American Journal of Respiratory and Critical Care Medicine/AJRCCM

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Journal:	*American Journal of Respiratory And Critical Care Medicine*
Manuscript ID:	Blue-201306-1150OC.R3
Manuscript Type:	OC - Original Contribution
Date Submitted by the Author:	23-Dec-2013
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Keywords:	Delirium, Statin, Inflammation, CRP, CAM-ICU

Statin Use and Risk of Delirium in the Critically Ill

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VJP has grant funding from the NIHR Research for Patients Benefit programme. DD is funded by the Wellcome Trust (090661/Z/09/Z) and is a member of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged. SN was funded in part by NIHR CLAHRC for Cambridgeshire and Peterborough. DM is Co-Director of Research for the UK Intensive Care Foundation and their support is gratefully acknowledged.

Subject code: 4.6

Word count: 3651

At a glance commentary

Scientific Knowledge on the subject

Neuro-inflammation is believed to be a significant factor in delirium pathophysiology. Statins have a number of anti-inflammatory properties and have been investigated as a potential therapy for conditions thought to be related to systemic inflammation.

What This Study Adds to the Field

This observational study found a link between ongoing administration of statins and a reduction in risk of delirium, which could be mediated through a reduction in systemic inflammation.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale

Delirium is common in intensive care unit (ICU) patients and is a predictor of worse outcomes and neuroinflammation is a possible mechanism. The anti-inflammatory actions of statins may reduce delirium.

Objectives

To determine whether critically ill patients receiving statin therapy had a reduced risk of delirium than those not on statins.

Methods

A prospective cohort analysis of data from consecutive ICU patients admitted to a UK mixed medical and surgical critical care unit between August 2011 and February 2012; the Confusion Assessment Method for ICU (CAM-ICU) was used to determine the days each patient was assessed as being free of delirium during ICU admission.

Measurements

Delirium free days, daily administration of statins and serum C-reactive protein (CRP) were recorded.

Main results

Four hundred and seventy consecutive critical care patients were followed from August 2011 to February 2012 of whom 151 patients received statins. Using random-effects multivariable logistic regression, statin administration the previous evening was associated with the patient being assessed as free of delirium (OR = 2.28, (CI 1.01 to 5.13) $p < 0.05$) and with lower CRP ($\beta = -0.52$, $p < 0.01$) the following day. When the association between statin

and being assessed as free of delirium was controlled for CRP, the effect size became non-significant (OR = 1.56, (CI 0.64 to 3.79) p=0.32).

Conclusions

Ongoing statin therapy is associated with a lower daily risk of delirium in critically ill patients. An ongoing clinical trial, informed by this study, is investigating if statins are a potential therapy for delirium in the critically ill.

Keywords

Delirium; statin; inflammation; CRP; critical care; CAM-ICU

Introduction

Delirium is a form of acute brain dysfunction, with a prevalence of up to 65% in critically ill patients requiring mechanical ventilation in the UK.(1) It is associated with significantly worse clinical outcomes. Delirium is independently associated with a 3-fold increased risk of mortality at 6 months, and for survivors, a 10-fold increased risk of cognitive impairment at 12 months. (2,3) Long-term cognitive impairment after critical illness reduces quality of life, increases health care costs and leads to institutionalization. (4, 5)

While the pathogenesis of delirium remains poorly understood, there is evidence for ongoing neuroinflammation driving oxidative damage and apoptosis, which is hypothesized to drive the development of cognitive impairment. (6) Irrespective of whether patients have sepsis or not, during critical illness, higher levels of procalcitonin is associated with patients being free of delirium, while higher C-reactive protein (CRP) levels showed trends towards fewer delirium-free days. This implicates systemic inflammation in the pathophysiology of delirium in ICU. (7)

Statins exert pleiotropic effects independent of inhibiting cholesterol synthesis, and a significant proportion of these effects are anti-inflammatory and may be evident within 24 hours. (8, 9) Simvastatin is known to decrease systemic inflammation as measured by serum CRP in healthy volunteers and in critically ill patients with acute lung injury. (10, 11) In adult mice, surgical stress causes inflammation-mediated, hippocampal-dependent, cognitive dysfunction. Postoperative elevation of serum inflammatory cytokines was associated with memory impairment, reactive microgliosis and increased interleukin-1b expression in the hippocampus. (12) For these reasons, it has been suggested that statins might have a

clinical effect on reducing delirium. (13) Although statins have been investigated in clinical trials to modify organ dysfunction in critically ill patients, none have assessed delirium as an outcome. (7, 11, 14)

The aim of this study was to determine if statin use in critically ill patients was associated with delirium, as assessed using the Confusion Assessment Method-ICU (CAM-ICU). (15) The hypothesis to be tested that statin usage would be associated with less delirium, and would be associated with a reduction in systemic nflammation.

