Evaluating early administration of the hydroxymethylglutaryl-CoA reductase inhibitor simvastatin in the prevention and treatment of delirium in critically ill ventilated patients: a randomised, placebo-controlled trial (MoDUS)

Valerie J Page[1, 2], A Casarin[3], E Wesley Ely[4,5], Xiao Bei Zhao[1], C McDowell[6], L Murphy[6] and Danny F McAuley[7, 8]

1. Intensive Care Unit, Watford General Hospital, Vicarage Road, Watford WD18 0HB UK
2. Faculty of Medicine, Imperial College, South Kensington Campus London SW7 2AZ, UK
3. Research Design Service (NIHR) Coton House, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ UK
4. Department of Medicine, Vanderbilt University School of Medicine Nashville USA
5. VA TN Valley Geriatric Research Education Clinical Center (GRECC), Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville USA
6. Northern Ireland Clinical Trials Unit, Royal Victoria Hospital, Belfast Health and Social Care Trust, Grosvenor Road, Belfast, BT12 6BA, N Ireland
7. Centre for Experimental Medicine, The Queen's University of Belfast, Health Sciences Building, 97 Lisburn Road, Belfast, BT9 7BL, N Ireland
8. Royal Victoria Hospital, Belfast Health and Social Care Trust, Grosvenor Road, Belfast, BT12 6BA, N Ireland

Corresponding author:

Dr Valerie J Page

Department of Anaesthesia

Watford General Hospital

Vicarage Road

Watford

WD18 0HB

UK

Telephone number +44 1923217604

Fax number +44 1923217141

Email v.page@imperial.ac.uk

Key Words: Delirium, statin, intensive care.

Word count: 5107

Summary

Background. Delirium in the critically ill is associated with poor clinical outcomes. It is believed that neuroinflammation is an important mechanism in the pathogenesis of delirium. Simvastatin has anti-inflammatory properties and may reduce delirium. The aim of this study was to establish whether early treatment with simvastatin would decrease the time that survivors of critical illness spent in delirium or coma.

Methods. This double-blind, placebo-controlled randomised trial was conducted in a general adult intensive care unit (ICU). Critically ill patients (≥18 years) needing mechanical ventilation within 72 h of admission were enrolled. Patients were randomised in a 1:1 ratio to receive either simvastatin 80mgs or placebo daily for up to a maximum of 28 days treatment, irrespective of coma or delirium status. Delirium was assessed using the confusion assessment method for the ICU (CAM-ICU). The primary outcome was alive, delirium-free and coma-free days, in the first 14 days after randomisation. ICU clinical and research staff and patients were blinded to treatment. Analyses were by intention to treat and no extrapolation was performed. This trial was registered with the International Standard Randomised Controlled Trial Registry, number ISRCTN89079989.

Findings. One hundred and forty-two patients were randomised, and included in the final analysis, 71 simvastatin, and 71 placebo. The mean number of days alive without delirium and without coma at day 14 did not differ significantly between the two groups (5·7 ± 5·1 days with simvastatin and 6·1 ± 5·2 days with placebo; mean difference, 0 days [95% CI, -1·3 to 2·1]; P = 0·66). The most common adverse event was an elevated creatine kinase to over ten times the upper limit of normal (eight (11·3%) in the simvastatin group vs. three (4.2%) in the placebo group p=0·208). No patient had a serious adverse event related to the study drug.

Interpretation. These results do not support the hypothesis that simvastatin modifies duration of delirium and coma in critically ill patients.

Funding. National Institute for Health Research.

Research in context

Systematic review

We searched PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews without language or date restrictions for published research that assessed the use of statins for mechanically ventilated patients in intensive care units with delirium as either the primary or a secondary outcome. The most recent search was done on 19th March, 2017. We searched PubMed with the key words “intensive care”, “critical care”, “delirium”, and “statins”. We included only studies in adult patients.

A systematic review and meta-analysis evaluating the role of statins in the prevention of delirium in critically ill and cardiac surgical patients included six studies. While it did not show a benefit with statin therapy all of the studies included were observational. A preplanned secondary analysis of the SAILS trial dataset, a randomised controlled trial of rosuvastatin versus placebo in patients with sepsis-associated acute respiratory distress syndrome, assessed the impact on delirium in 272 patients. It showed no benefit of rosuvastatin in reducing delirium or cognitive impairment during 12 months of follow up. The study was not powered for superiority and in view of the low lipophilicity of rosuvastatin the study was unable to conclude that a different statin would not be beneficial.

There are no relevant Cochrane reviews for delirium.

Added value of this study

This randomised controlled trial evaluated the effects of enteral simvastatin on delirium in critically ill mechanically ventilated patients. Simvastatin did not modify the duration of brain dysfunction according to number of patient days assessed to be in coma and days in delirium. Its use is not recommended for the management of delirium in this patient population.

Implications of all the available evidence

Simvastatin is not beneficial in increasing the number of days patients spend without coma or delirium in this vulnerable population at high risk of delirium. Statins should not be used in the management of critically ill patients at risk of, or with delirium.

Background

Delirium is a clinical syndrome characterised by acute brain dysfunction and associated with worse outcomes including long-term cognitive impairment, increased length of hospital stay and costs.[1-4] The prevalence of delirium in patients in critical care is reported to be up to 74% in critically ill patients with a high severity of illness and approximately 50% in patients who require mechanical ventilation or over 48 hours.[3],[4] There is evidence in animal and human studies that neuroinflammation is a contributing factor to long term cognitive imparirment.[5] Literature includes a relationship between elevated serum inflammatory markers in critically ill patients regardless of the presence of sepsis,[6] higher levels of CSF:serum IL-1β ratios in delirious than non-delirious patients and an upregulation of CNS inflammation in patients who died with delirium unrelated to infection.[7,8]

