The association between prior statin usage 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 has over 2200 beds, of which 39 are critical care beds. Over a five-year period (2000–2005) 414 patients were identified with a presumed diagnosis of sepsis, and 672 patients were identified with a planned ICU/HDU admission following elective major surgery. Patients prescribed statins prior to hospital admission were compared with those who were not. Demographics, past medical history, drug history, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were examined. Univariate and multivariate analyses were applied using the primary endpoint of survival at five years after admission.

Results:

Patients prescribed statins prior to critical care admission were, on average, older, with higher initial APACHE II scores and more pre-existing comorbidities. Statins were almost invariably stopped following admission to critical care. Statin usage was not associated with significantly altered survival during hospital admission, or at five years, for either patients with sepsis (9%

v 15%, *P*=0.121; 73% v 84%, *P*=0.503 respectively), or post-operative patients (55% v 58%, *P*=0.762; 57% v 63%, *P*=0.390).

Conclusions:

Prior statin usage was not associated with improved or worsening outcomes in patients admitted to critical care after elective surgical cases or with a presumed diagnosis of sepsis.

Introduction

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are a widely prescribed class of drugs. While primarily intended to treat hypercholesterolaemia, 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-usage 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 usage has been associated with increased mortality for patients who acquired infections while in ICU, but associated with decreased mortality in patients with multi-organ 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 i) patients admitted to ICU or HDU as an emergency with presumed sepsis, and ii) patients electively admitted to ICU or HDU after major surgery.

Methods

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

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

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

Any patient with unavailable or incomplete notes was excluded. Post-operative patients were excluded if their admission followed surgical or anaesthetic complications, or if surgery was otherwise non-elective (e.g., 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 post-operative 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 usage was recorded along with that of other cardiovascular medications: including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor antagonists (ARAs), long-acting nitrates, beta-blockers, and calcium channel antagonists (CCAs). 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 pre-admission medication usage.

Patients were defined as having a significant comorbidity if it was recorded in the case-notes under the section “past medical history” on admission to hospital or on admission to ICU. Comorbidities recorded included ischemic heart disease (pre-defined 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, gender 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 nine years by recording hospital attendances. This made it possible to calculate survival at five-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 three or more systemic

inflammatory response syndrome (SIRS) criteria, and evidence of cardiovascular instability (defined as the need for inotropic or vasopressor support within the first twenty-four hours of admission).

Baseline characteristics were compared between cohorts, with Chi-squared analysis of nominal data and independent sample t-tests for continuous data (e.g. age and APACHE II scores). Univariate analysis was also used to compare the raw outcomes for comparing prior statin usage and no prior statin usage. Binary logistic regression was also performed to calculate odds ratios adjusted for potential confounders including: age, gender, APACHE II score, presence of premorbid diabetes or cardiovascular illness, and premorbid use of other cardiovascularly-active medications. Kaplan Meier estimates of five-year survival were calculated and analysed using log rank tests. Analyses were carried out using SPSS (IBM SPSS Statistics for Macintosh, Version 14.0, Chicago) and statistical significance was deemed as a *P*-value less than 0.05.

Results

Approximately 6590 patients were admitted to the critical care units between January 1st 2000 and December 31st 2005. (Figure 1). Of these, a cohort of 414 patients was admitted for presumed sepsis, and 672 patients were admitted following major elective surgery. All study patients had their statin usage interrupted for at least some period of their admission to a critical care environment.

Patients who had been prescribed statins prior to admission were more likely to be older, and have marginally-higher APACHE II scores (Table 1).

Statins users also had a higher incidence of related comorbidities (diabetes, vascular disease, ischaemic heart disease), and co-prescribed cardiovascular medications. In the surgical cohort, statins users were more likely to have had vascular surgery prior to elective admission. Within both cohorts approximately 13% of patients had been prescribed statins, with simvastatin and atorvastatin being the most widely used: these two medications accounted for approximately 80% of all statins.

Data analysis revealed few differences in outcomes when comparing patients prescribed statins compared with those not prescribed statins (Table 2). There was no difference in in-hospital mortality between patients not previously prescribed statins and those who had been taking statins (9% v 15%, *P*=0.121, for post-operative patients; 55% v 58%, *P*=0.762, for patients with presumed sepsis); nor was there any difference in five year survival (57% v 63%, *P*=0.390; 73% v 84%, *P*=0.503). ICU-LOS was also unaffected. Only ICU mortality was statistically different between the two groups in the cohort of post-operative patients (where absolute numbers were small).

