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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

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Summary

Background—Delirium is common in mechanically ventilated patients and is associated with cognitive impairment lasting at least 1 year after hospital discharge. Preclinical and observational studies suggest that the use of statins might reduce delirium in intensive care. We assessed

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Contributors

DMN, EC, and ROH designed the study. DMN, EC, VDD, CLH, AWW, JCJ, PEM, PAM-T, EWE, and ROH analysed and interpreted data. DMN drafted the report and all other authors revised it. All authors gave final approval of the report to be published.

Declaration of interests

We declare no competing interests.

See Online for appendix

For more on the **development of a core set of outcomes** see http://www.comet-initiative.org/studies/details/796

whether the pleiotropic effects of statins can reduce delirium in intensive care and decrease subsequent cognitive impairment in a randomised controlled trial.

Methods—We did this ancillary study within the SAILS trial, a randomised controlled trial assessing mortality and ventilator-free days for rosuvastatin versus placebo for patients with sepsis-associated acute respiratory distress syndrome. This study was done at 35 hospitals in the USA. Patients were randomly assigned in permuted blocks of eight and stratified by hospital to receive either rosuvastatin (40 mg loading dose and then 20 mg daily until the earliest of 3 days after discharge from intensive care, study day 28, or death) or placebo. Patients and investigators were masked to treatment assignment. Delirium was assessed with the validated Confusion Assessment Method for intensive care. Cognitive function was assessed with tests for executive function, language, verbal reasoning and concept formation, and working, immediate, and delayed memory. We defined cognitive impairment as having one of these domains at least two SDs below population norms or at least two domains at least 1·5 SDs below norms. The primary endpoint was daily delirium status in intensive care up to 28 days in the intention-to-treat population and secondary endpoints were cognitive function at 6 months and 12 months. This trial is registered with ClinicalTrials.gov (NCT00979121 and NCT00719446).

Findings—272 patients were assessed for delirium daily in intensive care. The mean proportion of days with delirium was 34% (SD 30%) in the rosuvastatin group versus 31% (29%) in the placebo group; hazard ratio 1·14, 95% CI 0·92–1·41, p=0·22. At 6 months, 19 (36%) of 53 patients in the rosuvastatin group versus 29 (38%) of 77 in the placebo group had cognitive impairment, with no significant difference between groups (treatment effect 0·93, 95% CI 0·39–2·22; p=0·87). At 12 months, 20 (30%) of 67 patients versus 23 (28%) of 81 patients had cognitive impairment, with no significant difference between groups (treatment effect 1·1, 95% CI 0·5–2·6; p=0·82).

Interpretation—Most patients had delirium, with around a third of survivors having cognitive impairment over 1 year of follow-up. Despite encouraging preclinical and observational studies, this trial shows no benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment during 12 months of follow-up although the study was not powered for superiority. Thus, there is continued need to evaluate interventions aimed at attenuating intensive care and post-intensive-care cognitive impairments commonly observed in this population.

Introduction

Critically ill patients are at high risk for delirium, which occurs in up to 80% of mechanically ventilated patients.[1] In such patients, a longer duration of delirium is associated with impaired cognitive function, lasting more than 12 months after discharge.[1] Such cognitive impairment reduces quality of life and delays return to work, while increasing admission to care or residential homes and health-care costs.[2,3] Despite the importance of this neurocognitive morbidity, few drugs can reduce delirium and long-term cognitive impairment.[4]

Data from both animal and human studies[5–8] offer indirect evidence that neuroinflammation, with associated oxidative damage and apoptosis, is an important part of the pathophysiology of delirium in the intensive care unit and subsequent long-term cognitive impairment. Severe sepsis is an archetype of systemic inflammation, including neuroinflammation.[9] Statins have

pleiotropic properties, including fast-acting anti-inflammatory effects, and might improve neuronal function via effects on neurotransmitters and endothelial function.[10–15] In a mouse model of sepsis,[16] 48 h of treatment with statins reduced systemic inflammation, decreased oxidative damage in the brain, and protected against cognitive impairment assessed 2 weeks later. Studies of patients having cardiac or vascular surgery[17,18] suggest that statins might protect against delirium. Moreover, two large, well-designed, observational studies[19,20] of critically ill patients provide data showing strong and consistent associations between statin use and reduced odds of daily delirium in intensive care, particularly in patients with sepsis early in their intensive care unit stay. This potential benefit is hypothesised to be mediated through a reduction in systemic inflammation.[20] Consequently, there is great interest in further evaluating the effect of statins on delirium in intensive care and subsequent cognitive function in randomised trials.[8,19–22]