Methods

This was a prospective cohort study. The cohort comprised all consecutive patients admitted to a 19 bed mixed medical and surgical adult critical care unit in Watford General Hospital, a UK district general hospital. The study started on August 1st 2012 and included all patients admitted from that date on until February 29th 2012. Data was from ICU admission collected up until discharge from ICU. There were no exclusions, and therefore the study population included a variety of admissions including elective emergency, medical and surgical admissions. All patients were allocated a study number and data collected were anonymized. The ICU clinical staff was not informed regarding the study or hypothesis although they were aware data was being collected.

In order to derive a propensity score additional information was collected: age, sex, primary hypercholesterolemia, ischemic heart disease, diabetes, peripheral and cerebrovascular disease, admission following aortic aneurysm surgery. In addition the admitting diagnosis, data required to calculate daily modified severity of illness scores, presence of sepsis,

number of ventilator days, emergency or elective admission and pre-admission statin use were also documented. Additional detail regarding the collection of the data is provided in an online data supplement.

Outcome measures

For ICU patients the number of days without delirium or not in coma (any cause including sedation) is an indicator of normal cognitive status, i.e. awake and no delirium. The presence of delirium was assessed using the CAM-ICU. The CAM-ICU is a delirium screening tool developed for use by the bedside nurse as part of routine patient assessment. It has been validated in intubated critically ill patients against the reference DSM-IV criteria. (16) Patients were allocated to the 'never statin' group if they did not receive statins throughout ICU admission regardless of whether they had been on statins before admission. For daily comparison the patients in the 'statin' group were then allocated to the 'no statin received' group on an individual day if they did not receive their statin medication for whatever reason.

Clinical Assessments

Patients were routinely assessed by nurses first for level of sedation using the Richmond Agitation Sedation Scale (RASS) and then for delirium using the CAM-ICU. (17)

All daily nursing charts of study patients were reviewed to determine the number of days when an individual patient was assessed throughout a 24 hour period (8am to 8am) as CAM-ICU negative i.e. free of delirium. Patients are assessed using the CAM-ICU on an average of 2 times per 12 hour shift, the number of daily assessments of individual patients were not collected. If any CAM-ICU assessment on a given day recorded as positive or the patient was unable to be assessed due to lack of response, that day was counted as not delirium

free or coma free. Routine delirium screening was introduced in 2007 and there is ongoing nurse-led training.

Statins were given according to our standard practice, where in patients previously taking statins as soon as the attending physician made the decision that enteral therapy could be started the statin was administered if there were no contraindications e.g. elevated liver enzymes or ongoing macrolide therapy. It was not necessary for enteral feeding to be fully established. In keeping with evidence that simvastatin is more effective in cholesterol reduction if given in the evening, all statins were administered at approximately 22:00 Blood for serum CRP measurement was drawn at 06:00. (18) A member of the research team collected the data regarding statin administration (XZ). Additional detail regarding the assessements and measurement of CRP is provided in an online data supplement.

Statistical analysis

All analyses were conducted using STATA 12.1 (Stata Corp, Texas). Distributions of each variable were first examined in relation to statin use. The distribution of CRP was positively skewed, necessitating log-transformation for analyses. Crude differences in continuous variables were assessed with t-test and Mann-Whitney U test; differences in categorical variables were assessed using χ^2 and Fisher's exact test. Associations were assessed with 95% confidence intervals (CI) and considered significant at $p<0.05$.

Demonstrating mediation requires four steps; the effect of the independent variable (statin) on the dependent variable (delirium free) must be significant, the path from the independent variable (statin) to the mediator (CRP) must be significant, the path from the

mediator (CRP) to the dependent variable (delirium free) must be significant and the independent variable (statin) has a reduced or no effect on the dependent variable after adjustment for the mediator (CRP). (19) Accordingly, the analysis sought to address the following questions:

1. Is statin use associated with being delirium free (when not controlling for CRP)?
2. Is statin use associated with serum CRP levels?
3. Is CRP associated with being delirium free?
4. Does the association between statin use and being delirium free change when simultaneously adjusting for CRP so as to suggest CRP mediates this relationship?