When comparing factors associated with inflammation or shock, the only statistically significant finding was that post-operative patients who had used statins were more likely to require inotropes (53% of patients in this group were prescribed adrenalin, noradrenaline or dopamine, compared with 38% of patients who had no prior statin usage, *P*=0.007).

Odds ratios were calculated for five-year survival, taking into account potential confounders (Table 3). Increased age, APACHE II score at ICU admission, and admissions following cancer surgery were all associated with increased five-year mortality. For those admitted non-electively with presumed

sepsis, the presence of vascular disease or ischaemic heart disease was associated with increased five-year mortality (*P*=0.035 and *P*=0.036 respectively). There was no statistically significant difference in Kaplan Meier estimates of five-year survival in either cohort when comparing patients prescribed statins versus those not prescribed statins (Figures 2 and 3).

An analysis of the crude mortality associated with different types of statin revealed a potential difference in survival (Table 4). Simvastatin was associated with worse hospital survival when compared with patients not prescribed statins (or prescribed atorvastatin). This association was only found in patients admitted with sepsis.

Discussion

We found little or no evidence of any association between statin usage and improved survival. This was true in the short-term (during ICU stay); the medium term (during hospital stay); the longer term (up to 5 years); and regardless of whether patients were admitted as an emergency (for presumed sepsis) or electively (after major surgery).

Following sepsis, previous studies have intimated that pre-existing statin therapy may reduce cytokine levels (specifically TNF-alpha and interleukin-6); may protect against progression from bacteraemia to severe sepsis; may mitigate the need for ICU admission; and may decrease overall mortality.[21-26] Studies have also reported a reduction in attributable mortality from 20% to 3% (*P* = 0.010).[9] In contrast, our five-year study found no associated mortality-benefit between sepsis-survival and pre-prescription of a statin.

Studies have also reported an association between prior statin use and lower morbidity and mortality after cardiac surgery, non-cardiac vascular surgery, and other non-cardiac surgery.[17-18,27-28] Again, this was not duplicated in our study which found no survival advantage with a statin. Our goal was to investigate longer-term survival following major surgery in patients likely to have inflammation (as defined by the SIRS criteria), but not caused by sepsis.

Our study has many limitations that reduce the generalizability of our conclusions. These include: the retrospective nature, reliance upon chart records and presumptive diagnoses from a single centre; and the loss to follow up of twelve percent of patients. We did not confirm (or compare) patient's statin dose, or duration of therapy, or pre-admission compliance. Nor did we confirm any effect of statins in lowering serum-lipids or specific inflammatory markers. We also did not establish whether statins were continued (or started) after ICU-to-ward discharge, or after hospital-discharge.

Some patients were lost to follow up, most notably after major elective surgery. In 23 cases we know that the patients moved to another location. For the remainder all that is known is that after finishing attending follow-up clinics these patients did not require any further hospitalisation at our institution over the subsequent nine years. Some patients may have died in the community, without requiring hospital admission; or may have been admitted to other hospitals.

Also, although we strived to control for likely confounders, there could be others: this includes treating all sepsis as if it is a homogeneous disease. Despite our aforementioned limitations, we also found no significant

association between statins and crude approximations of inflammation (three or more SIRS criteria)

Age, APACHE II score, and the presence of co-morbidities did negatively affect survival, as has been shown in other studies. Yet statin usage – despite being associated with older age, increased numbers of comorbidities, and increased APACHE II scores – did not alter outcome. The possibility remains that statins might protect against the development of sepsis or inflammation, but that any gain is, in the long run, offset by age or pre-existing illness.

Alternatively, perhaps patients receive a pre-ICU benefit thus avoiding ICU admission, or patients who are sick enough to need ICU patients have progressed beyond where statins could help. Our post-operative patients, who were not obviously septic but are known to be at risk, also did not demonstrate a benefit associated with statins. The counter argument could be that post-operative (non-septic) patients have too small an inflammatory response for statins to exert any effect.