The Statins for Acutely Injured Lungs from Sepsis (SAILS) trial was a large, multicentre randomised trial done by the ARDS Network to assess the short-term effects of rosuvastatin versus placebo on mortality and ventilator-free days in critically ill patients with sepsis.[23] We did an ancillary study of the SAILS trial to assess whether rosuvastatin reduced delirium in patients in intensive care and improved later cognitive function.

Research in context

Evidence before this study

Animal research and human observational studies have shown indirect evidence of potential beneficial effects of statins for delirium and cognition. Two large observational studies of critically ill patients showed strong associations between statin use and reduced odds of daily delirium in intensive care. We searched PubMed, Embase, and Cochrane on June 30, 2015, with no language or date limitations, for any randomised trials assessing statins in critically ill patients. We did not find any completed trials of statins for which the primary outcome was delirium or post-discharge cognitive outcomes, nor any trials that reported them as secondary outcomes.

Added value of this study

To our knowledge, this is the first ancillary study of a multicentre, randomised, double-blind, placebo-controlled trial evaluating the effect of rosuvastatin compared with placebo to evaluate effects on delirium in intensive care and subsequent cognitive function in patients with sepsis-associated acute respiratory distress syndrome. Delirium occurred in 72% of patients and cognitive impairment, over 1 year of follow-up, occurred in roughly a third of survivors but we found no benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment at 6 months and 12 months.

Implications of all the available evidence

There is continued need to evaluate interventions to attenuate intensive care and post-intensive care cognitive impairments common in patients with sepsis-associated acute respiratory distress syndrome.

Methods

Study design and participants

This prospective ancillary study is part of the ARDSNet Long-Term Outcomes Study, which assessed several long-term effects in the SAILS trial,[23] a randomised controlled trial. The SAILS trial was done at 37 hospitals in the USA between March 18, 2010, and Sept 30, 2013. Initially, delirium and cognition were recorded for patients at only 12 hospitals, with delirium assessed as a potential confounder for the assessment of long-term cognitive outcomes. On the basis of new data showing that statin use was associated with reduced odds of delirium in intensive care,[24] the SAILS protocol was amended on Aug 8, 2012, to establish this substudy and expand assessment of delirium and cognitive outcomes to 23 additional hospitals. For the two other hospitals in SAILS, government regulatory issues prevented their participation in our ancillary study and so were not included.

As reported previously for the SAILS trial,[23] inclusion criteria included: meeting criteria for acute respiratory distress syndrome, receiving mechanical ventilation through an endotracheal tube, and meeting criteria for systemic inflammatory response with a known or suspected infection. The main exclusion criteria were: presence of acute respiratory distress syndrome for more than 48 h, pre-existing condition adversely affecting survival or weaning from mechanical ventilation, receiving statins within 48 h of randomisation, and high (above 5 times the upper limit of normal) creatine kinase, aspartate aminotransferase, or alanine aminotransferase.

For the assessment of cognitive function, we also excluded patients aged younger than 18 years, who were non-English speaking, or who were homeless or had pre-existing cognitive impairment (based on patients' status before admission using medical records or an interview with the patient or their proxy).

SAILS was stopped early because of futility, after recruiting 745 of 1000 patients, with no significant differences in short-term mortality, ventilator-free days, and intensive care unit-free days.[23] The first 75 patients in the present analysis were also previously enrolled in ARDSNet's EDEN study, a randomised trial of 1000 patients comparing initial trophic with full enteral feeding for up to 6 days after acute respiratory distress syndrome, which showed no significant difference in short-term outcomes (ventilator-free days, intensive-care-free days, organ failure-free days),[25] or cognitive function at 6 months and 12 months.[26]

Institutional review boards at each participating site approved this study. All patients (or a proxy, if patients were unable to provide consent) provided written or oral informed consent.