Three regression models were used to test each of the hypotheses, with 3 and 4 tested simultaneously. (20) Random-effects accounted for the clustered nature of the data. The association between being free of delirium and CRP the following day was assessed using a linear mixed-effect model. Three mixed-effects logistic regression models tested (i) the lagged association between statin use and being free of delirium the following day, (ii) the association between CRP and being free of delirium the same day, and (iii) the lagged association between statin use and being free of delirium the following day controlling for CRP. The term "lagged" refers to the temporal structure of the data, i.e. that statins were routinely given the previous evening. Thus, the statin (exposure) was used to estimate the odds of being delirium free the next day (outcome). Without this lag, exposure and outcome would have been assigned to the same day and since statins were administered following delirium assessment would not have been a causally appropriate model for the purposes of this study.

In order to reduce confounding introduced by nonrandom patient associated factors for statin therapy, a propensity score analysis was included. Variables for the propensity score were selected from among demographic and clinical variables associated with statin prescription: age, sex, primary hypercholesterolemia, ischemic heart disease, diabetes, peripheral and cerebrovascular disease, admission following aortic aneurysm surgery. In addition all models were adjusted by age, sex, daily modified daily SOFA score (excluding the neurological component, Glasgow Coma Score (GCS)), sepsis on admission, propensity score, need for ventilator support (known risk factor for delirium), emergency admission and pre-admission statin use. Any day of observation on which a participant died was excluded from the analysis. Data were assumed to be missing at random, as any predictors of missingness were included as covariates in the random-effects models to account for this.

Results

In total, 470 consecutive critical care patients with 2927 person-days follow up were included in the analysis (median 5 days). There were no exclusions. Clinical characteristics of the 151 (32.1%) who received statins during their stay, compared to the 319 (67.9%) who did not, are given in Table 1. There were no patients started on statins as a new therapy, statins were only prescribed for patients who had been on statins before admission. The group receiving statins was more likely to be older and have lower median CRP levels (70 versus 88 mg/l). Patients who were not on statins before admission were more likely to require ventilatory support. For reasons for admission see Table E1 in the online supplement. In total 167 patients were assessed as having delirium at least once of which 44

had delirium throughout the admission. The median duration of delirium was two days (IQR 1, 5)

Table 2 shows each pair of associations between statins, CRP and being free of delirium on any given day, using a random-effects logistic regression model to adjust for the covariates age, sex, daily severity of illness, sepsis, requiring ventilator support, emergency admission and the propensity score. The difference between the number of subjects (N) in table 2 used to calculate the pair-wise associations results from missing data, see Tables E2 and E3 in online supplement. The decision was made to use random effects model as one technique that estimates robust standard errors where covariates are predictors of data missing i.e. missing at random. As expected patients were more likely to develop delirium if they were admitted as an emergency and if more seriously ill and required ventilatory support. CRP levels were higher in patients with sepsis.

There was variability in statin administration such that statins were omitted 46% of total admission days for patients who had been receiving statins pre-admission. This was for a variety of reasons including unable to receive or absorb medication, liver enzyme rise or concurrent macrolide prescription.

Association between statin use and being free of delirium

For ongoing statin therapy, the independent variable was statin (yes / no) administered the previous evening with being free of delirium the following day as the dependent variable. When accounting for this dosing schedule, an association between statin and being free of delirium was observed (OR = 2.28, 95% CI 1.01 to 5.13, p=0 < 0.05) (Table 2).

Association between statin use and CRP

The independent variable was statin use the previous evening (yes / no) with log CRP as the dependent variable. Statin use was associated with lower CRP levels (figure 1a) Linear regression demonstrated a significant association with statin administration (β = -0.52, 95% CI -0.7 to -0.33, p <0.01) (Table 2). This reduction in log CRP when statins were given the previous evening is the equivalent to CRP 100 mg/l lowering to 59 mg/l or CRP 250 mg/l lowering to 148 mg/l on the natural scale.

Association between statin use and being free of delirium after adjustment for CRP

The independent variables were statin use the previous evening (yes / no) and log CRP with being free of delirium as the dependent variable. The observed effect size of statin administration on the probability of being free of delirium was reduced (OR = 1.56, 95% CI 0.64 to 3.79) and became non-significant (p=0.32) when accounting for CRP (Table 3). A significant relationship between CRP and being free of delirium remained (OR 0.68, 95% CI 0.51– 0.90 (Table 3). The probability of being free of delirium had a strongest association with CRP when CRP is less than 100 mg/l; there is an attenuated decrease in the probability of being delirium free at the highest levels of CRP.

For every day a statin user continued to receive a statin the odds of being delirium-free and coma-free increased by 39% (OR 1.39 (95% CI 1.18 to 1.63) p <0.001 (Table 4)).