No medications that have been shown to prevent or reduce delirium in mechanically ventilated, critically ill adults, studies undertaken in elective cardiac surgical patients are not applicable to this population. Statins, in addition to decreasing cholesterol synthesis, have complex pleiotropic effects.[9] These pleiotropic effects may prevent or attenuate delirium in critical illness by acting on causative mechanisms including neuroinflammation, blood-brain barrier injury, neuronal apoptosis, ischaemia, haemorrhage and microglia activation. In vitro and animal studies have shown that statins suppress the up-regulation of toll- like receptors (which trigger inflammation) and reduce the release of TNF-α, IL-1β and MCP-1 as well as leukocyte adhesion molecules implicated in the development of endothelial damage and blood-brain barrier alterations.[10] In animal studies statins have been shown to preserve post-operative memory retrieval and in traumatic brain injury to increase hippocampal neuron survival with improved neurological function.[11]

Two large cohort observational studies found an association between reduction of the risk of delirium in critically ill patients with ongoing use but not pre-hospital statin alone raising the hypothesis that statins would potentially decrease delirium in this patient population.[12, 13] An in vitro study comparing different statins for prevention of neurodegenerative conditions concluded that monacolin J derivatives (natural and semi-synthetic statins), which includes

simvastatin, were the most beneficial due to better lipophilicity and capacity to penetrate the blood–brain barrier. [14] A preplanned secondary analysis of days in delirium was undertaken as part of a study in to determine the effects of statin therapy on mortality in mechanically ventilated patients with acute respiratory distress syndrome.[15] Rosuvastatin, known to be relatively hydrophilic, was used and there was no improvement in days spent in delirium or cognitive outcomes.

The aim of the Modifying Delirium Using Simvastatin (MoDUS) trial was to test the hypothesis that treatment with enteral for a maximum of 28 days will increase the number of days alive and assessed as being delirium-free and coma-free, in mechanically ventilated patients at high risk of delirium.

Methods

This was a randomised, double-blind, placebo-controlled trial of enteral simvastatin in adult (≥ 18 years) mechanically ventilated patients. Patients were recruited from the general mixed medical–surgical adult ICU in Watford General Hospital (Watford, UK).

The trial was approved by a national research ethics committee (12/NE/0383) and the MHRA (CTA number 18300/0002/001-0001and EudraCT Number: 2012-003114-13) and research governance department at West Hertfordshire Hospitals NHS Trust. The trial was registered on the International Standard Randomised Controlled Trial Registry (ISRCTN89079989). The trial was sponsored by West Hertfordshire Hospitals NHS Trust and was coordinated by the Northern Ireland Clinical Trials Unit (CTU). The trial design has been published in detail previously and the trial protocol and is available in the online supplement.[16] The trial is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[17]

Patients

Patients receiving invasive mechanical ventilation within the first 72 hours of ICU admission were eligible for inclusion in the study. The main exclusion criteria are listed in Figure 1 and

the full list is provided in the study protocol. The eligibility criterion for creatinine clearance was decreased from 30 ml/minute to 15 ml/minute on 22nd July 2015. Patients or their representatives provided written informed consent.

Randomisation and masking

The dosage of simvastatin administered in this trial was chosen based on data from a retrospective observational study of statin usage in patients with sepsis, which showed a greater mortality benefit in patients who were receiving a higher dose of statin.[18] A nested cohort study found that statin therapy reduced hospital mortality in patients with sepsis only when higher doses of statins, in particular simvastatin, were given.[19] Moreover, simvastatin at a dose of 80 mg is well tolerated in acute lung injury patients, with no increase in adverse events.[20] A multi-centre prospective cohort study that included 197 ICU statin users reported simvastatin was the most frequent statin drug used with a median dose of 40mg (interquartile range 20mgs to 80 mgs).[12]

Patients were randomly assigned in a 1:1 ratio to receive either 80mgs simvastatin or identical placebo enterally. The study statistician generated the randomisation schedule in advance using nQuery Advisor, randomisation was by variable block size, without stratification. Patient drug packs were prepared by Victoria Pharmaceuticals according to the prearranged order and distributed to site. Each pack was numbered with a unique patient trial identifier allocated to each patient at the time of randomisation. Study drug packs were stored by hospital pharmacy in a secure area and dispensed by pharmacy to ICU as required.

Simvastatin 40mg or identical placebo tablets were packaged in white opaque HDPE plastic containers sealed with a tamper-evident seal. The placebo and active tablets were indistinguishable when crushed and dispersed in water for enteral administration. All ICU clinical and research staff, legal representatives, and the patients were masked to study drug. The data monitoring and safety committee reviewed blinded data reports. The study

statisticians were not masked to allocation. The success of blinding was not formally assessed.

Procedures

Demographic characteristics were recorded at the time of enrolment. The risk of developing delirium during critical care admission was calculated using the PRE-DELIRIC delirium prediction model.[21] Data were recorded daily while the patient remained in ICU up to a maximum of 28 days. Treatment was initiated within 72 h of admission to ICU, irrespective of the presence of coma or delirium.

Patients received the study drug via a feeding tube or orally daily. The first dose of the study drug was administered as soon as possible and ideally within 4 hours after randomisation. For all subsequent days the study drug was given at midday. Study drug was discontinued on ICU discharge, after a maximum of 28 days treatment, death, discharge, creatine kinase 10 times more than the upper limit of normal, alanine transaminase eight times upper limit of normal, development of a clinical condition requiring immediate treatment with statin, discontinuation of active treatment, request for discontinuation by patient or legal representative, request for discontinuation by attending clinician or contraindication to enteral drug administration.

Patients were sedated using fentanyl and propofol infusions titrated to a Richmond agitation sedation scale (RASS) target of 0 to –1,[22] unless the consultant intensivist responsible for clinical management decided a deeper level of sedation was needed on a given day. RASS was assessed every four hours. We did not use a formal pain score and analgesics were titrated according to the bedside nurse's judgment of the patient's level of comfort and pain. Weaning from ventilation was according to a standard protocol and included spontaneous breathing trials (Appendix). All patients were actively mobilised by the critical care physiotherapy team from admission using a step-wise programme according to daily clinical status, from passively moving the patient's limbs to walking with assistance. ICU patients with RASS scores of –2 and upward were routinely sat out of bed unless there was a

contraindication. Episodes of agitation were managed according to a standard guideline (Appendix). The frequency and dose of any adjunct psychotropic or antipsychotic drugs were recorded.