In fact, post-operative patients appeared to be more likely die during their ICU stay if they had previously been prescribed statins (9% vs 3%, *P*=0.021; Table 2). Assuming this result to be a “true” one, the argument could be made that statin usage is harmful, or that it acts as a surrogate marker for high-risk patient groups (in which case any beneficial effect of statins could be masked by the risk of pre-existing illness). Equally, it is likely that a note of caution is required when interpreting this particular finding: the absolute numbers were small, and the increased mortality was not sustained to hospital discharge.

Establishing the role of statins in ICU patients may be further complicated by ICU patient heterogeneity, especially when compared to cardiac patients (all of whom will presumably have vascular disease) or those with isolated lipid abnormalities (versus ICU patients who often have multi-system disease).

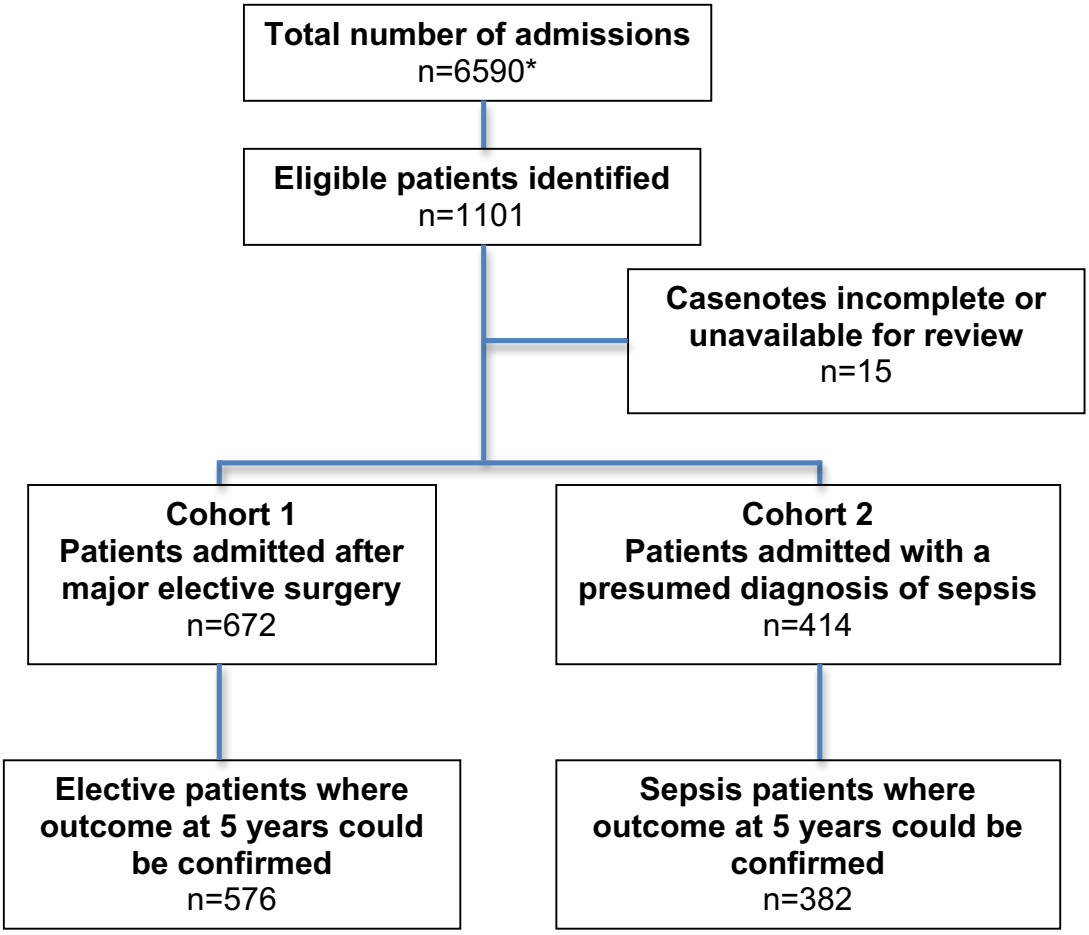
Pragmatically, one could argue that this study supports the conclusion that prior statin use does not seem to have a negative impact on long-term outcomes after admission to ICU. It has also been suggested that abrupt discontinuation of statins is associated with rapid loss of any inflammatory or endothelial benefit, and that there might be increased cardiac myonecrosis if statins are discontinued after major vascular surgery.[29-33] Accordingly, over time, a body of opinion has developed recommending that statins should be continued (where possible) upon ICU admission — a practice now adopted at NUH.[34-35]