Discussion

In this population of patients admitted to critical care, after adjusting for age, sex, daily illness severity, ongoing statin therapy was associated with a lower daily risk of delirium as well as a concomitant reduction in serum CRP. These findings are the first to suggest that ongoing statin use reduces brain dysfunction as assessed using the CAM-ICU in consecutive critical care admissions. These data raise the suggestion that an anti-inflammatory action may form part of the basis of the statin-delirium relationship and are consistent with the neuroinflammatory hypothesis of delirium however additional research is required to confirm this.

Statins are known to have a number of anti-inflammatory properties in addition to their lipid lowering actions. (6, 7, 21) In a rat model, it has been demonstrated that surgery under anesthesia but not anesthesia alone causes inflammation-mediated, hippocampal-dependent, cognitive dysfunction. (22) Moreover in statin-treated animals there is preservation of memory retrieval following head injury, while in a separate study following unilateral nephrectomy there was a decrease in functional neurological deficits in animals who received statins. (23, 24) Published studies on the use of statins and delirium in intensive care unit patients have conflicting results. (25-27) They are limited to pre-operative use of statins in patients following cardiac surgery. Importantly in all these studies, it is not specified whether the statins were withdrawn on ICU admission.

Two small trials support a plausible anti-inflammatory effect of statins used at clinically relevant doses over the short-term. One study in 42 patients comparing one dose of 80 mgs simvastatin with placebo demonstrated significant reductions in serum median and mean CRP concentrations measured 48 hours later. (28) Another trial compared 17 patients who received standard therapy for unstable angina or non-Q wave myocardial infarction with 13

patients also given one dose of cerivastatin. (29) At 24 hours cerivastatin treated patients had significantly lowered CRP levels.

There is increasing evidence neuroinflammation has a major part in the development and maintenance of delirium. (30-33) Pre-admission statins did not effect the risk of delirium, but this study did show a risk reduction in developing delirium on a day-by-day basis with the administration of statins, suggesting that statins actively protect against delirium rather than indicating this was a statin withdrawal syndrome. The observed effect following statin administration suggests a biologically plausible causal pathway whereby a reduction in systemic inflammation mediates the statin-delirium relationship. In the analyses the criteria for mediation were largely met: statin use (dependent variable) was associated with being free of delirium (independent variable); statin use was associated with CRP (mediating variable); and adjusting the association between statin use and being free of delirium by CRP showed a reduction in effect size. Previous studies assessing markers of inflammation and delirium during critical illness have had conflicting results; a recent study of 138 critically ill patients measuring CRP on enrollment and day 5 did not demonstrate an association with delirium.(11, 34)

The main strength of this study is that a large number of consecutive patients with data on daily mental status assessment, CRP measurements and administration of statin therapy, in a general intensive care unit were included. In addition data regarding severity of illness over time were collected using a modified SOFA score. The SOFA is a well-established measure of severity of illness in the critically ill, however we did not include the neurological component (GCS). This is consistent with other analyses. (35) It is important to recognise that the inclusion of a neurological measure of arousal (GCS), which is a cardinal component

of delirium, as a covariate for illness severity would lead to over-adjustment. In other words, it would not be appropriate to have GCS represented as both a covariate and outcome measure.

The models were also adjusted for daily severity of illness using a modified SOFA score in order to address the concern that the attending physician's decision to commence with administration of enteral therapy medication with or without nutrition may have coincided with clinical improvement and consequently a lower delirium risk. By estimating multiple separate models, one per individual day of admission for each patient, it could be shown that the reduction in delirium occurred on the days in which a statin had been given the previous evening. This takes into account the patients on statins before admission who did not receive them during ICU admission as those days were analysed as no statin given.

The patient group in this study is broadly representative of the case mix of patients admitted to a mixed critical care unit in contrast to other studies of delirium in the critical care environment where the population recruited has largely been post-operative cardiac patients. Previous studies of statin and CRP have measured plasma CRP levels at specified time points during patients admission, the most frequent being a recent study in patients with severe sepsis in which CRP was measured every other day for the first week and only twice in the second. (36) Our study has a robust data set based on longitudional observations providing a depth that studies with less frequent observations have lacked.

Several limitations should be acknowledged. Firstly, this is a single site study, and as with any observational study, despite the multiple adjustments, residual confounding remains a possibility. The possibility that the administration of statins is more likely as a patient's clinical condition improves is a potential confounding factor. However given the relation

between statin usage and delirium persisted when adjusted for the daily severity of illness means this is unlikely. Data collected regarding patients receiving statins were limited to the daily administration of statins while on ICU, not whether the patients had been taking statins before admission.