Plasma was collected on days three, seven, 14, 21 and 28 while they were on the ICU to measure creatine kinase (CK) and alanine transaminase (ALT) levels for the purposes of safety monitoring. The frequency of the following pre-specified adverse events were reported; CK over 10 times the upper limit of normal, ALT over eight times the upper limit of normal, patients whose CK is elevated over 10 fold who required new renal replacement therapy. Adverse events were assessed for up to 30 days after enrolment, for seriousness, relationship to the study drug and expectedness.

Outcomes

The primary outcome was delirium-free and coma-free days, defined as the number of days in the first 14 days after randomisation during which the patient was alive without delirium and not in coma from any cause. Patients who died within the 14-day study period were recorded as having zero days free of delirium and coma. The incorporation of delirium-free and coma-free days was a means of having a measure of normal or returning to normal brain function, where being assessed as confusion assessment method-ICU (CAM-ICU) negative was defined as normal.[23] The recording of patients who die within the study period as having zero days free of delirium or coma is to address the situation where an intervention may increase the number of delirium-free and coma-free days but causes harm and increases mortality.

Secondary outcomes were delirium-free and coma-free days to day 28, ventilator-free days to day 28, mortality at six months, length of critical care and hospital stay, and safety with regard to elevated CK and ALT, and serious adverse events attributed to study drug. We defined ventilator-free days as the number of calendar days after a patient started unassisted breathing, for patients who survived at least 48 consecutive hours after the start

of unassisted breathing. Patients who died within 28 days of randomisation were counted as having no delirium-free and coma-free days or ventilator-free days.

Cognitive outcomes at six months were assessed by use of the Brief Test of Adult Cognition by Telephone (BTACT).[24] The BTACT assesses multiple dimensions central for effective cognitive functioning including episodic memory, working memory, reasoning, verbal fluency, and executive function. In addition the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) at baseline was compared with IQCODE data at six month follow up.[25] Cognitive outcome data was only collected from survivors recruited up until 1st February 2016 to ensure the trial was completed within the time window defined by the available funding.

Patients were defined as delirious if they were assessed with a RASS of –2 to +4, and screened positive for delirium by the bedside nurse using the confusion assessment method-ICU (CAM-ICU). Patients with a RASS score of –3 to –5 were classified as if in a coma, irrespective of whether the state was induced by disease or sedation, and therefore unable to be assessed (UTA) for delirium. While the validation studies for the CAM-ICU have demonstrated that delirium can be diagnosed in patients of RASS -3 (movement or eye opening to voice but no eye contact) at our centre, along with other centres,[26] we routinely classify a patient at RASS -3 as unable to be assessed (usually due to sedation). This unit decision was made because identifying a patient as 'unable to assess' acts as a prompt to the clinical staff to manage the level of sedation to enable patient screening for delirium at the same moving the patient out of a harmful level of sedation. RASS -3 is known to be associated with delayed extubation and increased mortality. [27] Delirium was assessed using the CAM-ICU twice during each 12 h shift with a minimum of 4 h between the two assessment points. All assessments in a 24 h period needed to be negative for a patient to be delirium-free and coma-free. If any assessment was CAM-ICU positive in a midnight to midnight 24 h period, that day was recorded as "with delirium".

As part of the annual educational programme for unit nursing staff there is regular in house training on screening for delirium using the CAM-ICU, demonstrations every six weeks, ad-hoc spot checks and one to one training of new staff.

Statistical analysis

The sample size calculation for this study has been initially based on data from the Awakening and Breathing Controlled trial published in 2008, using the mean delirium- and coma-free days of 10 at 28 days in patients in the standard care group.[28] The database for the observational 'Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) Study' showed a standard deviation of 4·1 in delirium and coma free days at day 14 in a similar cohort.[2] Assuming this standard deviation, and a type I error of 0.05 and 80% power, a sample size of 64 patients per group was powered to detect a difference of approximately two delirium-free, coma-free days between the intervention and control groups, or approximately 0·5 SD. Allowing for an estimated 10% loss to follow-up, the sample size required was 142. nQuery AdvisoR version 4.0 was used for the sample size analysis (Elashoff, JD 2000). Analyses were conducted on all outcome data obtained from all participants as randomised and regardless of protocol adherence, i.e. intention to treat analysis.

The primary outcome (delirium-coma free days) has a heavily skewed distribution (generally bimodal with peaks at 0 and 14 days). The primary outcome was analysed using an independent samples t-test. A secondary analysis of the primary outcome measure involving a bootstrapped t-test was also conducted to support the findings of the original analysis. Further to recommendations by Colantuoni and others on statistical methods for evaluating delirium in the ICU, a further analysis using a joint modelling approach via the R statistical package frailty pack was included in the statistical analysis plan and conducted.[29] This was in response to the problems that exist when using delirium-free days as an endpoint including the assumption of being delirium-free on discharge and the complication presented by days in coma. For each patient days in delirium, delirium-free and days of exposure (not in coma) are calculated. Instead of presenting delirium over 14 days (the primary outcome)

as a single value, this approach combined two survival models: one for the repeated daily indicator of delirium and another for the terminating event of ICU discharge or death. A random effect (frailty) is included in the survival model linking all delirium events and the terminating event.

ANCOVA was used to adjust for baseline severity of illness (Sepsis-related Organ Failure Assessment SOFA) and chance of delirium development for the primary outcome and to adjust for baseline IQCODE for the 6 month IQCODE.[30] Dichotomous outcomes were analysed using risk ratios and 95% confidence intervals, where appropriate. Time to event outcomes such as duration of hospital stay were analysed by survival methods and reported as hazard ratios and 95% CI's. Primary analyses were based on patients with outcome data (i.e. available case analysis). All analyses were conducted at the 5% level of significance. As ventilator free days and organ failure free days have a bimodal distribution, the groups were initially analysed by t-test with difference in means and 95% confidence intervals (CI) presented. A secondary analysis of these outcome measures involving a bootstrapped t-test was also conducted to support the findings of the t-tests. In all analyses statistical diagnostic methods were used to check for violations of the assumptions, and transformations were performed where required. Time-to-event data were presented using Kaplan-Meier plots. In all time-to-event analyses, patients who had not experienced the event in question were censored on the date last seen or 60 days. Time-to-event data was tested using a log-rank $\chi 2$ test. Hazard ratios (HRs) were calculated to test the difference between the treatment arms. All HRs are presented with a 2-sided 95% CI. Median follow-up time was calculated. The BTACT composite score was calculated by averaging the standardised values of each variable, and then standardising that mean score.[31]

Role of funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. VJP, CM, and DFM had access to the raw data. The corresponding author (VJP) had full access to all data and final responsibility for the decision to submit for publication.