We performed a sub-analysis, comparing the crude outcome data associated with different statins. Although we identified a potential increase in mortality associated with simvastatin in our cohort of septic patients, this was not replicated in post-operative patients. This should encourage further study, though we are mindful that statistical error can rise as sample size decreases. Accordingly, the numbers of patients prescribed fluvastatin, pravastatin and rosuvastatin were too small to perform meaningful subanalysis. Nevertheless, there may be heterogeneity amongst statins.[36] It remains unclear whether, unlike their lipid lowering effects, any putative pleiotropic effects belong to the entire class of statins or not; and how critical illness affects each agent's

pharmacokinetics and pharmacodynamics.[37-39] In short, much work remains to be done.

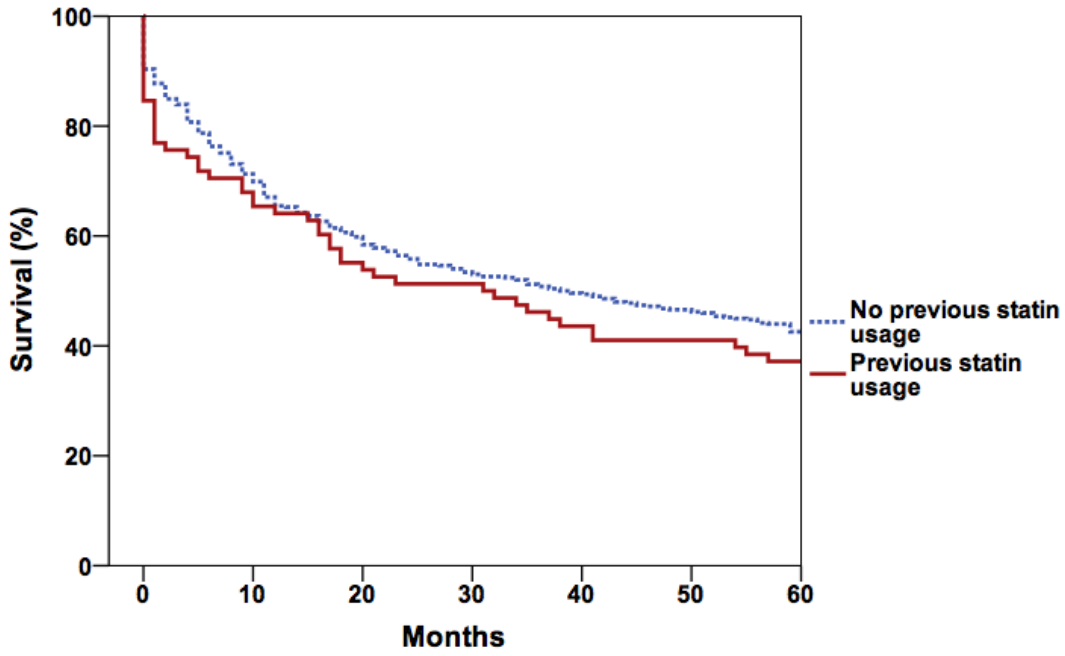
Figure 1: Flowchart of numbers of patients screened and identified at each stage of data collection.

