Continuation of Statin Therapy in Patients with Presumed Infection

A Randomized Controlled Trial

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Rationale: **In patients on prior statin therapy who are hospitalized for acute infections, current literature is unclear on whether statins should be continued during their hospitalization.**
Objectives: **To test the hypothesis that continuation of therapy with statins influences the inflammatory response to infection and that cessation may cause an inflammatory rebound.**
Methods: **Prospective randomized double-blind placebo-controlled trial of atorvastatin (20 mg) or matched placebo in 150 patients on preexisting statin therapy requiring hospitalization for infection.**
Measurements and Main Results: **The primary end point was progression of sepsis during hospitalization. At baseline, the rate of severe sepsis was 32% in both groups. Compared with baseline, the odds ratio for severe sepsis declined in both groups: 0.43 placebo and 0.5 statins (Day 3) versus 0.14 placebo and 0.12 statins (Day 14). The rate of decline of severe sepsis was similar between the groups (odds ratio 1.17 [0.56–2.47], $P = 0.7$ Day 3; 0.85 [0.21–3.34], $P = 0.8$ Day 14). IL-6 and C-reactive protein declined in both groups with no statistically significant difference ($P = 0.7$ and $P = 0.2$, respectively). An increase in cholesterol occurred in the placebo group ($P < 0.0001$). Most patients were not critically ill. Hospital mortality was 6.6%, with no difference between the groups (6 [8%] of 75 statin group; 4 [5.3%] of 75 placebo group; $P = 0.75$).**
Conclusions: **This study does not support a beneficial role of continuing preexisting statin therapy on sepsis and inflammatory parameters. Cessation of established statin therapy was not associated with an inflammatory rebound.**
Clinical trial registered at the Australian New Zealand Clinical Trials Registry (ACTRN 12605000756628).

Keywords: statin; HMG Co A reductase inhibitor; sepsis; infection

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

A substantial number of patients requiring hospital admission are on statin therapy. Current literature is unclear on the appropriate balance between the risk of toxicity and emerging clinical data of beneficial effects of statins in sepsis.

What This Study Adds to the Field

This is the first randomized trial to provide guidance concerning ongoing statin therapy in patients presenting to the hospital with infection. We believe this information is new and of vital importance to a wide spectrum of the medical community. It has the potential to guide current practice and future research into the role of statin therapy in sepsis.

Several randomized controlled trials show that statins reduce the incidence of vascular events, nonfatal myocardial infarctions, stroke, and overall mortality. Recent publications highlight their antiinflammatory role independent of the lipid-lowering ability. These pleiotropic properties include effects on endothelial function, apoptosis, and plaque stabilization and are mainly caused by antioxidant and immunomodulatory roles (1–3).

Knowledge of the pleiotropic effects of statins has prompted several investigators to examine their role in various infective states. Several studies, largely retrospective, have reported improved outcomes and a reduced inflammatory response in patients who develop infection while on statin therapy (4, 5). Moreover, an increased mortality has been reported in patients whose prior statin therapy was halted (6). Current prescribing guidelines suggest caution in the continued use of statins in patients hospitalized for acute illness because of concern regarding serious side effects (7). The appropriate balance between the risk of toxicity and emerging clinical data of possible benefit is unclear. This study tested the hypothesis that continuation of therapy with statins influences the inflammatory response to sepsis and that cessation may cause an inflammatory rebound.

Literature from a variety of patient groups suggests improved outcomes with continued statin therapy while in the hospital. These include patients with acute coronary syndromes (8), acute stroke (9), and having major noncardiac surgery (10). The question remains unanswered for patients hospitalized with infection. This is clinically relevant because a substantial number of patients requiring hospitalization for infection are on established statin therapy (4, 6).

The aim of this study was to evaluate whether administration of atorvastatin influences inflammation or organ dysfunction in patients admitted to the hospital with infection who were taking statins before hospital admission. Some of the results of this study have been previously reported in the form of abstracts (11, 12).

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METHODS

This prospective randomized double-blind placebo-controlled trial was approved by the Princess Alexandra Hospital Research Ethics Committee and Guardianship administration tribunal. The study was conducted between May 2006 and October 2008. It was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12605000756628) before commencement. Informed consent was obtained from all patients or their next of kin before enrolment in the study.

Inclusion Criteria

All patients admitted to a university-affiliated teaching hospital (Princess Alexandra Hospital, Brisbane, Australia) in whom infection was suspected were screened. Patients admitted to both the general wards and the intensive care unit (ICU) were eligible for inclusion. These patients were identified from a computerized admissions database for the hospital. Patients with any of 97 potential infection-related diagnoses (ICD-9 diagnostic database) were identified and further evaluated. Some patients admitted over weekends and public holidays were excluded because no facility was available for randomization outside normal working hours. Patients admitted to the hospital security unit (prison) were excluded because they could not be readily reviewed by the research staff.