Confounding by indication is another potential limitation, patients prescribed statins prior to admission may have differing risks for delirium, compared to those not on statins. In our analysis we have used a propensity score based on a number of variables relating to the likelihood of statin prescription. It may be that, despite including the obvious variables such as diabetes and ischemic heart disease, we have not captured other factors, for instance one that would make it less likely a patient would seek medical attention. (37)

There were three statins prescribed, simvastatin, atorvastatin and pravastatin, although the majority, 134 of the 151 patients, was given simvastatin. It is not clear if a specific statin may be superior particularly given statins are known to have varying degrees of brain penetration. (38) In addition, information regarding the dose of individual statins was lacking such that dose-response thresholds could not be examined. With regard to effective doses, clinical trials have found that high-dose, compared with conventional-dose, statin therapy reduces the risk of cardiovascular events in patients with stable CHD and acute coronary syndromes. (39) There were no data collected regarding other known confounding factors, particularly the sedative agents used or doses administered. The standard sedation protocol for ventilated patients at our hospital uses fentanyl and propofol infusions with daily sedation interruption as clinically appropriate. Midazolam is used occasionally and antipsychotics are reserved for patients who have hyperactive delirium. While it is likely the sedation exposure was similar in all patients, this cannot be assumed.

We did not investigate trajectories of CRP change in order to determine a rate or limit of reduction. Instead we estimated a separate model for each day with statin, SOFA, CRP and delirium information, linked together using random-effects for each individual in order to demonstrate the association between statin and delirium.

We used delirium-free days as the outcome i.e. when patients could be assessed as not in delirium using the CAM-ICU rather than the incidence of delirium in patients. The limitations of cognitive assessments in critically ill patients are recognised. Although the CAM-ICU has been shown to lack sensitivity it is one of the only two tools validated and recommended for use by the recent Pain, Analgesia and Delirium (PAD) Clinical Practice Guidelines from the American College of Critical Care Medicine. (40) It indicates normal brain function in critically ill patients, rather than a patient being in coma (whether sedative induced or due to a medical cause), or having delirium. For the purposes of this observational trial, being assessed as delirium free is clinically desirable and therefore relevant for critically ill patients.

In conclusion, this is the first report to indicate a beneficial effect of ongoing statin therapy on delirium in a UK critically ill population. These results suggest that in patients receiving statins prior to ICU admission, statin therapy should be continued to prevent delirium, albeit with appropriate safety monitoring. In order to test the hypothesis generated by this study that daily statin therapy reduces delirium in the critically ill, a phase 2 randomised placebo controlled trial in critically ill ventilated patients is ongoing (ISRCTN89079989). It is underpinned by investigations to determine the mechanisms by which statins may be effective

Acknowledgments

The authors would like to thank Ms Hannah Payne RN (Watford General Hospital) for her assistance in compiling the database, and Dr Alessandro Morandi MD, MPH (Department of Rehabilitation and Aged Care Unit, Ancelle della Carità Hospital, Cremona, Italy; Geriatric Research Group, Brescia, Italy; Center for Quality of Aging, Vanderbilt) and Dr Tim Girard MD, MSCI (Vanderbilt University Medical Center, Nashville, Center for Quality of Aging, (Vanderbilt) for their advice and support on the design and analysis of this project.

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Figure legends

Figure 1.

[a]. The relationship between levels of CRP according to statin use the previous evening. Each point shows the average CRP after adjustments for covariates in each group along with 95% confidence intervals (whiskers above and below the point estimate). There is little overlap in the width of the confidence intervals in each group, suggesting that statin use significantly influences CRP ($p<0.01$).

[b]. The relationship between adjusted CRP and probability of being free of delirium free, adjusting by statin use. Each point shows the probability of being free of delirium along with 95% confidence intervals (whiskers above and below point estimate). The higher the CRP, the lower the probability of being free of delirium. For example, if CRP is 20 mg/l the probability of being delirium free on a given day is 65%; if CRP is 100 mg/l, the probability is 42%.

Together, these figures show that statin use is associated with lower CRP, and this in turn is associated with a higher probability of being free of delirium.

Table 1. Clinical characteristics of study population, stratified by statin use.