Total number of patients screened



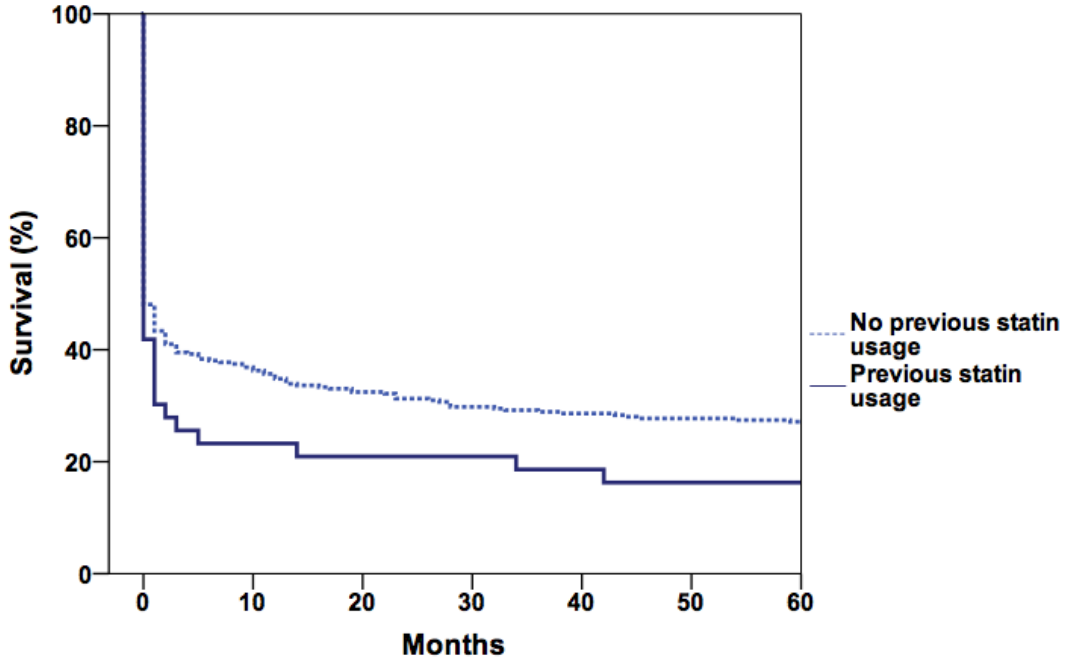
*Estimated from average yearly admissions over the time period as exact figure not available.

Figure 2: Kaplan Meier estimates of five year survival of patients admitted to intensive care after major elective surgery, comparing those known to have been prescribed statins prior to admission with those not prescribed statins



Log rank test significance *p*=0.302

Figure 3: Kaplan Meier estimates of five year survival of patients admitted to intensive care with a diagnosis of presumed sepsis, comparing those known to have been prescribed statins prior to admission with those not prescribed statins



Log rank test significance *p*=0.093

Table 1: Baseline characteristics of patients stratified by prior statin usage

	Post-operative patients, n=672		
	No prior statins (n=584)	**Prior statins (n=88)**	*P*-value*
Age, mean (SD)	61.6 (15.6)	67.7 (13.1)	0.001
Male gender, n (%)	366 (63)	66 (75)	0.024
APACHE II score, mean (SD)	13.2 (5.1)	14.5 (6.4)	0.029
Other comorbidities and medication usage			
Ischaemic heart disease, n (%)	56 (10)	53 (60)	<0.005
Other vascular disease, n (%)	65 (11)	33 (38)	<0.005
Diabetes, n (%)	33 (6)	22 (25)	<0.005
ACE inhibitors / ARAs, n (%)	57 (10)	41 (47)	<0.005
Ca^{2+} channel antagonists, n (%)	58 (10)	17 (19)	0.017
Beta-blockers, n (%)	72 (12)	28 (32)	<0.005
Nitrates, n (%)	10 (2)	10 (11)	<0.005
Type of surgery			
Oesophagectomy, n (%)	210 (36)	28 (32)	0.476
Hepato-biliary/pancreatic, n (%)	66 (11)	6 (7)	0.267
Vascular, n (%)	44 (8)	24 (27)	<0.005
Neurosurgery, n (%)	33 (6)	2 (2)	0.299
Type of statin			
Simvastatin, n (%)		37 (42)	
Atorvastatin, n (%)		30 (34)	
Other statin, n (%)		21 (24)	

	Patients with presumed sepsis, n=414		
	No prior statins (n=364)	**Prior statins (n=50)**	
Age, mean (SD)	60.0 (16.8)	69.6 (8.1)	<0.005
Male gender, n (%)	199 (55)	28 (56)	0.881
APACHE II score, mean (SD)	21.6 (8.1)	23.3 (8.6)	0.168
Other comorbidities and medication usage			
Ischaemic heart disease, n (%)	44 (12)	24 (48)	<0.005
Other vascular disease, n (%)	26 (7)	15 (30)	<0.005
Diabetes, n (%)	26 (7)	20 (40)	<0.005
ACE inhibitors / ARAs, n (%)	38 (10)	22 (44)	<0.005
Ca^{2+} channel antagonists, n (%)	23 (6)	16 (32)	<0.005
Beta-blockers, n (%)	32 (9)	13 (26)	0.001
Nitrates, n (%)	5 (1)	6 (12)	0.001
Type of statin			
Simvastatin, n (%)		23 (46)	
Atorvastatin, n (%)		22 (44)	
Other statin, n (%)		5 (10)	