The inclusion criteria were (*1*) proven or suspected infection (defined using the CDC Atlanta criteria) (13) for which antibiotic therapy had been commenced; (*2*) the presence of at least two of the four criteria of the systemic inflammatory response syndrome (SIRS) (14); and (*3*) the patient had to be on preexisting statin therapy and the treating physician prepared to either continue or discontinue this therapy.

Exclusion Criteria

Exclusion criteria included pregnancy; acute liver failure; chronic liver disease (Childs B or C); not expected to survive 24 hours; already enrolled in another clinical trial; rhabdomyolysis or myopathy of any cause; acute coronary syndrome or an acute stroke; and patients in whom systemic manifestations of inflammation (two or more SIRS criteria) had abated for more than 36 hours. Patients in whom enteral intake was clearly not possible within 72 hours of hospitalization, thus precluding study drug administration, and patients who had missed more than two doses of their usual statin before randomization were also excluded.

Randomization Procedure

Groups were stratified before randomization into those requiring ICU at admission and those admitted for ward care. Patients were randomized in permuted blocks of four using a computer-generated list to receive either atorvastatin or placebo. Trial packs of identical capsules were prepared by an independent pharmacy and contained either atorvastatin, 20 mg, or matched placebo. Allocation concealment was by sealed opaque envelopes. All clinical and study personnel and patients remained blinded to the study group assignment throughout the trial. Study drug was administered orally or via nasogastric tube at the earliest opportunity and was continued daily for the duration of hospital admission up to a maximum of 28 days. All other clinically indicated therapies were at the discretion of the treating specialists.

Trial medication was ceased when a patient was discharged from the acute care facility or at Day 28, whichever came first. Ongoing therapy was at the discretion of the treating specialist with a default plan to return to the previous statin therapy on discharge.

Data Collection

All patient data were deidentified and stored using a study identification number on a single computer in a protected database. Basic demographic data included age; sex; underlying medical conditions; concurrent medications (including usual statin); microbiologic data (including antibiotics commenced); hospital length of stay; and 28-day mortality. Clinical parameters, oral intake, and the presence of vomiting or high nasogastric aspirates were recorded. Each patient was assessed on the day of randomization before commencement of the trial medication (baseline, Day 1) and then on Days 3, 5, 10, 14, and 28 if they remained in the acute care hospital. Organ dysfunction as determined by the Sepsis-related Organ Failure Assessment (SOFA) score (15) was calculated for all patients on each assessment day.

Laboratory Testing

The results of laboratory investigations, including full blood count, coagulation studies, liver function tests, urea, electrolytes, creatinine kinase (CK), and blood gas analysis (if available) were recorded. In addition, serial plasma C-reactive protein (CRP), IL-6, and lipid profile (nonfasting) were measured on each study day. Lipid profiles (cholesterol, triglycerides, and high-density lipoprotein [HDL] cholesterol) were performed by an enzymatic colorimetric method (Roche Diagnostics) and CRP analysis by immunoturbidimetric assay (Roche/Hitachi Modular systems, Sydney, Australia). Serum was stored at −80°C and later batch assayed for IL-6 by ELISA immunoassay (Jomar Bioscience Ltd, Kensington, South Australia).

Outcomes

The primary end point of this study was the progression or regression of sepsis during hospital admission assessed by the proportion of patients with severe sepsis at specified time points. Severe sepsis (Appendix 1) and organ dysfunction were defined according to previously published criteria (15, 16). Secondary end points include 28-day mortality, requirement for ICU admission, and changes in biologic markers of inflammation and lipid profile. A planned subgroup analysis was defined *pre hoc* examining differences in the bacteremic versus nonbacteremic groups.