	Statin use				
	No (n=319)		Yes (n=151)		p
Age (years, SD)	63	(19)	77	(11)	<0.01
Sex (Male, %)	165	(52)	86	(57)	0.51
Days delirium free (days, IQR)	3	(1-5)	2	(1-5)	0.81
Delirium (Y/N)*n (%)	125/188	(40%/60%)	50/100	(33%/67%)	0.17
CRP (median (mg/l), IQR)†	88	(47-207)	70	(33-193)	<0.01
ICU length of stay (days, IQR)	5	(3-8)	4	(2-7)	0.07
APACHE II score (SD)	17	(7)	18	(7)	0.32
ICU mortality (%)	63	(20)	27	(18)	0.71
Ventilated (n %)	148	(46)	49	(32)	<0.01
Ventilated (days, IQR)	2	(0-9)	1	(0- 13)	0.75
Indication for statin (%‡)					<0.01
IHD or CVD	62	(18)	67	(56)	
Peripheral vascular disease	9	(3)	4	(3)	
Abdominal aortic aneurysm	10	(3)	6	(5)	
Diabetes mellitus	21	(6)	15	(13)	
Hypercholesterolemia	4	(1)	20	(19)	
None	202	(57)	0	(0)	
Missing	44	(13)	7	(6)	

SD standard deviation, IQR interquartile range, CRP C-reactive protein; APACHE acute physiology and chronic health evaluation score; IHD ischemic heart disease; CVD cerebrovascular disease.

*Y = Assessed with delirium on at least one occasion. N = Unable to be assessed (coma) or assessed free of delirium throughout admission.

†CRP on admission (not adjusted), ‡Percentages are given for the columns, by statin use.

Table 2. Random-effects logistic regression model showing pairwise associations between statin, CRP and being free of delirium.

	Statin : free of delirium N = 228 Person.days = 1246			Statin : CRP N = 226 Person.days = 1123		
	OR	**(95% CI)**	**P**	**β**	**(95% CI)**	**P**
Statin	2.28	(1.01 to 5.13)	< 0.05	-0.52	(-0.70 to -0.33)	<0.01
Age (per year)	0.99	(0.96 to 1.03)	0.71	-0.00	(-0.01 to 0.00)	0.35
Sex (women v men)	0.48	(0.20 to 1.19)	0.11	0.03	(-0.19 to 0.24)	0.81
mSOFA (per point)	0.59	(0.47 to 0.73)	<0.01	0.13	(0.09 to 0.18)	<0.01
Sepsis (yes v no)	1.53	(0.62 to 3.76)	0.36	0.29	(0.07 to 0.51)	0.01
Propensity score*	2.90	(0.35 to 23.83)	0.32	0.02	(-0.49 to 0.53)	0.94
Ventilated (yes v no)	0.78	(0.72 to 0.84)	<0.01	-0.01	(-0.03 to 0.00)	0.14
Emergency (v elective)	12.81	(3.05 to 53.82)	<0.01	0.36	(0.05 to 0.66)	0.02

CI confidence intervals; CRP C-reactive protein; mSOFA modified sequential organ failure assessment (minus Glasgow Coma Score)

OR odds ratio; β is the slope from linear regression

CRP quantities $\log_{(e)}$ transformed to obtain normal distribution. When used as a dependent variable, OR is per increase in standard deviation of $\log_{(e)}$ CRP.

*Propensity score according to age, sex, primary hypercholesterolemia, ischaemic heart disease, diabetes, peripheral and cerebrovascular disease and admission for aortic aneurysm surgery

All models allow for random-effects for each individual.

Table 3. Random-effects logistic regression model showing the relationship between statin and free of delirium, adjusted by CRP.

	Statin + CRP : free of delirium N = 225 Person.days = 1117		
	OR	**(95% CI)**	**P**
Statin	1.56	(0.64 to 3.79)	0.32
CRP	0.68	(0.51 to 0.90)	0.01
Age (per year)	0.99	(0.96 to 1.02)	0.46
Sex (women v men)	0.62	(0.25 to 1.53)	0.30
mSOFA (per point)	0.60	(0.48 to 0.76)	<0.01
Sepsis (yes v no)	2.46	(0.95 to 6.36)	0.06
Propensity score*	3.63	(0.41 to 31.8)	0.24
Ventilated (yes v no)	0.74	(0.68 to 0.81)	<0.01
Elective (vs. Emergency)	17.6	(3.96 to 78.1)	<0.01

OR odds ratio, CI confidence intervals; CRP C-reactive protein; mSOFA sequential organ failure assessment (minus Glasgow Coma Score) CRP quantities log(e) transformed to obtain normal distribution. (When used as a dependent variable, OR is per increase in standard deviation of log(e) CRP.)

*Propensity score according to age, sex, primary hypercholesterolemia, ischaemic heart disease, diabetes, peripheral and cerebrovascular disease and admission for aortic aneurysm surgery.

All models allow for random-effects for each individual.

Table 4. The relationship between statin continuation and the odds of being delirium free coma free in persons prescribed statins prior to admission.