Table 2: Crude outcome data stratified by statin usage

	Post-operative patients, n=672		
	No prior statins (n=584)	**Prior statins (n=88)**	*P*-value*
Died in ICU, n (%)	20 (3)	8 (9)	0.021
Died in hospital, n (%)	53 (9)	13 (15)	0.121
Median ICU stay, days (range)	2 (0-30)	2 (1-20)	0.517
Inotropes prescribed within 24hours of admission, n (%)	221 (38)	47 (53)	0.007
Presence of SIRS criteria**, n (%)	276 (49)	40 (46)	0.567
Died within 5 years, n (%)	286 (57) **[n=498]**	49 (63) **[n=78]**	0.390

	Patients with presumed sepsis, n=414		
	No prior statins (n=364)	**Prior statins (n=50)**	
Died in ICU, n (%)	159 (44)	24 (48)	0.649
Died in hospital, n (%)	197 (55)	29 (58)	0.762
Median ICU stay, days (range)	4 (1-31)	3 (1-31)	0.203
Presenting in shock, n (%)	326 (90)	43 (86)	0.466
Inotropes prescribed within 24hours of admission, n (%)	293 (81)	40 (80)	0.849
Presence of SIRS criteria**, n (%)	321 (91)	44 (90)	0.503
Died within 5 years, n (%)	247(73) **[n=339]**	36(84) **[n=43]**	0.142

**P*-values are for chi-squared tests except length of ICU stay where Mann-Whitney *U*-test was used

**Modified SIRS criteria (≥ 3 variables) was used

Table 3: Adjusted odds ratio for post-operative patients and patients presumed to have sepsis.

	Five year mortality for all patients			
	Post-operative patients, n=576		Patients with presumed sepsis, n=382	
	Adjusted odds ratio	*P*-value	**Adjusted odds ratio**	*P*-value
Age	1.02 - 1.05	<0.005	1.02 - 1.06	<0.005
Male gender	0.71 - 1.51	0.866	0.77 - 2.19	0.323
APACHE II score	1.00 - 1.09	0.017	1.05 - 1.13	<0.005
Other comorbidities and medication usage				
Ischaemic heart disease	0.59 - 1.94	0.825	0.09 - 0.93	0.035
Other vascular disease	0.80 - 2.26	0.266	0.24 - 1.723	0.036
Diabetes	0.28 - 1.09	0.090	0.96 - 5.81	0.060
ACE inhibitors / ARAs	0.66 - 1.99	0.623	0.39 - 2.29	0.896
Ca^{2+} channel antagonists	0.43 - 1.43	0.428	0.39 - 3.16	0.845
Beta-blockers	0.80 - 2.20	0.272	0.21 - 1.68	0.586
Nitrates	0.50 - 3.81	0.531	0.16 - 18.52	0.660
Cancer surgery	0.30 - 0.66	<0.005	-	-
Statin usage	0.46 - 1.59	0.630	0.31 - 2.87	0.917

Cox & Snell R^2 = 0.178

Table 4: Crude survival data stratified by type of statin

Post-operative patients

	Hospital mortality (n=672)	*P*-value*	5 year mortality (n=576)	*P*-value*
No statins, n (%)	53 (9)		286 (57)	
Atorvastatin, n (%)	3 (12)	0.735	14 (56)	0.999
Simvastatin, n (%)	7 (19)	0.096	25 (69)	0.167
Other statins, n (%)	3 (18)	0.407	10 (59)	0.999

Patients with presumed sepsis

	Hospital mortality (n=414)	*P*-value*	5 year mortality (n=382)	*P*-value*
No statins, n (%)	197 (54)		247 (73)	
Atorvastatin, n (%)	9 (50)	0.473	12 (67)	0.591
Simvastatin, n (%)	18 (86)	0.005	20 (95)	0.02
Other statins, n (%)	2 (50)	0.999	4 (100)	0.577

**P*-values are for chi-squared tests with Fisher's exact test

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