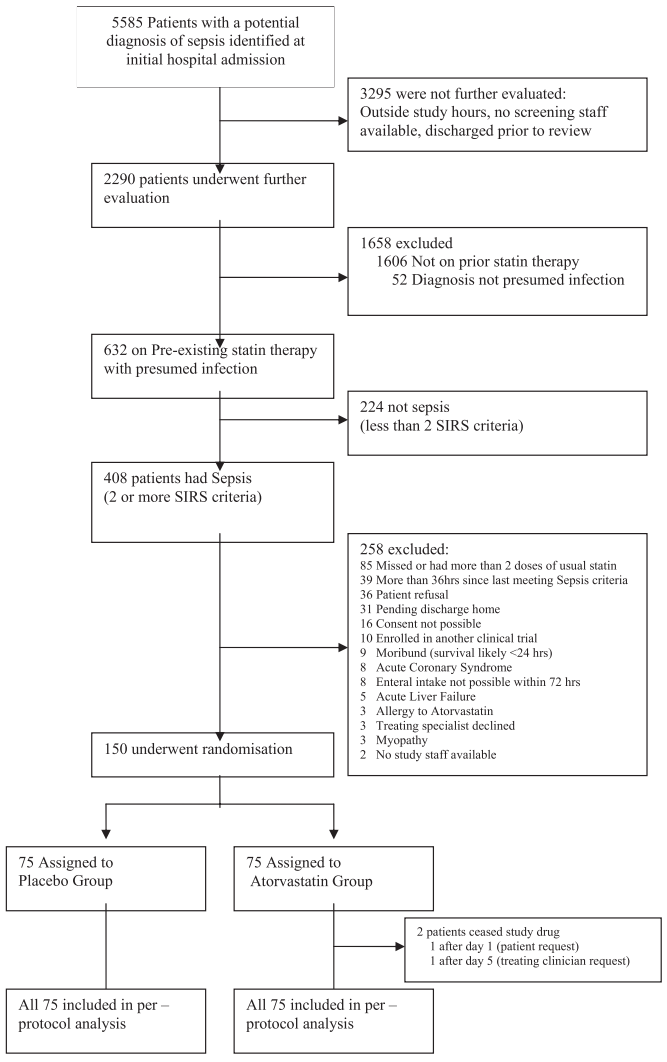

Figure 1. Screening, enrolment, and randomization of study patients. SIRS = systemic inflammatory response syndrome.

TABLE 1. BASELINE CHARACTERISTICS FOR PLACEBO AND ATORVASTATIN GROUPS

	Atorvastatin Group ($n = 75$)	Placebo Group ($n = 75$)	*P* Value
Age, y (mean, SD)	68.2 (12.7)	68.5 (11.9)	0.87
Male sex, n (%)	48 (64)	49 (65)	1.0
Comorbid disease, n			
Heart failure	15	17	0.84
Ischemic heart disease	41	39	0.87
Hypertension	51	54	0.72
Cerebrovascular disease	11	5	0.18
Chronic obstructive lung disease			
Mild	13	19	0.31
Moderate	2	3	1.0
Severe	2	3	1.0
Diabetes			
Diabetes not treated with insulin	18	18	1.0
Diabetes treated with insulin	13	12	1.0
Chronic renal failure			
Not on dialysis	7	9	0.79
Requiring dialysis	11	11	1.0
Immunosuppressed	2	6	0.27
Medications during admission			
Steroids (oral or intravenous)	13	20	0.24
Intravenous antibiotic	74	75	1.0
Oral antibiotic	21	21	1.0
Amiodarone	5	5	1.0
Warfarin	13	8	0.35
Fibrates	0	1	1.0
Azole antifungal	0	1	1.0
Clinical source of infection, n			0.93 for group
Respiratory	29	34	
Skin	14	12	
Urologic	11	9	
Gastrointestinal	15	13	
Line related	2	4	
Pyrexia of unknown origin	2	2	
Other	2	1	
Feeding			0.29 for group
Normal diet	61	65	
Enteral feeds	2	1	
Escalating diet after nil by mouth	12	7	
Nil by mouth (continued oral medication)	0	2	
Number of patients meeting each SIRS criteria at baseline, n (%)*			
Pulse rate >90 per min	47 (62.6)	48 (64)	1.0
Respiratory rate >20 per min	25 (33.3)	32 (42.6)	0.3
Temperature <36°C or >38°C	29 (38.6)	27 (36)	0.9
White cell count <4 or >12 $\times$ 10^9/L	37 (49.3)	46 (61.3)	0.2
Organ dysfunction or failure†			
Respiratory SOFA	13	15	0.48
Coagulation SOFA	13	22	0.13
Liver SOFA	16	19	0.57
Cardiovascular SOFA	30	22	0.23
Central nervous SOFA	8	7	1.0
Renal SOFA	25	21	0.57

Definition of abbreviations: SIRS = systemic inflammatory response syndrome; = Sepsis-related Organ Failure Assessment.
* Fisher exact test.
† Defined as SOFA score of 1 or more.

Statistical Analysis and Sample Size

Statistical analysis was performed with SAS (Cary, NC) version 9.2 for Windows and Graph Pad PRISM (Version 4; San Diego, CA). All patients were analyzed on an intention-to-treat basis. Continuous variables were compared using Student test or Mann-Whitney test and categorical variables compared using chi-square or Fisher exact test. We used a longitudinal analysis to compare the two treatment groups. For all outcomes, the change from baseline Day 1 was estimated at Days 3, 5, 10, and 14 for each treatment group. Treatment groups were compared at each follow-up time-point and overall. A logistic model was used for the proportional outcomes and a linear model was used for the continuous outcomes. Generalized estimating equations with an autoregressive correlation structure were used to take account of correlations within patients. The correlation structure assumed correlations within patients decrease over time. For modeling the proportional outcomes, it was assumed patients dying had the outcome (severe sepsis or organ dysfunction) at all subsequent time-points, and conversely if a patient was discharged it was assumed they did not have the outcome at all subsequent time-points. We made no assumptions regarding missing laboratory data and all proportions were calculated as percentages of the patients with available data.