Results

Between 1st February 2013 and 29th July 2016, 1164 patients were screened and 142 patients were enrolled as planned; 71 patients were allocated to placebo and 71 to simvastatin (figure 1).

The two groups were similar at baseline with regard to demographics, severity of illness, ICU admission diagnoses and predicted risk of delirium on admission (table 1). The mean ± SD number of days on treatment was 7·9 ± 6·6 in the simvastatin group and 10·1 ±7·8 in the placebo group which was not statistically significantly different (p=0.07). The mean ± SD number of days from ICU admission to first dose of study drug was 1.7 ±0.8 in the simvastatin group and 1.6 ± 0.9 in the placebo group. The reason study drug was ·discontinued in the majority of patients was discharge from critical care or discontinuation of active treatment (table 2). Vasopressor therapy was also similar between groups with 55(77.5%) receiving at least 1 type of vasopressor therapy on at least one day in the placebo group and 52(73.2%) in the simvastatin arm.

Outcomes

The mean number of days alive without delirium and without coma at day 14 did not differ significantly between the two groups (5·7 ± 5·1 days with simvastatin and 6·1 ± 5·2 days with placebo; mean difference, 0·4 days [95% CI, -1·3 to 2·1]; P = 0.66 using a two-sample t-test). There was also no significant difference in the number of days alive without delirium and without coma after adjustment for the baseline SOFA score and risk of delirium (mean difference 0·42 days [95% CI, -1·2 to 2·0]; P = 0·60). In addition using the joint modelling approach combining two survival models, one for the repeated (recurrent) daily indicator of delirium and another for the terminating event, after which patients can no longer be assessed for delirium, of ICU discharge or death there was no difference between the two groups (table 3).

The number of days assessed as spent in delirium (as opposed to coma or normal) did not differ between the two groups (mean 5·6 ± 4.3 in the simvastatin group vs 5·5± 4·5 days in

the placebo group; p=0·92). In addition there was no difference in the number of patients alive without delirium and without coma between the groups by study day for each of the first 14 days (Appendix Table 1)

A post-hoc analysis of patients who were not CAM-ICU positive (ie were CAM-ICU negative or unable to assess due to coma) at randomisation showed no difference in the mean delirium-free, coma-free days at 14 days between the groups (Appendix Table 2).

A post-hoc analysis in 41 patients who had sepsis and/or ARDS on admission also showed no difference in the mean delirium-free, coma-free days at 14 days between the groups (Appendix Table 3).

There were no differences in secondary outcomes, including ventilator-free days, length of critical care stay, length of hospital stay, and all cause mortality at six months (table 3, figures 2 and 3). Cognitive outcomes were available at 6 months on 42 survivors. There was no difference in the BTACT composite scores (-0·2 in the simvastatin compared to 0·1 in the placebo group; mean difference 0·3, 95% CI 0·0 to 0·6, p = 0·1), or the difference between the IQCODE at baseline and six month follow up between the groups (Table 4).

The most common adverse event was a rise in creatine kinase to over 10 times the upper limit of normal with eight (11·3%) in the simvastatin group versus 3 (4·2%) in the placebo group. There was no difference in the frequency of a rise in alanine transaminase to over eight times the upper limit of normal with two (2·8%) in the simvastatin group versus three (4·2%) in the placebo group. No serious adverse events were attributable to the study drug.

As CRP data decreased over time due to the effects of patients being discharged or dying within the study period a linear mixed model was applied to compare changes in CRP by group and over time. This model takes into account all available data, allows for missing values, and estimates fixed effects while adjusting for correlation due to repeated measurements on each subject. Although CRP levels decreased over time there was no difference between the treatment groups (figure 5).

Additional investigation into biological mechanisms including the measurement of plasma inflammatory response biomarkers are listed in the study protocol but are not reported in this

paper.

Discussion

In this study, early treatment with simvastatin did not increase the number of days critically ill patients needing mechanical ventilation spent without delirium or coma. The average duration of delirium in these patients was approximately six days in both groups. Furthermore, simvastatin did not have an effect on any secondary clinical outcomes**.**
This is the first prospective, randomised double-blind and placebo-controlled trial to determine if administration of a statin drug impacts on brain dysfunction in critical illness. To address the issues regarding delirium and coma, which may or may not be part of a spectrum, we chose the outcome of being free of delirium and coma to incorporate an overall indicator of brain dysfunction throughout a patient's critical illness. The mean duration of coma in study patients was 1.4 days in the simvastatin group vs. 0.9 days in the placebo group, and there were two patients, one in each group, who were persistently assessed as in coma throughout the study period.

The drivers for delirium in critically ill patients occur early, and are multiple including sepsis, renal failure, hepatic impairment, sedative exposure. Some drivers take time to resolve. It is possible that any anti-inflammatory effect of simvastatin leading to a reduction in delirium is overwhelmed in the critically ill by these other confounding factors. The magnitude and duration of any anti-inflammatory effect in order to reduce delirium may have been inadequate in this patient population. This would be supported by the fact that there was no difference in patient's serum CRP levels between the two groups through to 14 days following randomisation. The six month mortality was higher in the simvastatin group patients but did not reach significance and would suggest that there are no longer term benefits with regard to persistent subclinical inflammation postulated as a contributing factor to long term mortality following critical illness.[32] There was no difference in cognitive

outcomes at six months, which would be in keeping with the absence of any acute effect on delirium.

The pathophysiology of delirium remains unclear although it is believed that neuroinflammation is important. Those patients who develop delirium, but then it quickly subsides, may not have significant neuroinflammation and therefore would not benefit. It may be that there are other non-inflammatory factors that maintain delirium in the absence or reduction of neuro-inflammation.

