The association between prior statin use and long-term outcomes after critical care admission☆

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ABSTRACT

Background: Statins may have immunomodulatory effects that benefit critically ill patients. Therefore, we retrospectively examined the association between survival and the prescription of statins prior to admission to an intensive care unit (ICU), or high dependency unit (HDU), as a result of major elective surgery or as an emergency with a presumed diagnosis of sepsis.
Methods: We retrospectively studied critical care patients (ICU or HDU) from a tertiary referral UK teaching hospital. Nottingham University Hospitals have more than 2200 beds, of which 39 are critical care beds. Over a 5-year period (2000-2005), 414 patients were identified with a presumed diagnosis of sepsis, and 672 patients were identified who had planned ICU/HDU admissions following elective major surgery. Patients prescribed statins prior to hospital admission were compared with those who were not. Demographics, medical history, drug history, and Acute Physiology and Chronic Health Evaluation II scores were examined. Univariate and multivariate analyses were applied using the primary end point of survival at 5 years after admission.
Results: Patients prescribed statins prior to critical care admission were, on average, older and had higher initial Acute Physiology and Chronic Health Evaluation II scores and more preexisting comorbidities. Statins were almost invariably stopped following admission to critical care. Statin use was not associated with significantly altered survival during hospital admission, or at 5 years, for either patients with sepsis (9% vs 15%, $P = .121$; 73% vs 84%, $P = .503$, respectively) or postoperative patients (55% vs 58%, $P = .762$; 57% vs 63%, $P = .390$).
Conclusions: Prior statin use was not associated with improved outcomes in patients admitted to critical care after elective surgical cases or with a presumed diagnosis of sepsis.

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1. Introduction

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are a widely prescribed class of drugs. Although primarily intended to treat hypercholesterolemia, statins may have other relevant therapeutic properties independent of lipid-lowering effects [1–3]. For example, investigators have suggested that statins may have pleiotropic vascular endothelial effects that are immunomodulatory, anti-inflammatory, or antithrombotic [4–8]. As such, studies have sought to establish if there is an association between statin use and outcomes following critical illness such as infection, pneumonia, acute respiratory distress syndrome, and traumatic brain injury or stroke [9–16]. Studies have also examined the putative link between the prior statin use and any reduction in the morbidity and mortality from major elective surgery [17,18].

Despite widespread interest, there is still confusion regarding whether prescribing statins before admission to an intensive care unit (ICU), or high dependency unit (HDU), is associated with any subsequent increase or decrease in survival. For example, prior statin use has been associated with increased mortality for patients who acquired infections while in ICU but associated with decreased mortality in patients with multiorgan dysfunction [19,20]. Moreover, most studies have only concentrated on short-term outcomes. As a result, it is also unclear whether statins should be continued or discontinued during critical illness. This study will further explore the association between prior use of statins and outcome in (1) patients admitted to ICU or HDU as an emergency with presumed sepsis and (2) patients electively admitted to ICU or HDU after major surgery.

2. Methods

Nottingham University Hospital (NUH) consists of the Queens Medical Centre and Nottingham City Hospital and is located in the Midlands of England. These 2 sites provide critical care support to a population of between 1 and 4 million, depending on the condition being treated.

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Ethics approval was obtained to perform a retrospective chart review of all adult patients admitted to NUH between January 1, 2000, and December 31, 2005 (inclusive). At that time, there were 21 multidisciplinary ICU beds and 18 HDU beds.

Patients were identified using 3 databases which encompassed different critical care areas and were continuously maintained: the Intensive Care National Audit and Research Centre and 2 locally maintained Microsoft Access databases. Two cohorts were identified: (1) those with a presumed diagnosis of sepsis and (2) those with elective admission following major surgery.

Any patient with unavailable or incomplete notes was excluded. Postoperative patients were excluded if their admission followed surgical or anesthetic complications, or if surgery was otherwise nonelective (eg, surgery for abscess drainage or perforated viscus). Only the first admission was counted for those with multiple admissions. If patients were deemed (from chart review) to be both septic and elective postoperative, they were only included once and in the first cohort to which they presented.