Sample Size Calculation

Previous observational studies have reported a rate of severe sepsis of 2.4% in those who use statin and 19% in the group never on statin therapy (17). Limited data in other patient groups suggest that

TABLE 2. USUAL STATIN AND TRIAL DRUG ADMINISTRATION FOR BOTH GROUPS

	Atorvastatin Group ($n = 75$)	Placebo Group ($n = 75$)	*P* Values
Usual statin			0.65 for group
Atorvastatin	41	36	
Simvastatin	25	27	
Pravastatin	7	8	
Rosuvastatin	2	2	
Fluvastatin	0	2	
Doses in hospital of usual statin before randomization, n			0.71 for group
0	33	28	
1	41	46	
2	1	1	
Trial medication			
Number of trial doses given, median (IQR)	5 (3–8)	5 (3–8)	0.80
Number of patients missing at least one trial dose	16	16	1.0
Percentage of trial doses actually given, median (IQR)	100 (80–100)	100 (85.7–100)	0.62

Definition of abbreviation: IQR = interquartile range.

cessation of statin therapy results in an increased risk of an adverse outcome above that seen in comparable patients not usually on statin therapy (6, 8). As a conservative assumption we postulated that ceasing statin therapy in patients with sepsis may increase the risk to near that of never being on statin therapy. This would require 47 patients in each group to demonstrate a difference in the rate of severe sepsis ($\alpha = 0.05$; power 80%). Because nonrandomized studies overestimate the magnitude of effect, we included 150 patients (75 in each group). A planned independent interim analysis was performed after 94 patients with the ability to cease the study for safety reasons.

RESULTS

A total of 5,585 patients were identified by the initial screening process and 2,290 of these had further evaluation as outlined in Figure 1. Of the 632 on preexisting statin therapy, sepsis (presumed infection plus two or more SIRS criteria) was present in 408 (64.5%). After the exclusions detailed in Figure 1, 150 patients were randomized to participate in the study (atorvastatin, n = 75; placebo, n = 75). Two patients had the study drug ceased and both patients were included in the final analysis.

The two groups were matched at baseline with no statistically significant differences with respect to demographic variables, coexisting disease, clinical source of infection, or SIRS criteria (Table 1). Atorvastatin was the most common usual statin (77 [51%] of 150) with no significant difference between the groups (Table 2). Doses of usual statin therapy before randomization and trial medication did not differ significantly between the groups (Table 2). Most patients in the trial (126 [84%] of 150) tolerated oral intake with no statistically significant difference between the groups (Table 1). Intravenous antibiotics were administered to 149 of the 150 patients at enrolment (Table 1).

Four patients had no microbiology samples collected (one in the atorvastatin group and three in the placebo group). The bacteremia rate was similar in both groups (13 of 75 in the atorvastatin group, 12 of 75 in the placebo group; $P = 1$). All patients in this subset survived to hospital discharge. Although this was a prespecified subgroup the small numbers preclude meaningful analysis.

At Day 28 only four patients (two in each group) remained in the hospital. None of these patients had severe sepsis and only one in each group had any organ dysfunction. The other patient in each group had no organ dysfunction. Therefore, outcome analysis is presented only up to the Day 14 assessment.

Outcomes

Primary outcome. Severe sepsis was present at baseline in 32% (24 of 75) of patients in both groups. This significantly decreased over time ($P < 0.01$) in each group (Table 3) with no significant difference between treatment groups at each follow-up time point (Table 4) (overall $P = 0.6$). Analysis of only those 118 patients (59 in each group) who had complete compliance with assigned therapy gave a similar estimate of treatment effect ($P = 0.6$).

Organ dysfunction (defined as SOFA score of 1 or more in any organ system) was similar in both groups at baseline (65.3% atorvastatin, 70.6% placebo; $P = 0.60$). This significantly decreased over time ($P < 0.01$) in each group (Table 4) with no difference between treatment groups ($P = 0.2$).

Secondary outcomes. The overall cohort had a hospital mortality of 6.6% with no significant difference between the groups (statin, 6 [8%] of 75; placebo, 4 [5.3%] of 75; $P = 0.75$). The median hospital length of stay after the episode of sepsis was 7 days (interquartile range 4–12) and 6 days (interquartile range 4–11) in statins and placebo groups, respectively ($P = 0.73$). Twenty-four patients (16%) of the cohort required ICU (atorvastatin group, 13 of 75; placebo group, 11 of 75). This cohort had a mortality of 20.8% with no difference between the atorvastatin group (3 of 13) and placebo group (2 of 11). Only 23 patients (15%) were in ICU at randomization and only one ward patient (atorvastatin group) required subsequent intensive care.

Median IL-6 for the cohort at baseline was 43.8 pg/ml (interquartile range 16.9–100.5), with no significant difference between the groups (Figure 2). In both groups this decreased over time ($P < 0.01$) with no significant difference between the groups at any follow-up time-point (Table 5, overall $P = 0.7$). CRP also declined during the study ($P < 0.01$) in both groups (Figure 3) with no significant difference between the groups (Table 5, overall $P = 0.2$).