Randomisation and masking

Patients were randomly assigned in permuted blocks of eight, with stratification by hospital, via a web-based system to receive daily enteral rosuvastatin (a 40 mg loading dose and daily 20 mg dose) or a matched placebo, administered from randomisation until the earliest of death, 3 days after discharge from intensive care, or 28 days.[23] Patients, and investigators giving treatments and assessing outcomes were masked to treatment allocation.

Procedures

All patients were managed with simplified protocols for lung protective ventilation, ventilator weaning, and fluid and haemodynamic management.[27,28] Loss to follow-up was minimised through cohort retention methods.[29–35]

Delirium status was assessed once a day by research or clinical personnel with the validated and reliable Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[36–38] Patients who were non-responsive to verbal stimulation (eg, Richmond Agitation Sedation Scale; RASS[39] score of −4 or −5), referred to hereafter as coma, were excluded from delirium assessment for that day.

At 6 months and 12 months follow-up after randomisation, occurring from 2010 to 2014, research personnel performed a series of reliable standardised tests to assess the cognitive domains of greatest relevance in survivors of acute respiratory distress syndrome.[26,40] This test battery was validated for administration by phone or face to face.[40] Based on this test battery, we defined a conservative binary assessment of overall cognitive impairment, as in previous research,[26] as having either one cognitive test score at least 2 SDs below population norms (ie, in the bottom 2·5%) or at least two test scores at least 1·5 SDs below norms (ie, in the bottom 6·7%).[41] We also present individual results on specific cognitive tests as both continuous scores and binary outcomes (≥1·5 SD below the norm). The following cognitive domains were assessed in the test battery: executive function, evaluated with the Hayling Sentence Completion Test scaled score (range 1–10; higher is better);[42] language, assessed with the Verbal Fluency Test total score (higher score is better);[43] verbal reasoning and concept formation, assessed with the Similarities age-adjusted scaled score (range 1–19; higher is better) from the Wechsler Adult Intelligence Scale (third edition);[44,45] attention and working memory, assessed with the Digit Span age-adjusted scaled score (range 1–19; higher is better) from the Wechsler Adult Intelligence Scale (third edition);[44,45] and immediate and delayed memory, assessed with the Logical Memory I and II age-adjusted scaled scores (range 1–19; higher is better) from the Wechsler Memory Scale (third edition).[44,45]

Outcomes

The prespecified primary outcome was daily delirium status in intensive care up to 28 days. The prespecified secondary outcomes were cognitive function at 6 months and 12 months.

Statistical analysis

We used descriptive statistics to compare data across the two treatment groups. We compared daily delirium status in each treatment group using a joint survival model that allowed for recurrent events (ie, the repeated within-patient daily delirium status) and for a terminating event (death or discharge from the intensive care unit).[46] The recurrent event model included a main effect of treatment only, quantified as the relative hazard of delirium on any day in intensive care for the rosuvastatin group versus the placebo group. The terminating event model included two main effects: treatment group and the type of terminating event (death or discharge), and their interaction. A random intercept linked the

models for daily delirium status within a patient over time and the possible terminating event. Patients alive and in intensive care at 28 days were administratively censored.

We did the primary analysis for the intention-to-treat population, with patients contributing to the model on days when delirium was able to be assessed (ie, no coma). The joint survival model used in the primary analysis is valid under the missing at random assumption, with missing data as follows: CAM-ICU never available for three (1%) of 275 patients and for 527 (25%) of 2089 non-comatose patient-days plus 230 patient-days in which coma status was not available. We did a sensitivity analysis with multiple imputation of the missing coma and delirium status using regression models that included information on baseline patient and intensive care data, daily intensive care data, and coma and delirium status from the previous day.

We compared cognitive impairment at 6 months and 12 months using linear regression models for continuous measures and logistic random intercept regression models for binary measures, which included the main effect of time only. We estimated treatment effects separately at 6 months and 12 months using the same models with the addition of an effect of treatment group and its interaction with time. Sensitivity analyses included repeating the statistical analyses of cognitive impairment for only patients with data for both delirium and cognitive impairment.