The strengths of this study include that patients were started on the study drug early regardless of coma or delirium status to maximize any benefit there may have been for prevention the development of more delirium or a decrease in the delirium days. This trial is, essentially, a delirium reduction trial; ie the aim was to determine if simvastatin would reduce delirium developing or persisting in patients at high risk of delirium. The study recruited a population similar to the population used to generate the data used in the sample size calculation therefore there is no reason to believe that the trial is not powered for the outcomes as planned. There was no indication of imbalance in baseline variables measured, including predicted risk of delirium and history of alcohol dependency. The low mean number of days spent in coma in the first 14 days, 1 day [S.D 1·4] in the simvastatin group vs 0·9 day [S.D 1·5] in the placebo group) suggests that patients were managed in keeping with a RASS range of 0 to –2, ie, not deeply sedated.

The study has several limitations. We did not use a marker of simvastatin absorption, however prior studies in the critically ill indicate that simvastatin 80mg daily administered enterally produces systemic drug concentrations that are in the high therapeutic range, and that drug absorption is seen even in patients with high nasogastric aspirates.[33]

There was a 72 hour window following admission by which time the patients had to be recruited and mean (sd) time in days from admission to the first study drug for the simvastatin arm was 1·7(0·8) and in the placebo arm was 1·6(0·9). It is possible that the neuroinflammation driving delirium was established before simvastatin levels in the CNS reached therapeutic levels. There was, however, no signal seen for delirium reduction

throughout the trial period and the study drug was given for up to 28 days in order that a delayed effect might be detected.

This was a single site study, although the population of patients was broadly representative of the general adult ICU population, and on that basis we did not exclude the seven patients admitted with neurological injuries. Neurologic or neurosurgical patients admitted to our hospital requiring specialist intervention or monitoring are transferred to a London centre and not admitted to our ICU.

The study population was heterogeneous and it may be a subset of critically ill patients exists who could benefit from routine simvastatin, although further studies would be required to investigate this. In common with other delirium studies in critically ill patients we used a valid instrument to determine the presence of coma or delirium and used the combination of the absence of coma and delirium as indicative of a patient's brain recovering towards a normal state. This is a constraint as it is not possible to be confident regarding the significance of a coma state in many ICU patients although it is known that deep sedation is a predictor of adverse outcomes.

The bedside nurse, rather than a skilled study investigator undertook the delirium screening. Delirium screening is embedded in routine practice at our centre, and there is evidence that sensitivity is improved in centres that use the CAM-ICU to guide clinical practice.[34] In addition it meant regular screening was spread throughout any 24-hour period and was not restricted to daytime hours. Given the high detection rate of delirium it is unlikely that the use of a delirium assessment protocol would have found delirium missed using the CAM-ICU alone.[35] The confusion assessment method-ICU (CAM-ICU) is a reliable tool recommended for use in this patient population in the USA Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit and in the UK National Institute for Health and Care Excellence, Delirium: prevention, diagnosis and management guidelines.[36,37] .A multi-centre European trial, however, concluded that specificity of the CAM-ICU as performed in routine practice was high but sensitivity is low.[38]

There was an assumption that once a patient was discharged from ICU, they were free of delirium. We also used the joint modelling approach, which makes no assumption about delirium for patients who are discharged from ICU and there was no evidence of any treatment effect with simvastatin. [29]

The incidence of delirium is recorded at 93% in the simvastatin group and 94% in the placebo group with the predicted prevalence on admission of 70.9%. These data are similar to those recorded in our Hope-ICU trial.[39] Comparable incidences have been reported in centres that undertake robust delirium screening, for instance van den Boogaard et al in a before and after haloperidol prophylaxis study documented an incidence of 90% in one study group and 97% in high risk patients.[40] The high admission prevalence may be due in part to our unit practice of targeting early light sedation as compared with other studies that report admission prevalence where the majority of patients were in coma and therefore could not be assessed for delirium. The SPICE/ANZICS observational trial of sedation practice reported that at four hours after starting mechanical ventilation most patients (191 [76%]) were deeply sedated (RASS -3 to -5).[27] Deep sedation continued throughout the first 48 hours in 171 (68%) patients. The SPICE group found similar findings in a prospective longitudinal multicentre cohort study in Malaysia with deep sedation reported in 182 (71%) of patients at first assessment and in 159 (61%) of patients and 1,658 (59%) of RASS assessments at 48 hours.[41]

The low numbers of patients assessed as free of delirium and coma could also be due to the frequency and timing of RASS and CAM-ICU assessments; study patients were assessed four times daily and only needed to screen positive once for delirium for that day, to count as not being delirium-free. It is routine practice at our centre that CAM-ICU assessments are undertaken as the nurse detects a change in the patient's mental status. It is likely that delirium assessments were done as the patient's level of arousal and sedation were changing and that in the earliest stages of waking up they were inattentive with a reduced level of arousal. Patel and others study demonstrated that in 12% of patients in whom sedation was stopped for two hours will revert from screening positive for delirium using the

CAM-ICU to negative.[42] Nine patients in the placebo arm and six patients in the simvastatin arm had one day of delirium, which would be consistent with the Patel findings. It is also noteworthy that in our study only 43 (61%) in each group had days in delirium when not on sedation. Finally, the CAM-ICU, unlike the Intensive Care Delirium Screening Checklist (ICDSC), does not capture delirium severity. Grading delirium severity would have added more context to the prevalence data in this study, and this is recognized as a limitation. Other randomised controlled placebo-controlled drug trials aimed at the prevention or treatment of delirium using pharmacological interventions i.e. antipsychotics or melatonin, have similarly showed no benefit. [38,43,44] Rivastigmine did not decrease delirium and might increase mortality.[45]There is a continued need to explore pharmacological interventions to modify delirium in critically ill patients in clinical practice. Delirium, however, is a syndrome with any number of causes, and there is a need to develop prognostic and predictive enrichment strategies, such as identifying valid biomarkers, in order to design more efficient studies in those subgroups most likely to benefit powered for patient-centred outcomes. However, in addition efforts need to be made within individual units to use non-pharmacological strategies believed to minimise the risk in non-ICU patients developing and remaining in delirium.[46-47]

In conclusion our study showed that simvastatin, as compared with placebo, did not increase the number of days critically ill patients spend without coma or delirium, although it had an acceptable safety profile. These results do not support the use of simvastatin in the management of delirium.