TABLE 3. RATES OF SEVERE SEPSIS* FROM BASELINE (DAY 1) TO DAY 28 DURING THE HOSPITAL STAY

	Atorvastatin Group	Placebo Group	Total Remaining in Hospital
Baseline Day 1	24 of 75	24 of 75	150
Day 3	12 of 56	11 of 56	112
Day 5	5 of 53	6 of 53	106
Day 10	1 of 20	0 of 19	39
Day 14	0 of 13	2 of 14	27
Day 28	0 of 2	0 of 2	4

* As defined in Appendix 1.

TABLE 4. THE ODDS RATIO AND COMPARISONS FOR SEVERE SEPSIS AND ORGAN DYSFUNCTION AT FOLLOW-UP TIME-POINTS COMPARED WITH BASELINE DAY 1

Day	Placebo Group OR Compared with Day 1	Atorvastatin Group OR Compared with Day 1	Comparison Placebo and Atorvastatin Groups OR (*95% CI*)	*P* Value
Severe sepsis*				
3	0.43	0.50	1.17 (0.56–2.47)	0.7
5	0.25	0.20	0.80 (0.28–2.25)	0.7
10	0.08	0.15	1.96 (0.42–9.13)	0.4
14	0.14	0.12	0.85 (0.21–3.34)	0.8
Any organ dysfunction				
3	0.41	0.46	1.12 (0.60–2.09)	0.7
5	0.19	0.30	1.55 (0.82–2.94)	0.2
10	0.13	0.11	0.86 (0.40–1.85)	0.7
14	0.09	0.06	0.71 (0.29–1.77)	0.5

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* As defined in Appendix 1.

Plasma cholesterol, low-density lipoprotein (LDL), triglyceride, and HDL are presented in Figure 4. Total cholesterol and LDL steadily increased in the control group ($P < 0.0001$). Values were significantly lower in the atorvastatin group (overall $P = 0.002$ for cholesterol and 0.004 for LDL) (Table 6). In both groups HDL was statistically significantly lower than the conventionally accepted lower limit of normal (1.2 mmol/L), for the first 10 days of hospital stay ($P < 0.01$ for all except Day 10 placebo $P < 0.05$). No statistically significant difference was seen in HDL or triglyceride levels between the groups over the time course of the study ($P = 0.4$ for HDL and $P = 0.9$ for triglyceride).

Adverse reactions. To assess potential toxicity, serial CK and hepatocellular enzymes were followed. No statistically significant difference was noted between the groups in CK or alanine aminotransferase. Three patients developed elevations in alanine aminotransferase greater than 225 U/L (>5 times the upper limit of normal). In two cases these elevations were shortly before death and thought by the treating clinician to represent a component of multiple organ failure rather than a result of trial medication (one atorvastatin and one placebo). In the third patient the treating clinician believed the clinical picture was of ischemic hepatopathy and the study drug was continued at their discretion. The alanine aminotransferase level fell gradually over time and the patient was discharged home from hospital on Day 9. No patients in either group had a CK greater than 1,400 U/L (10 times the upper limit of normal) recorded at any time during the study.

DISCUSSION

This study is the first randomized prospective trial to examine the use of continued statin administration on progression and regression of sepsis and inflammation in patients admitted to hospital with infection who were taking statins before hospital admission. The cardinal finding is that continuation of prior statin therapy was not associated with an attenuation of the inflammatory response or organ failure. Conversely, cessation of statins was not associated with an inflammatory rebound and worsening organ dysfunction.

Previous retrospective and observational studies have reported improved outcomes and a reduction in inflammatory response in patients who develop infection while on statin therapy (4, 5). Moreover, an increased mortality has been reported in patients with bacteremia who ceased prior statin therapy, prompting speculation of an inflammatory rebound (6, 18).

There are several possible reasons why this study did not show the benefits previously suggested. First, prior studies were retrospective or observational and therefore selection bias, variation in therapy, and presence of confounding variables cannot be discounted. The potential impact of retrospective adjustment is well illustrated in prior observational studies in patients with pneumonia (19). The reported conclusions varied from potentially helpful to potentially harmful depending on adjustments for confounding variables (19). Other possible reasons why this study did not show a benefit include study design, sample size, magnitude of effect, or bioavailability and drug dosing.

The trial was designed to assess all patients admitted to hospital (including ward patients) with presumed infection. This dilutes the event rate because not all patients had severe sepsis. The other unique feature of this trial was to address the clinical question of continued statin use in hospitalized patients with infection. It is possible that persisting pleiotropic effects even after ceasing therapy may reduce the influence of any temporary cessation.