We did prespecified subgroup analyses for the primary and secondary analyses to assess whether the treatment effect differed by age, shock at baseline, use of statins at baseline (obtained for a subset of SAILS patients), APACHE III severity of illness score, and being in intensive care on treatment on study day 7 (reflecting more prolonged exposure to rosuvastatin). We did post-hoc analyses for both the primary and secondary outcomes with adjustment for potential clustering of patient outcomes within hospitals and adjustment for risk factors for delirium (eg, age, APACHE III, mean arterial pressure, steroid use).[47,48]

We did not do a prospective sample size calculation for the assessment of delirium or cognitive impairment. We did all the prespecified analyses according to an a-priori written statistical analysis plan. We did the primary analysis with the frailtypack package in R (version 3.1.3) and we did the secondary analyses with Proc Mixed and Proc NLMixed[49] in SAS (version 9.3). We considered a two-sided p less than 0·05 significant.

The primary analysis of SAILS and the long-term outcomes study are registered with ClinicalTrials.gov (NCT00979121 and NCT00719446).

Role of the funding source

The funders had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or in the decision to submit for publication. DMN and EC had full access to all the outcomes data.

Results

568 patients were enrolled in the SAILS trial, of whom 329 were eligible for this study: 164 (50%) assigned to rosuvastatin and 165 (50%) assigned to placebo. 275 (84%) of 329

patients were enrolled at a hospital that assessed delirium. Three (1%) of 275 patients were excluded because of missing data for delirium (two patients in the rosuvastatin group and one in the placebo group), leaving 137 (50%) of 272 assigned to rosuvastatin and 135 (50%) of 272 assigned to placebo for analysis of the primary outcome of delirium in intensive care (figure 1). 83 (51%) of 164 patients assigned to rosuvastatin and 106 (64%) of 165 assigned to placebo were eligible for the long-term cognitive assessment (figure 1).

Baseline patient and intensive care unit characteristics were similar in each group (table 1, appendix p 2). As also reported in SAILS,[23] patients in the rosuvastatin group had significantly fewer renal and hepatic organ-failure-free days (table 1). During follow-up, three (2%) of 174 patients who had additional data collected had a stroke, six (4%) were admitted to hospital for neurological reasons, and 26 (15%) began taking psychiatric drugs.

195 (72%) of 272 patients assessed had delirium during the study. A mean of 32% (SD 30%) of patients had delirium each day and 14% (SD 21%) were in a coma. Of 192 delirious patients with coincident assessments of sedation, ten (5%) had exclusively hyperactive (Richmond Agitation Sedation Scale >0), 112 (58%) had exclusively hypoactive (Richmond Agitation Sedation Scale ≤0), and 70 (37%) had mixed delirium during their stay in intensive care. For cognition, roughly 40% of assessments were done face-to-face and 60% were done by telephone in each treatment group. 149 patients were assessed for cognitive outcomes at 12 months, but one patient had incomplete tests, therefore we analysed 148. 48 (37%) of 130 patients had evidence of overall cognitive impairment at 6 months, as did 43 (29%) of 148 patients at 12 months, with no significant change over time (p=0·17; table 2). At 6 months follow-up, the most commonly impaired domains of cognition were executive function, verbal fluency, immediate memory, and delayed memory, with only executive function having significant improvement in both continuous and binary measures at 12 months (table 2, figure 2).

For the rosuvastatin versus the placebo group, patients had similar mean proportions of days with delirium (34% [SD 30%] ***vs*** 31% [29%]; p=0·39) and coma (13% [SD 20%] ***vs*** 15% [SD 22%]; p=0·34). We found no significant effect of rosuvastatin compared with placebo for days with delirium in intensive care (hazard ratio 1·14, 95% CI 0·92–1·41; p=0·22). The results of the primary analysis were consistent after multiple imputation for missing delirium status (data not shown). No subgroup had a significant benefit of rosuvastatin compared with placebo for reducing delirium (data not shown).