Authors' contribution

VJP, DM and EWE conceived and designed the trial. VJP and DM obtained the funding for and managed the trial. All authors made a substantial contribution to the protocol development. CM was the study statistician and analysed the data. VJP wrote the first draft

of the manuscript and all authors have contributed to the writing of, reviewed and approved this final version of the manuscript.

Acknowledgments

This Article presents independent research funded by the National Institute for Health Research under its research for patient benefit programme (grant reference number PB-PG-0211-24123). VJP has received honoraria from Orion pharma (UK) and the BMJ. EWE is supported by grants AG 027472, AG035117, and HL111111 from the National Institutes of Health, VA Merit Review Award from the VA Clinical Science Research and Development Service and received honoraria from Orion, Abbot and Pfizer. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health. We thank the UK Intensive Care Foundation for its support. We also thank Neil Soni, chair of the trial steering committee, and members of the safety monitoring committee: Martin Kuper (chair; Whittington Health, London, UK), Mike Grocott (University of Southampton, Southampton University Hospitals, Southampton, UK; and NIAA Health Services Research Centre, Royal College of Anaesthetists, London, UK), Yogen Amin (National Hospital for Neurology and Neurosurgery, University College London Hospital, London, UK), and David Wellsted (Centre for Lifespan and Chronic Illness Research, University of Hertfordshire, Hatfield, UK We thank all patients and their legal representatives who participated in the trial. We thank all the staff of the Northern Ireland Clinical Trials Unit for their support in delivering this trial.

References

1. Mehta S, Cook D, Devlin JW, et al Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. *Crit Care Med.* 2015; **43** :557-66.
2. P.P. Pandharipande, T.D. Girard, J.C. Jackson, et al. Long-Term Cognitive Impairment after Critical Illness. *N Engl J Med* 2013; **369**:1306-16.
3. Vasilevskis E, Holtz C, Girard T, et al. The Cost of Delirium in the Intensive Care Unit: Attributable Costs of Care Intensity and Mortality [abstract]. *J Hosp Med* 2015; **10** (suppl 2). Accessed 29th March 2017
4. Milbrandt, E.B., Deppen, S., Harrison, P.L. et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med* 2004; **32**: 955-62.
5. Cerejeira J1, Nogueira V, Luís P, Vaz-Serra A, Mukaetova-Ladinska EB. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J Am Geriatr Soc*. 2012; **60** :669-75
6. Ritter C, Tomasi CD, Dal-Pizzol F, et al. Inflammation biomarkers and delirium in critically ill patients. *Crit Care* 2014, **18**:R106
7. Cape E, Hall RJ, van Munster BC, et al. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1β in delirium after hip fracture. *J Psychosom Res* 2014; **77**: 219-25
8. Munster BC, Aronica E, Zwinderman AH, Eikelenboom P, Cunningham C, Rooij SE. Neuroinflammation in delirium: a postmortem case-control study. *Rejuvenation Res* 2011; **14**: 615–22.
9. Bu DX, Griffin G, Lichtman H Mechanisms for the anti-inflammatory effects of statins. *Curr Opin Lipidol* 2011; **22**: 165-70
10. Niessner, A., Steiner, S., Speidl, W.S, et al. Simvastatin suppresses endotoxin-induced upregulation of toll-like receptors 4 and 2 in vivo. *Atherosclerosis* 2006: **189**,: 408-13.

11. Wang, H., Lynch, J.R., Song, P, et al. Simvastatin and atorvastatin improve behavioral outcome, reduce hippocampal degeneration, and improve cerebral blood flow after experimental traumatic brain injury. *Exp Neurol*, 2007; **206**,: 59-69.
12. Morandi, A, Hughes CG, Thompson JL, et al. Statins and delirium during critical illness: a multicenter, prospective cohort study *Crit Care Med*. 2014; **42** :1899-909
13. Page VJ, Davis D, Zhao XB, et al. Statin use and risk of delirium in the critically ill. *Am J Respir Crit Care Med* 2014; **189**; 666-73
14. Sierra S, Ramos MC, Molina P, Esteo C, Vazquez JA, Burgos JS. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death*. J Alzheimers Dis*. 2011; **23**: 307-18.
15. Needham DM, Colantuoni E, Dinglas VD, et al. Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial *Lancet Resp Med* 2016; **4**: 203-12
16. Casarin A, McAuley DF, Alce TM, et al. Evaluating early administration of the hydroxymethylglutaryl-CoA reductase inhibitor simvastatin in the prevention and treatment of delirium in critically ill ventilated patients (MoDUS trial): study protocol for a randomized controlled trial *Trials* 2015; **16**: 218
17. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010; **340**: c332.
18. Shah AI, Sobnosky S, Shen AY, Jorgensen MB. High dose statins are associated with a reduced all cause mortality in patients hospitalized with sepsis and severe sepsis. *Crit Care Med*. 2009; **36**:A15.
19. Al Harbi SA, Tamin HN, Arabi YM. Association between statin therapy and outcomes in critically ill patients: a nested cohort study. *BMC Clin Pharmacol*. 2011; **11:12**.
20. McAuley DF, Laffey JG, O'Kane CM, et al. Simvastatin in the Acute Respiratory Distress Syndrome. *N Engl J Med* 2014; **371**:1695-703