The sample size of 150 patients represents the largest randomized trials of statins in sepsis to date. With this sample size, when comparing the longitudinal recovery from severe sepsis over the trial follow-up (Days 1–14) there was no

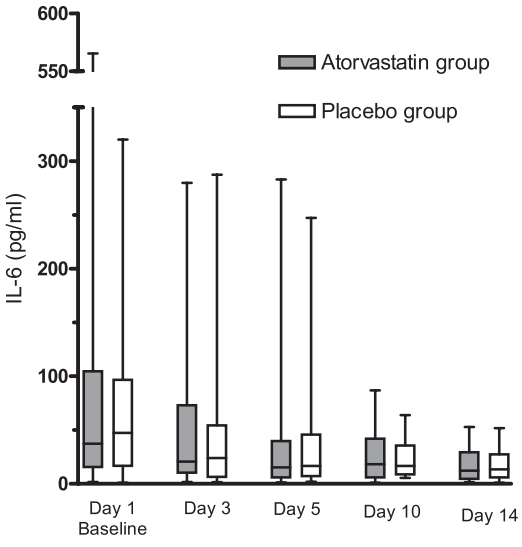

Figure 2. Changes in IL-6 over time for patients with sepsis in the atorvastatin or placebo groups during their hospital stay. The number of samples at each time point is detailed in Table 4. The *box* represents the interquartile range, the *horizontal line* represents the median, and the *whiskers* show the maximum and minimum values.

TABLE 5. INFLAMMATORY MARKERS (IL-6 AND CRP) FOR PLACEBO AND ATORVASTATIN GROUP PATIENTS AT FOLLOW-UP TIME-POINTS COMPARED WITH BASELINE DAY 1*

Day	Placebo Difference from Day 1 (*n*)†	Atorvastatin Difference from Day 1 (*n*)†	Comparison Placebo and Atorvastatin Groups Difference (*95% CI*)	*P* Value
IL-6, pg/ml				
3	−22 (49 of 56)	−34 (48 of 56)	−12 (−32 to 8)	0.2
5	−42 (43 of 53)	−35 (42 of 53)	7 (−12 to 26)	0.5
10	−49 (18 of 19)	−46 (18 of 20)	3 (−10 to 16)	0.7
14	−55 (9 of 14)	−57 (11 of 13)	−2 (−18 to 14)	0.8
CRP, mg/L				
3	−60 (53)	−37 (54)	23 (−3 to 50)	0.09
5	−105 (52)	−88 (53)	18 (−10 to 46)	0.2
10	−141 (19)	−135 (20)	6 (−32 to 43)	0.8
14	−149 (9)	−164 (11)	−15 (−51 to 22)	0.4

Definition of abbreviations: CI = confidence interval; CRP = C-reactive protein.

* Values represent mean differences obtained from the regression model.

† Number of samples available for analysis, denominator of number of patients remaining in hospital is the same for both IL-6 and CRP.

difference between treatment groups (odds ratio = 0.99; 95% confidence interval, 0.67–1.48). This confidence interval excludes a treatment effect of greater than a 33% relative reduction in the odds ratio. A smaller reduction in benefit is not excluded by this study and the clinical significance of any such reduction remains unclear. Most patients were not critically ill. With a hospital mortality of 6.6%, the study was not powered to assess mortality as an end point.

Another possible reason why this study did not show the benefits previously suggested is bioavailability of the trial medication. Although statin levels were not measured, the dose used (20 mg) was similar to a recent pharmacokinetic study that has shown elevated plasma statin levels in acutely ill patients with sepsis (20). A 20-mg dosage was selected to address concerns in current prescribing guidelines regarding potential toxicity in patients who are acutely ill (7). The changes seen in total and LDL cholesterol confirm the expected pharmacodynamic effect, supporting adequate drug absorption. Although at a dose of 20 mg no effect was seen on organ dysfunction or inflammation as measured by CRP or IL-6, a different effect at higher doses is not excluded. We used a dose at the lower end of usual dosing and excluded the highest-risk patients with rhabdomyolysis and significant liver dysfunction. Although it is reassuring that continued administration of atorvastatin was well tolerated in this study, it was not powered to provide safety data.

Previous work has suggested that IL-6 levels reflect the severity of sepsis (21). A recent randomized trial of simvastatin in statin-naive patients with sepsis showed a significant reduction in IL-6, although differences existed both at baseline and in the direction of change in IL-6 (22). In our study IL-6 was well matched at baseline and declined over the duration of the study. A similar pattern of decline in other inflammatory markers and organ dysfunction further strengthens the validity of our results.

This study confirms previous observations of the profound decrease in HDL seen in patients with sepsis (23). No significant change in HDL was seen in the atorvastatin group compared with placebo. Such agents as simvastatin and rosuvastatin are regarded to have superior HDL elevating properties (24) and could have different effects.