At 6 months, 19 (36%) of 53 patients in the rosuvastatin group versus 29 (38%) of 77 in the placebo group had cognitive impairment, with no significant difference between groups (treatment effect 0·93, 95% CI 0·39–2·22; p=0.87; figure 3, table 3). At 12 months, 20 (30%) of 67 patients versus 23 (28%) of 81 patients had cognitive impairment, with no significant difference between groups (treatment effect 1·1, 95% CI 0·5–2·6; p=0·82). There were significant associations between assignment to rosuvastatin and worse delayed memory, with a worse mean continuous score and a greater percentage of patients with impaired delayed memory (table 3).

For patients who were in intensive care for 7 days or longer, those receiving rosuvastatin had higher odds of impairment in language at 6 months, and lower (ie, worse) scaled scores for both immediate and delayed memory at 6 months than did those receiving placebo (data not shown). These differences were not significant at 12 months, with the exception of delayed memory for which patients in the rosuvastatin group had higher (ie, better) scaled scores (data not shown). We detected no other significant effects of rosuvastatin versus placebo in subgroup analyses (data not shown).

Post-hoc analyses of the primary and secondary outcomes accounting for clustering of patient outcomes within hospitals (appendix p 3) and adjusting for risk factors for delirium (appendix p 4) did not materially change the results for the primary outcome (data not shown). For the secondary outcomes, the only change was with the Similarities (verbal reasoning and concept formation) age-scaled score, for which the adjusted average treatment effect was significantly lower (ie, worse) in the rosuvastatin group than in the placebo group at 6 months (−1·43, 95% CI −2·67 to −0·18; p=0·025; appendix p 4).

As reported previously,[23] the occurrence of high creatine kinase concentrations was much the same in each treatment group (16 patients ***vs*** 13 patients; p=0·65), as was the occurrence of high alanine aminotransferase concentrations (ten ***vs*** 12; p=0·39). However, significantly more patients had high aspartate aminotransferase concentrations (16 ***vs*** two; p<0·001). Additionally, hyperthermia, a serious adverse event, occurred in three patients in the rosuvastatin group versus none in the placebo group.

Discussion

In this ancillary study of a randomised, double-blind, placebo-controlled trial of rosuvastatin versus placebo for sepsis-associated acute respiratory distress syndrome, 72% of patients had delirium while in intensive care and roughly one-third had cognitive impairments at 6 months and 12 months of follow-up after randomisation, with executive function being the only cognitive domain with significant improvement in both continuous and binary measures over time. Despite indirect evidence from preclinical studies and results from two observational studies of statin use in intensive care, this trial showed no benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment at 6 months and 12 months of follow-up.

The prevalence of delirium in this study was similar to the 77% reported in a two-site observational study of statins and delirium in patients with acute respiratory failure or shock.[19] Not surprisingly, the prevalence was lower (36%) in the other observational study of statins for delirium,[20] which assessed all consecutive patients admitted to a single intensive care unit in which only 42% of patients were mechanically ventilated, and lower than the pooled prevalence in a meta-analyses of critically ill patients (31·8%).[52] The prevalence of cognitive impairment at 6 months and 12 months in this report was very similar to a separate patient cohort from ARDSNet's EDEN trial (36% at 6 months, 25% at 12 months), which used an identical battery of cognitive tests and definition of cognitive impairment.[26] This prevalence was also very similar to that in a cohort of patients with

respiratory failure or shock, assessed at 3 months (40%) and 12 months (34%) with a different set of cognitive tests.[1]

The findings that rosuvastatin did not improve delirium in intensive care conflicts with two rigorous observational studies,[19,20] which showed strong and consistent associations between statin use and reduced daily delirium in intensive care, particularly for patients with sepsis early in their stay in intensive care.[19] The high overall prevalence of delirium in our study or heterogeneity in baseline risk for delirium within our study cohort might have affected our results. Additionally, the differences between our findings and those of observational studies might be a result of unmeasured confounders biasing the observational studies—a limitation minimised in a randomised, double-blind trial. Findings from the SAILS trail[23] also showed no significant effect of statins on short-term mortality and other infection-related complications in patients with infection and sepsis, in contrast to observational studies.[53–55] However, these differing results also might have arisen because of the greater lipophilic properties (and hence, greater crossing of the blood–brain barrier and tissue penetration) of simvastatin, used in most patients in the observational studies,[19,20,56] versus rosuvastatin, which was used in SAILS. Additionally, results of an observational study[20] have suggested that inflammation (measured by C-reactive protein) might be a mediator of the beneficial association between statins and delirium, but in the present study, C-reactive protein concentrations did not differ significantly between treatment groups (except on day 9).[23] In patients taking statins at baseline and then assigned to placebo, there are concerns regarding rebound inflammation after cessation of statins.[57,58] Because of the similar C-reactive protein concentrations in each treatment group, this possibility seems unlikely; however, data for baseline statin use were only recorded in a subset of patients, preventing full assessment of this issue.