		Statin continuation **N: 89** **Person.days 405**	
	OR	**(95% CI)**	**P**
Days on statin (per day)	1.39	(1.18 to 1.63)	<0.01
Age (per year)	0.97	(0.91 to 1.02)	0.22
Sex (women v men)	0.64	(0.19 to 2.10)	0.460
mSOFA (per point)	0.79	(0.56 to 1.11)	0.17
Sepsis (yes v no)	3.23	(1.01 to 10.47)	0.05
Propensity score*	2.03	(0.07 to 62.99)	0.69
Ventilated (yes v no)	0.71	(0.62 to 0.80)	<0.01
Emergency (v elective)	28.2	(5.20 to 153)	<0.01

OR odds ratio, CI confidence intervals, mSOFA modified SOFA excluding Glasgow Coma Scale

*Propensity score accounting for age, sex, primary hypercholesterolemia, ischemic heart disease, diabetes, peripheral and cerebrovascular disease and admission for aortic aneurysm surgery.

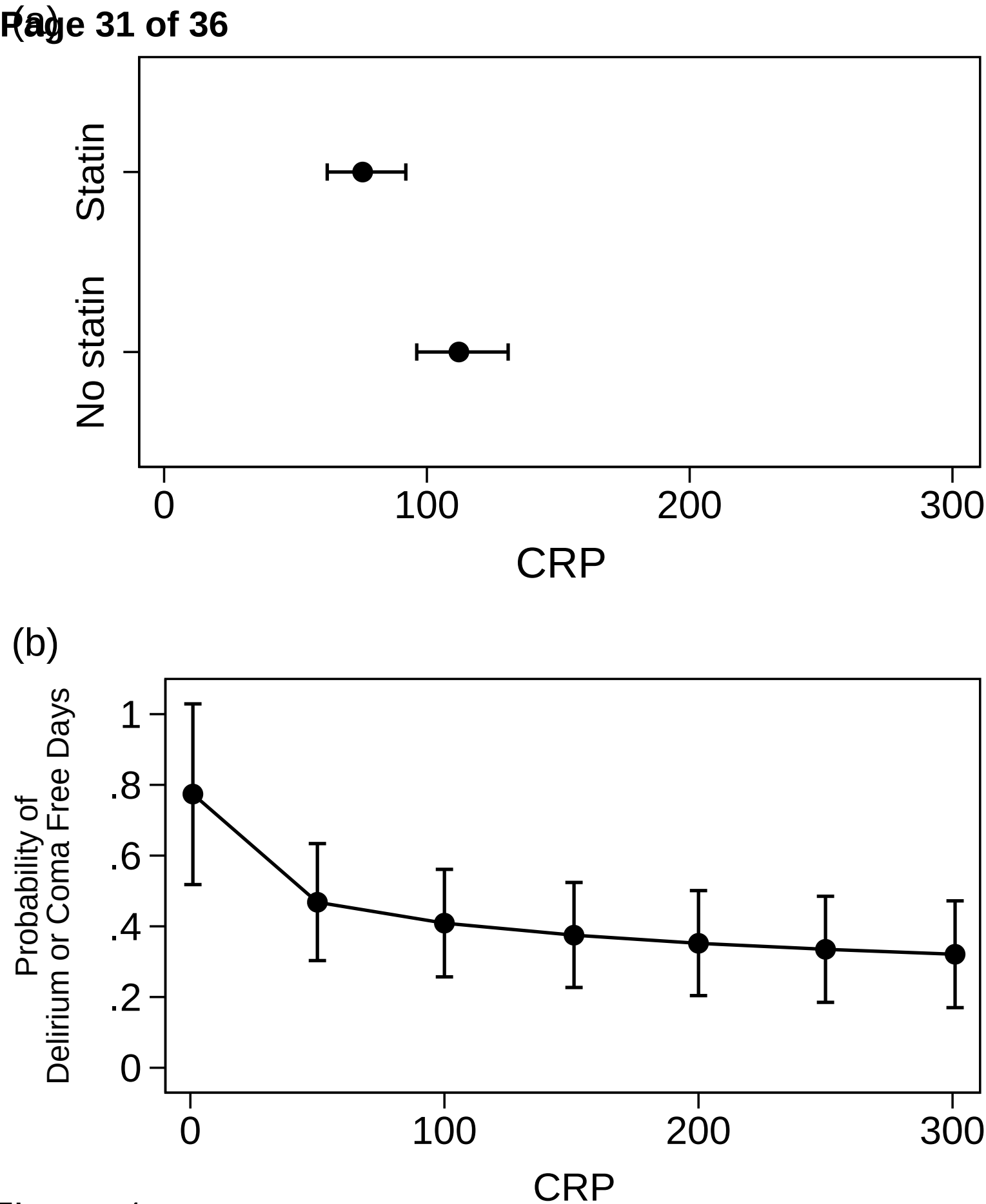
(a)
Statin
No statin
0
100
200
300
CRP
(b)
Probability of
Delirium or Coma Free Days
1
.8
.6
.4
.2
0
0
100
200
300
CRP