The mechanism of potential benefits of statin therapy in sepsis remains unclear (3, 25). The beneficial effects may be independent of the lipid-lowering effects, which could explain why benefits seen in acute cardiac and cerebrovascular disease were not reproduced in our study. It is possible that had we examined other end points of purported pleiotropic benefits, such as coagulation or endothelial dysfunction, differences may have been noticeable between the groups. Even if such differences existed they did not translate into a clinical benefit on sepsis severity. Because most patients in this study were not critically ill we have reported less severe organ dysfunction (SOFA score >1 in any organ system) in addition to the organ failure criteria for severe sepsis. Neither analysis showed a differential response between continued atorvastatin therapy and placebo.

The pleiotropic effects of statins may represent a class effect, although some potential differences between agents have been reported (26). For 51% of patients, this trial represented the continuation of prior atorvastatin therapy. The significance of this is unknown, although an analysis of only those patients who continued atorvastatin demonstrated a similar trend to that seen for the entire cohort (results not shown). For some patients usually taking atorvastatin the study dose represented a change from their usual dose. The impact of this alteration remains unknown.

In conclusion, our study does not support a beneficial role of continuing preexisting statin therapy on sepsis and inflammatory parameters. This is the first randomized trial to provide guidance concerning ongoing statin therapy in patients presenting to hospital with infection. This trial only assessed those patients on prior statin therapy and most patients were not critically ill. Further trials are required to delineate the place of

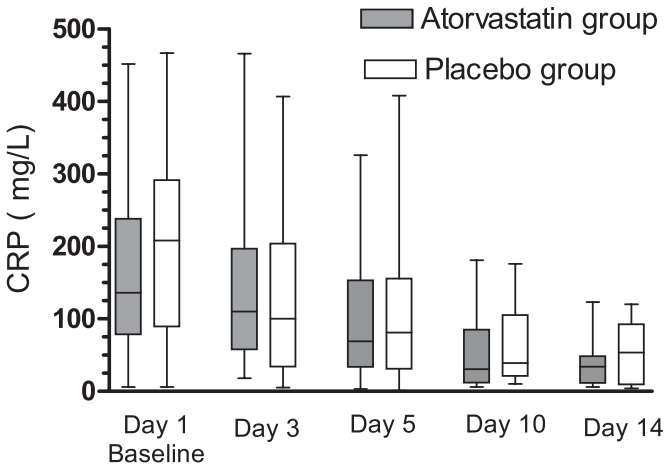

Figure 3. Changes in C-reactive protein (CRP) over time for patients with sepsis in the atorvastatin or placebo groups during their hospital stay. The number of samples at each time point is detailed in Table 4. The *box* represents the interquartile range, the *horizontal line* represents the median, and the *whiskers* show the maximum and minimum values.

