologic difference in IL-6 levels suggests de novo statin therapy in severe sepsis may not be associated with an attenuation of inflammation.

The optimal plasma level of atorvastatin as a potential treatment of sepsis is unknown. It is also possible any pleiotropic effects may not be mediated by inhibition of 3-hydroxy-3-methylglucaryl CoA reductase and therefore usual dosing and cholesterol changes may not be relevant. Our patients achieved higher plasma atorvastatin levels than are usually seen with 20-mg atorvastatin therapy in humans, in keeping with published studies in human volunteers injected with LPS and pretreated with statins (31), and the observational studies all involve prior statin use because of their opportunistic design. Previous studies have raised the possibility of worse clinical outcomes associated with cessation of established statin therapy, a subtle but potentially biologically important difference to a postulated improved outcome with continued therapy (10, 32, 33). Our present study showed no evidence of inflammatory rebound on cessation of prior statin use. However, the difference in clinical outcomes seen in this trial provides further evidence that this is a question worth clarifying.

**Strengths and Limitations**

Our study had significant methodologic strengths. It was a placebo-controlled multicenter double-blind randomized trial. We studied the sickest cohort of patients to assess the benefits of statins, we used a validated inflammatory marker as the primary endpoint, and we stratified at baseline for prior statin use. We demonstrated pharmacokinetic and pharmacodynamic effects of the trial drug based on the measured plasma concentrations accompanied by a reduction in plasma cholesterol. Additionally, we obtained preliminary evidence of the safety of atorvastatin use in critically ill patients with sepsis. This study was too small and the CIs too large to exclude small but important differences in rates of hepatotoxicity and rhabdomyolysis.

**TABLE 3. CLINICAL OUTCOMES**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Entire Cohort</th>
<th>De Novo = No Prior Statin Use</th>
<th>Prior Statin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atorvastatin</td>
<td>Placebo</td>
<td>Odds Ratio: Atorvastatin versus Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 123)</td>
<td>(n = 127)</td>
<td>P Value</td>
</tr>
<tr>
<td>ICU mortality, % (n)</td>
<td>7% (9)</td>
<td>12% (15)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospital mortality, % (n)</td>
<td>13% (16)</td>
<td>18% (23)</td>
<td>0.27</td>
</tr>
<tr>
<td>28-d mortality, % (n)</td>
<td>10% (12)</td>
<td>17% (22)</td>
<td>0.09</td>
</tr>
<tr>
<td>90-d mortality, % (n)</td>
<td>15% (18)</td>
<td>19% (24)</td>
<td>0.38</td>
</tr>
<tr>
<td>ICU LOS, d, median (IQR)</td>
<td>5.6 (3.1–9.7)</td>
<td>6.6 (2.9–13.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Hospital LOS, d, median (IQR)</td>
<td>18.3 (11.0–38.7)</td>
<td>22.7 (12.4–37.0)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** ICU = intensive care unit; IQR = interquartile range; LOS = length of stay.

**Figure 4.** Sequential Organ Failure Assessment Score (with no Glasgow Coma Score component) for the entire cohort during the course of the study. The box represents the interquartile range, the horizontal line represents the median, and the whiskers show the maximum and minimum values.
preliminary pharmacokinetic data (16). Although lower in the atorvastatin group, the plasma cholesterol was low in both groups. It is possible that 3-hydroxy-3-methylglutaryl CoA reductase is already inhibited in sepsis and this may be a potential factor influencing the study results. A 20-mg dosage was selected to address concerns in current prescribing guidelines regarding potential toxicity in acutely ill patients and in light of our preliminary pharmacokinetic data suggesting elevated plasma levels in patients with sepsis (16). This study does not exclude a different effect of higher doses. As a class, different statins show some variation in their pharmacology and it remains unknown if other statins may have a different effect in patients with sepsis than that seen with atorvastatin in this study. Patients received an average of four doses of study medication. This study does not exclude a different effect with more prolonged therapy. In patients with acute lung injury receiving simvastatin, significant improvements in physiologic outcomes were only seen after 14 days of treatment (34).

The lack of effect with de novo therapy may represent a type II error. In this regard our demonstration of the feasibility and the safety of de novo therapy would facilitate future investigations. Similarly, the survival advantage of continued atorvastatin therapy in prior statin users may represent a type I error and any potential benefit needs confirmation in larger clinical trials. It remains unknown if the duration of prior use or cessation influences outcome. The exclusion of patients that only recently commenced or ceased prior statin therapy was aimed to address concerns in current prescribing guidelines regarding potential toxicity in acutely ill patients and in light of our preliminary pharmacokinetic data suggesting elevated plasma levels in patients with sepsis (16). This study does not exclude a different effect of higher doses. As a class, different statins show some variation in their pharmacology and it remains unknown if other statins may have a different effect in patients with sepsis than that seen with atorvastatin in this study. Patients received an average of four doses of study medication. This study does not exclude a different effect with more prolonged therapy. In patients with acute lung injury receiving simvastatin, significant improvements in physiologic outcomes were only seen after 14 days of treatment (34).

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Conclusions

Atorvastatin at 20 mg/day in critically ill patients with severe sepsis does not affect IL-6 levels. It also does not seem to impact sepsis does not affect IL-6 levels. It also does not seem to impact

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References

APPENDIX 1: CRITERIA FOR ORGAN DYSFUNCTION

1. Cardiovascular system dysfunction:
   - Either
     - Systolic arterial blood pressure less than 90 mm Hg for at least 1 hour despite fluid resuscitation (as defined in PROWESS [35]);
     - or
     - Mean arterial blood pressure less than 70 mm Hg for at least 1 hour despite fluid resuscitation (as defined in PROWESS [35]);
     - or
     - The use of vasopressors to maintain a systolic blood pressure of greater than 90 mm Hg or a mean arterial pressure greater than 70 mm Hg
   - Renal dysfunction:
     - Urine output less than 0.5 ml/kg body weight for 1 hour despite adequate fluid resuscitation
   - Respiratory system dysfunction:
     - Either
       - $\text{PaO}_2/\text{FiO}_2$ ratio less than or equal to 250 in the presence of other dysfunctional organs or systems;
       - or
       - $\text{PaO}_2/\text{FiO}_2$ ratio less than or equal to 200 if the lung is the only dysfunctional organ
     - Hematologic dysfunction:
       - Platelets less than 80,000/mm$^3$ or 50% decrease in platelets in 3 days before enrolment
     - Unexplained metabolic acidosis:
       - pH less than or equal to 7.30 or base deficit greater than or equal to 5.0 mmol/L and plasma lactate greater than 1.5 × upper limit normal