21. van den Boogaard M, Pickkers P, Slooter AJC, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study *BMJ* 2012;**344**:e420
22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med*. 2002; **166**: 1338–44.
23. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. 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**:1370–9.
24. Tun PA, Lachmann ME. Telephone assessment of cognitive function in adulthood: the Brief Test of Adult Cognition by Telephone (BTACT) *Age Ageing* 2006; **35**: 629-33.
25. Jorm A. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): a review. *Int Psychogeriatr* 2004;**16**:1-19.
26. Confusion Assessment Method for the ICU (CAM-ICU) Frequently asked questions. Vanderbilt University Medical Centre 2014 http://www.icudelirium.org/docs/CAM_ICU_FAQs.pdf. Last accessed 5th April 2017
27. Shehabi Y, Bellomo R, Reade MC, et al. Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators; ANZICS Clinical Trials Group. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med*. 2012; **186**: 724–31
28. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet* 2008; **371**: 126–34
29. Colantouni E, Dinglas VD, Ely EW, Hopkins RO, Needham DM. Statistical methods for evaluating delirium in ICU. *Lancet Resp Med* 2016; **4**: 534-36

30. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707–10
31. Tun AP, Lachman ME. The Association between computer use and cognition across adulthood: use it so you won't lose it? Psychol Aging 2010; 25: 560-568
32. Yende S, D'Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008; **177**: 1242-47
33. Drage SM, Simpkin AL, Neuvonen PJ, Watkinson PJ, Barber VS, Young JD. Plasma simvastatin concentrations in critically ill septic patients. *J Intensive Care Soc* 2009;**10**:61.
34. van Eijk M, van den Boogaard M, van Marum RJ,,et al. Routine Use of the Confusion Assessment Method for the Intensive Care Unit A Multicenter Study *Am J Respir Crit Care Med* 2011; **184**: 340-44
35. Zaal IJ, Tekatli H, van der Kooi AW, et al. Classification of daily mental status in critically ill patients for research purposes. *J Crit Care*. 2015;**30**:375–30
36. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013: **41**: 263-306.
37. NICE clinical guideline [CG103] Delirium: prevention, diagnosis and management July 2010
38. van Eijk M, van den Boogaard M, van Marum RJ,,et al. Routine Use of the Confusion Assessment Method for the Intensive Care Unit A Multicenter Study *Am J Respir Crit Care Med* 2011; **184**: 340-44
39. Page VJ, Ely EW, Gates S, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2013; **1:**515–23.

40. van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. *Crit Care.* 2013 Jan 17;**17**:R9.
41. Shehabi Y, Chan L, Kadiman S, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intensive Care Med* 2013; **39**: 910-8
42. Patel SB, Poston JT, Pohlman A, Hall JB and Kress JP. Rapidly Reversible, Sedation-related Delirium versus Persistent Delirium in the Intensive Care Unit. *Am J Respir Crit Care Med*. 2014; **189**: 658-65
43. de Jonghe A, van Munster BC, Goslings JC, et al Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ.* 2014; **186** :E547-56.
44. Al-Qadheeb NS, Skrobik Y, Schumaker G, et al. Preventing ICU Subsyndromal Delirium Conversion to Delirium With Low-Dose IV Haloperidol: A Double-Blind, Placebo-Controlled Pilot Study. *Crit Care Med* 2016; **44**: 583–91
45. van Eijk MM1, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet.* 2010; 376: 1829-37
46. Siddiqi N1, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev.* 2016 Mar 11;**3**: CD005563.
47. Bannon L, McGaughey J, Clarke M, McAuley DF, Blackwood B. Impact of non-pharmacological interventions on prevention and treatment of delirium in critically ill patients: protocol for a systematic review of quantitative and qualitative research. *Systematic Reviews* 2016; **5**: 75 .

Table 1. Baseline demographic and clinical characteristics

	Simvastatin n = 71	**Placebo n = 71**
Age (years)	61.9±15.3	62.1 ± 17.3
Gender Male	45(63.4%)	37(52.1%)
Female	26(36.6%)	34(47.9%)
Diagnosis*		
Sepsis &/ ARDS	23 (32.4%)	18 (25.4%)
Pneumonia	33 (46.5%)	30 (42.3%)
MI or CCF	2 (2.8%)	3 (4.2%)
Renal or hepatic failure	4 (5.6%)	4 (5.6%)
COPD	7 (9.9%)	3 (4.2%)
Haemorrhage	1 (1.4%)	1 (1.4%)
Drug Overdose	3 (4.2%)	6 (8.5%)
Trauma	0 (0%)	0 (0%)
Other	19 (26.8%)	17 (23.9%)
IQCODE Score	n=67 3.2±0.4	n=60 3.1±0.3
RASS Score †		
Lowest	-4(-4,-3)	-4(-4,-3)
Highest	1(-1,2)	1(-1,2)
CAM-ICU Status		
Positive	56(78.9%)	56(78.9%)
Negative	0(0.0%)	4(5.6%)
Unable to assess	15(21.1%)	11(15.5%)
Predeliric Diagnose Group		
Surgical	19(26.8%)	17(23.9%)
Medical	48(67.6%)	50(70.4%)
Trauma	0	1(1.4%)
Neurology/Neurosurgical	4(5.6%)	3(4.2%)
Highest Creatinine (Umol/L)	111.6±73.7	118.5±104.9
Highest Bilirubin (Umol/L)	31.0±68.6	20.5±25.6
CRP (mg/L)	208.0±169.0	212.7±155.6
Fentanyl Total Dose (mgs)	0.6±0.7	0.6±0.7
Propofol Total Dose (mgs)	700.6±778.8	821.5±936.9
APACHE II Score	17.2±5.3	16.7±6.4
PRE-DELIRIC: risk of delirium development (%)	70.9±26.9	70.9±24.5
Alcohol Abuse present		
Yes	13(18.3%)	15(21.1%)
No	58(81.7%)	56(78.9%)
Total SOFA Score	8.8±3.7 n=70	8.9±3.1 n=71
CK (U/L)	240.4±294.7	219.7±250.0
ALT (U/L)	65.0±63.8	62.6±64.4