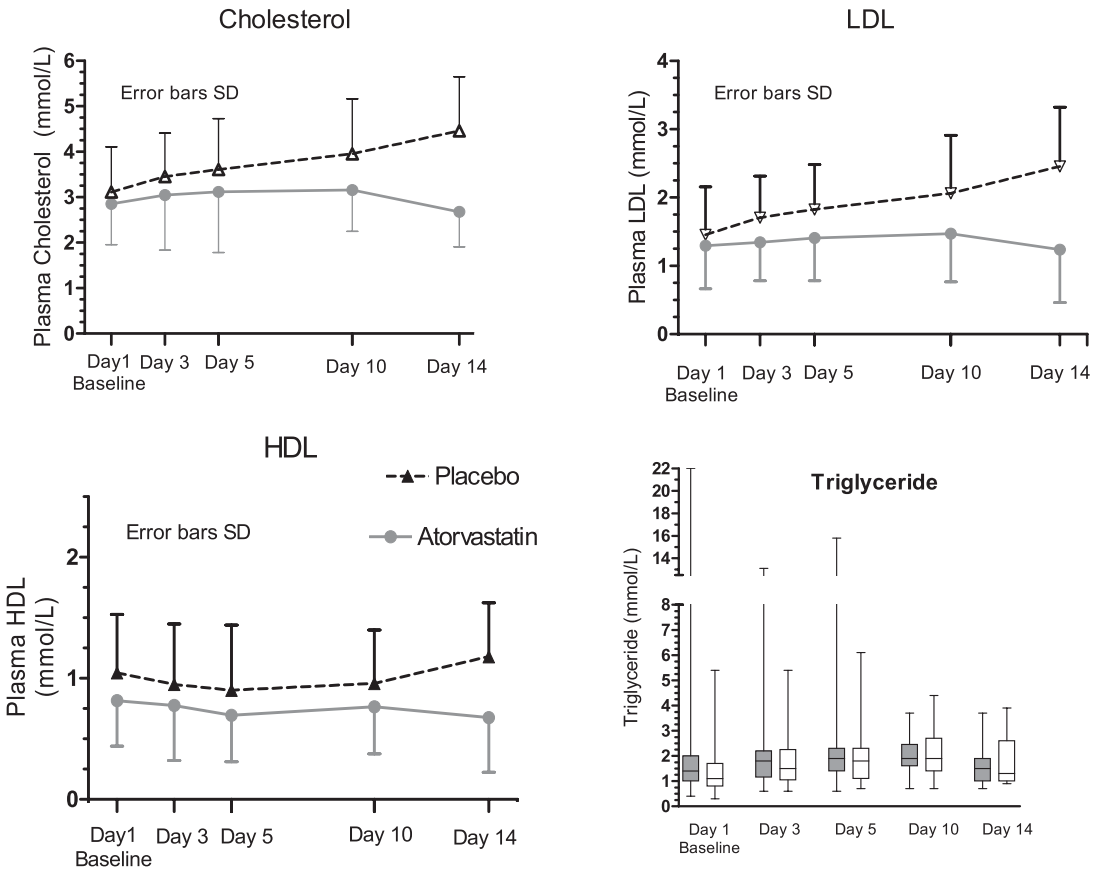

Figure 4. Lipid profiles (mean, SD) for cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in patients hospitalized with sepsis in both the atorvastatin and placebo groups. Triglyceride data are presented so the *box* represents the interquartile range, the *horizontal line* represents the median, and the *whiskers* show the maximum and minimum values. The number of samples at each time point is detailed in Table 5.

de novo and continuation of statin therapy in patients with sepsis and to clarify its impact in patients with severe sepsis.

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TABLE 6. PLASMA LIPID LEVELS FOR PLACEBO AND ATORVASTATIN GROUP PATIENTS AT FOLLOW-UP TIME-POINTS COMPARED WITH BASELINE DAY 1*

Day	Placebo Group Difference from Day 1 (*n*)†	Atorvastatin Group Difference from Day 1 (*n*)†	Comparison Placebo and Atorvastatin Groups Difference (*95% CI*)	*P* Value
Total cholesterol, mmol/L				
3	0.26 (52 of 56)	0.16 (56 of 56)	−0.10 (−0.33 to 0.12)	0.4
5	0.57 (51 of 53)	0.31 (53 of 53)	−0.26 (−0.54 to 0.03)	0.08
10	1.28 (19 of 19)	0.62 (20 of 20)	−0.66 (−1.11 to −0.20)	0.005
14	1.60 (9 of 14)	0.31 (13 of 13)	−1.29 (−1.87 to −0.71)	<0.0001
LDL, mmol/L				
3	0.23 (49)	0.03 (54)	−0.20 (−0.35 to −0.04)	0.013
5	0.43 (46)	0.13 (52)	−0.30 (−0.50 to −0.11)	0.002
10	0.83 (19)	0.25 (20)	−0.58 (−0.95 to −0.22)	0.002
14	1.09 (9)	−0.01 (13)	−1.09 (−1.59 to −0.60)	<0.0001
HDL, mmol/L				
3	−0.13 (52)	−0.07 (56)	0.06 (−0.04 to 0.16)	0.2
5	−0.15 (51)	−0.11 (52)	0.04 (−0.08 to 0.16)	0.5
10	−0.01 (19)	0.01 (20)	0.02 (−0.15 to 0.19)	0.8
14	0.06 (9)	−0.01 (13)	−0.06 (−0.25 to 0.13)	0.5
Triglyceride, mmol/L				
3	0.28 (52)	0.06 (56)	−0.22 (−0.84 to 0.40)	0.5
5	0.43 (51)	0.18 (53)	−0.25 (−1.04 to 0.53)	0.5
10	0.54 (19)	0.36 (20)	−0.19 (−0.80 to 0.43)	0.6
14	0.32 (9)	0.12 (13)	−0.20 (−0.85 to 0.45)	0.5

Definition of abbreviations: CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

* Values represent mean differences obtained from the regression model.

† Number of samples available for analysis, the denominator of number of patients remaining in hospital is the same for each plasma lipid group.

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Appendix 1. Criteria for Severe Sepsis (as Previously Described) (16)

Patients had to meet at least one of the following.

- Cardiovascular system dysfunction:

EITHER

Systolic arterial blood pressure $\leq$90 mm Hg for at least 1 hour despite fluid resuscitation

OR

Mean arterial blood pressure $\leq$70 mm Hg for at least 1 hour despite fluid resuscitation

OR

The use of vasopressors to maintain a systolic blood pressure of $\geq$90 mm Hg or a MAP $\geq$70 mm Hg

- Renal dysfunction:

  Urine output $<$0.5 ml/kg body weight for 1 hour despite adequate fluid resuscitation

- Respiratory system dysfunction:

EITHER

Pa_{O_2}:$F_{I_{O_2}}$ ratio $\leq$250 in the presence of other dysfunctional organs or systems

OR

Pa_{O_2}:$F_{I_{O_2}}$ ratio $\leq$200 if the lung is the only dysfunctional organ

- Hematologic dysfunction:

  Platelets $<$80,000/mm^2 OR 50% decrease in platelets in the 3 days before enrolment

- Unexplained metabolic acidosis:

  pH $\leq$7.30 OR base deficit $\geq$5 mmol/L AND plasma lactate $>$1.5 $\times$ upper limit normal