Figure 1

Online Data Supplement

Statin Use and Risk of Delirium in the Critically Ill

VJ Page, D Davis, X Zhao, S Norton, A Casarin, T Brown, EW Ely and DF McAuley

Methods

Data Collection

Daily data regarding statin prescription and administration, delirium assessment and mortality were collected by a member of the research team. Demographic data, admission diagnoses including presence of sepsis, elective or emergency, number of ventilator days and APACHE II scores used to describe the trial population were obtained from the ICU audit database set up for the requirements of the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme by a member of the research team.

Data for daily severity of illness scores – Sequential Organ Failure Assessment score (SOFA), were collected from daily nursing charts and available laboratory results on pathology computer system. If there were no blood gases available on a given day the oxygen saturation/fractional inspired oxygen ratio as previously described, was used. [E1] If complete SOFA data was not available on a given day, that was considered to be missing data. The daily mSOFA was calculated by omitting the Glasgow Coma Score contribution.

Data for the propensity score was collected from patient records.

Clinical Assessments

There were two components to the assessment of brain dysfunction: delirium and sedation/coma. Patients are routinely assessed by bedside nurses first for level of sedation using the Richmond Agitation Sedation Scale and then for delirium using the CAM-ICU by

nursing staff. [E2] The Richmond Agitation-Sedation Score consists of one value with response options ranging from +4 to -5 where a score of 0 is considered alert and calm, +4 is combative and -5 is no response to verbal or physical stimulation. Patients are defined as delirious if they respond to verbal stimulation with eye opening, equivalent to a Richmond Agitation Sedation Score (RASS) of –2 to +4) and screen positive for delirium using the CAM-ICU. [E3] Patients were defined unable to be assessed or comatose if they respond only to physical/painful stimulation with movement but no eye-opening or if they have no response to verbal or physical stimulation.

For the CAM-ICU, the patient is initially assessed for altered or fluctuating mental status, as well as inattention tested using a 10 letter sequence where the patient is required to squeeze the clinician's hand only when the letter A is stated. The patient is then assessed for disorganised thinking by their ability to answer four simple yes/no questions and a command, and finally for reduced level of consciousness. Patients are defined as delirious if altered mental status and inattention are present with disorganised thinking and/or reduced level of consciousness.

All daily nursing charts of study patients were reviewed to determine the number of days when an individual patient was assessed throughout a 24 hour period (8am to 8am) as CAM-ICU negative i.e. free of delirium.

Laboratory analyses

Serum C - reactive protein (CRP) levels were measured as a standard routine test in the local hospital pathology department. Patient blood samples were collected into tubes containing serum separation gel. The CRP concentration was measured using a sandwich immunoassay method with an Ortho Vitros Fusion 5.1 analyzer. [E4]

Table E1

Study Cohort Admission Diagnosis

Primary Diagnosis	N (%)
Elective surgery	104 (22%)
Sepsis/ARDS	89 (19%)
Pneumonia	59 (13%)
Cardiovascular/vascular embolism	49 (10%)
Hepatic or renal failure	49 (10%)
COPD or other respiratory causes	41 (9%)
Metabolic or toxins	38 (8%)
Haemorrhage/trauma	19 (4%)
Cerebral pathology	16 (3%)
Other*	5 (1%)

*Other includes three obstetric patients, two with musculoskeletal disorders and one with anaphylaxis.

Table E3: Missing data

	Denominator	Data	Percentage
Age	470	470	100%
Sex	470	470	100%
Ventilation	470	470	100%
Elective/Emergency	470	470	100%
Pre-admission statin use	470	470	100%
Indication for statin	470	420	89%
APACHE II*	470	418	89%
Sepsis	470	420	89%
Propensity score	470	357	76%

*APACHE – Acute Physiology and Chronic Health Evaluation

Table E4: Missing longitudinal data

	Denominator	Data	Percentage
Statin administration	2311	2311	100%
CRP	2868	2136	74%
mSOFA*	2868	1848	64%

*mSOFA – SOFA score minus Glasgow Coma Score component.

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E3 Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the Intensive Care Unit (CAM-ICU). *Crit Care Med.* 2001;29(7): 1370-79.

E4 Ortho-Clinical Diagnostics, Inc. document: Pub. No. J20123 Version 9.0 (Date of Revision 28-02-2012)