* Patients can have more than 1 diagnosis
† Median(IQR) presented

Table 2: Treatment after Trial Entry

	Simvastatin n = 71	**Placebo n = 71**
Study drug given (No. of patients receiving at least one dose)	71	71
No. of days on treatment*	7.9±6.6	10.1±7.8
Reasons for termination of study drug		
28 days after randomisation	6(8.5%)	4(5.6%)
Creatine Kinase>10 times upper limit normal	8(11.3%)	3(4.2%)
ALT>8 times upper limit normal	2(2.8%)	3(4.2%)
Development of a clinical condition requiring immediate treatment with statin	0(0.0%)	0(0.0%)
Death	5(7.0%)	4(5.6%)
Discontinuation of active treatment	10(14.1%)	11(15.5%)
Discharge from Critical Care	33(46.5%)	44(62.0%)
Request for discontinuation by patient or legal representative	4(5.6%)	3(4.2%)
Request for discontinuation by attending clinician	1(1.4%)	0(0.0%)
Contraindication to enteral drug administration	0(0.0%)	0(0.0%)
Other	2(2.8%)	0(0.0%)

*Mean ± SD no. of days on treatment

Table 3. Outcome measures

	Simvastatin n=71	**Placebo n=71**	**Difference / Risk Ratio (95% CI)**	**p-value**
Primary outcome; Delirium/Coma free to 14 days post randomisation*				
Two-sample t-test	5.7±5.1	6.1±5.2	0.4(-1.3, 2.1)	0.66
Bootstrap t-test (95% bias corrected CI)			0.4(-1.3, 2.0)	0.65
HR (95% CI) from Joint modelling approach using frailty pack in R††				
Recurrences			1.1 (0.9,1.2)	0.33
Terminal Event				
Assignment (Simvastatin)			1.3 (0.8,2.0)	0.25
Type (Death) †††			3.6 (1.1,11.8)	0.03
Assignment*Type			0.7 (0.2,3.3)	0.69
Delirium/Coma free to 28 days post randomisation*				
Two-sample t-test	14.3±11.2	15.4±10.9	1.1(-2.6,4.7)	0.56
Bootstrap t-test (95% bias corrected CI)			1.1(-2.0,5.1)	0.56
Incidence of Delirium	66(93.0%)	67(94.4%)	-0.0(-0.1,0.1)	0.81
Days in coma to 14 days	1.0±1.4	0.9±1.5	-0.1(-0.6,0.4)	0.82
Days in coma to 28 days	1.1±1.7	1.1±1.8	0.0(-0.6,0.6)	1.00
Days in delirium to 14 days	5.6±4.3	5.5±4.5	-0.1(-1.5,1.4)	0.92
Days in delirium to 28 days	6.4±6.0	6.79±6.6	0.3(-1.8,2.4)	0.80
VFDs to 28 days post randomisation*				
Two-sample t-test	13.7±11.9	15.5±11.4	1.8(-2.1,5.6)	0.36
Bootstrap t-test (95% bias corrected CI)			1.8(-2.0,5.3)	0.37
OFFDs in first 28 days*	14.3±12.1	15.7±11.2	1.5(-2.4,5.3)	0.45
Two-sample t-test Bootstrap t-test (95% bias corrected CI)			1.5(-2.2,5.0)	0.43
All cause mortality 6 months post randomisation[#,] **	30 (42.3%)	22 (31.0%)	1.4 (0.9,2.1)	0.22
Length of hospital stay until death or discharge from point of randomisation (days) †	20.3 ± 22.1 13 (7,25)	20.4 ± 16.6 16 (9,28)	0.2(-6.3,6.7) 2(-2,6)	0.96 0.3
Length of hospital stay until discharge from point of randomisation (days) †	n=47 23.3 ± 24.3 16(9, 26)	n=50 23.1±16.9 18(12,34)	-0.2(-8.6,8.2) 2(-3,7)	0.97 0.34
IQCODE difference from baseline to 6 months[£]	3.0±0.5 n=21	3.1±0.7 n=27	0.0(-0.4,0.4)	0.99

Mean ±SD presented for treatment arms and Difference (95%CI) from t-test unless indicated otherwise.
*Results from bootstrapped t-test (Delirium/Coma free days, Organ Failure free days and Ventilator Free days (VFDs)) and joint modelling approach (Delirium/Coma free days only) using frailty pack also presented
[#]No.(%) for treatment arms and Risk Ratio and 95% CI presented
**p-value from log-rank χ^2 presented
† Mean ± SD and the median (IQR) for duration of hospital stay until death or discharge for all patients and until discharge only. Hodges-Lehmann difference (95%CI) presented for median(IQR) Mann-Whitney p-value presented.
††The terminal event model included assignment (treatment arm), type (death or discharge) and type*assignment.
†††There were only 8 patients included in the frailty model who had type=death prior to 14 days resulting in a wide 95% CI.
[£]Difference(95%CI) from ANCOVA adjusting for baseline IQCODE

Table 4 Brief Test of Adult Cognition by Telephone (BTACT) outcomes at six months

Measure	Simvastatin	Placebo	Difference (95% CI)**	p-value
Word list recall (WLR) - proportion on 15	N=18 0.4 ± 0.2 (0,0.8)	N=24 0.4 ± 0.2 (0.1,0.9)		
Digits backwards (DB) – longest correct	N=18 4.4 ± 1.7 (2,8)	N=24 5.4 ± 1.9 (2,8)		
Category fluency (CF)– number produced	N=18 17.0 ± 4.9 (7,26)	N=24 18.2 ± 4.5 (9,27)		
Number series (NS) - proportion on 5	N=16 0.4 ± 0.3 (0,1)	N=22 0.5 ± 0.3 (0,1)		
Backward counting (BC) – number reached from 100	N=18 66.2 ± 11.6 (45,86)	N=23 71.8 ± 7.5 (61,91)		
Short delay recall (SDR) - proportion on 15	N=18 0.2 ± 0.2 (0,0.6)	N=22 0.3 ± 0.2 (0.0, 0.7)		
Stop and Go Switch Task (SGST)– Average Standardised scores*	N=18 -0.1 ± 1.1 (-4.3, 0.4)	N=23 0.0 ± 0.8 (-2.5,0.4)		
BTACT Composite – Average Standardised Scores*	N=18 -0.2 ± 0.5 (-1.6, 0.6)	N=24 0.1 ± 0.5 (-1.0, 1.3)	0.3(0.0, 0.6)	0.1

*SGST average and BTACT composite were calculated based on no. of tasks completed.
**Difference (95%CI) from t-test
Mean ± SD (min, max) presented