Chart review was performed (by MB, IJ, JC-S, KG, CL, and AA) to confirm demographics, reason for ICU/HDU admission, and any chronic disease or prescription medication prior to hospital admission. Statin use was recorded along with that of other cardiovascular medications, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARAs), long-acting nitrates, β-blockers, and calcium channel antagonists. Given the retrospective nature of the study, it was not possible to identify the indication, dosing, length of use, or compliance associated with any individual medication, nor was it possible to determine the efficacy of preadmission medication use.

Patients were defined as having a significant comorbidity if it was recorded in the casenotes under the section "past medical history" on admission to hospital or on admission to ICU. Comorbidities recorded included *ischemic heart disease* (predefined as any history of angina, heart failure, previous myocardial infarctions, or ischemic heart disease), other vascular disease (including cerebrovascular disease and peripheral vascular disease), diabetes (both non–insulin-dependent and insulin-dependent diabetes), and *chronic renal insufficiency* (defined as those with chronic kidney disease of stage 3 or worse: estimated glomerular filtration rate < 60 mL/[min 1.73 m^2]). Other admission variables recorded included age, sex, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Having retrospectively identified patients, both cohorts were passively followed in a prospective manner over the next 9 years by recording hospital attendances. This made it possible to calculate survival at 5 years after ICU admission (the primary outcome) for the majority of patients. Secondary outcomes were survival to ICU discharge, survival to hospital discharge, length of ICU stay (ICU-LOS), presence of 3 or more systemic inflammatory response syndrome (SIRS) criteria, and evidence of *cardiovascular instability* (defined as need for inotropic or vasopressor support within the first 24 hours of admission).

Baseline characteristics were compared between cohorts, with χ^2 analysis of nominal data and independent sample *t* tests for continuous data (eg, age and APACHE II scores). Univariate analysis was also used to compare the raw outcomes relating to prior statin use and no prior statin use. Binary logistic regression was also performed to calculate odds ratios adjusted for potential confounders including age, sex, APACHE II score, presence of premorbid diabetes or cardiovascular illness, and premorbid use of other cardiovascularly active medications. Kaplan-Meier estimates of 5-year survival were calculated and analyzed using log-rank tests. Analyses were carried out using SPSS (IBM SPSS Statistics for Macintosh, Version 14.0, Chicago, IL), and statistical significance was deemed as a *P* value less than .05.

3. Results

Approximately 6590 patients were admitted to the critical care units between January 1, 2000, and December 31, 2005 (Fig. 1). Of these, a cohort of 414 patients was admitted for presumed sepsis, and 672 patients

Total number of patients screened
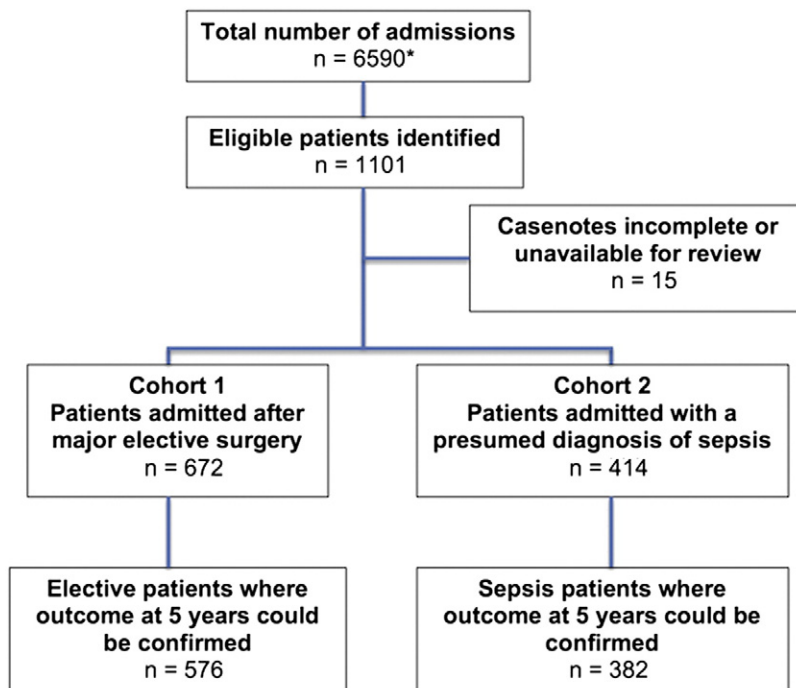
*Estimated from average yearly admissions over the time period as exact figure not available.

Fig. 1. Flowchart of numbers of patients screened and identified at each stage of data collection.