The associations between rosuvastatin and worse delayed memory (in our original analysis) and worse verbal reasoning and concept formation (in our post-hoc adjusted sensitivity analysis) at 6 months, were part of multiple secondary analyses. These analyses are intended to be hypotheses-generating for future research.

The methods and results from this ancillary study might help to inform the design of randomised trials on this topic. Future trials could assess more lipophilic statins to better understand the potential effect of statins on delirium. In addition, such trials should include secondary outcome measures to understand any benefits of reduced delirium, such as reduced length of stay and post-discharge cognitive impairment, as assessed in this study. Moreover, this study and previous research might help the development of a minimum set of outcome measures (ie, a core outcome set[59]) for trials of delirium in critically ill patients. Such a set of core outcomes would be recommended for use in all trials of delirium in critically ill patients to enable results of different studies to be compared and synthesised. Moreover, consideration of appropriate statistical methods to evaluate the effect of interventions in intensive care on the duration of delirium (when assessable—ie, when patients are not comatose), accounting for the competing risks of death and discharge from intensive care, is important and the method used in this study provides one example. Lastly, investigators designing trials should consider how best to strike a balance between assessing efficacy versus assessing effectiveness when deciding about standardising potentially

important co-interventions (eg, sedation) compared with allowing routine practice to be used during the trial.

This study has several strengths, including being part of a multicentre, randomised, double-blind, placebo-controlled trial, and detailed longitudinal assessments of cognitive function. However, there are also limitations. First, the primary outcome of delirium was subject to both missing data and possible measurement error. However, the randomised nature of this study (with stratification by hospital site) and the statistical methods (including sensitivity analyses using multiple imputation of missing data) helps reduce such concerns. Second, rosuvastatin has less antibacterial effects[60] and tissue penetration (given its lower lipophilicity) than do atorvastatin and simvastatin. Hence, we cannot conclude that a different statin would not be beneficial. Some experts have suggested that randomised trials of delirium should assess statins with both high and low lipophilic properties given the uncertainty about the effects on neuroinflammation.[8] However, both a lipophilic (ie, simvastatin) and non-lipophilic (ie, rosuvastatin) statin have been assessed in large randomised trials of patients with acute respiratory distress syndrome with similar findings of no beneficial effects on mortality and ventilator-free days.[23,61] Rosuvastatin was used in the SAILS trial on the basis of its superior bioavailability, risk of hepatic dysfunction, and drug–drug interactions.[23] Third, young patients with acute respiratory distress syndrome and sepsis were enrolled; hence, these results might not generalise to other populations of critically ill patients. Fourth, no validated screening instrument was used for excluding patients with pre-existing cognitive impairment from cognitive assessments. However, the randomised comparison of rosuvastatin versus placebo, the large proportion of exclusions for baseline cognitive impairment (11% in our study ***vs*** 6% in a previous study of intensive care that used a validated cognitive screening instrument[1]), and the similar prevalences of cognitive impairment[1,26,62] provide reassurance regarding this issue. Lastly, the study might have been underpowered to detect the superiority of rosuvastatin compared with placebo given that the sample size was dependent on the parent trial without any a-priori sample size calculation for this study. However, the results of the trial do not support the superiority hypothesis and the confidence interval of the treatment effect is valuable in offering a range of plausible values for treatment effects, as supported by the available data.[63]

Despite encouraging preclinical and observational studies showing that statins were associated with reduced daily delirium in intensive care, our findings show no benefit of rosuvastatin in reducing delirium in intensive care or cognitive impairment during the subsequent 12 months. Hence, there is a continued need to assess interventions to attenuate the cognitive impairments common in patients during and after admission to intensive care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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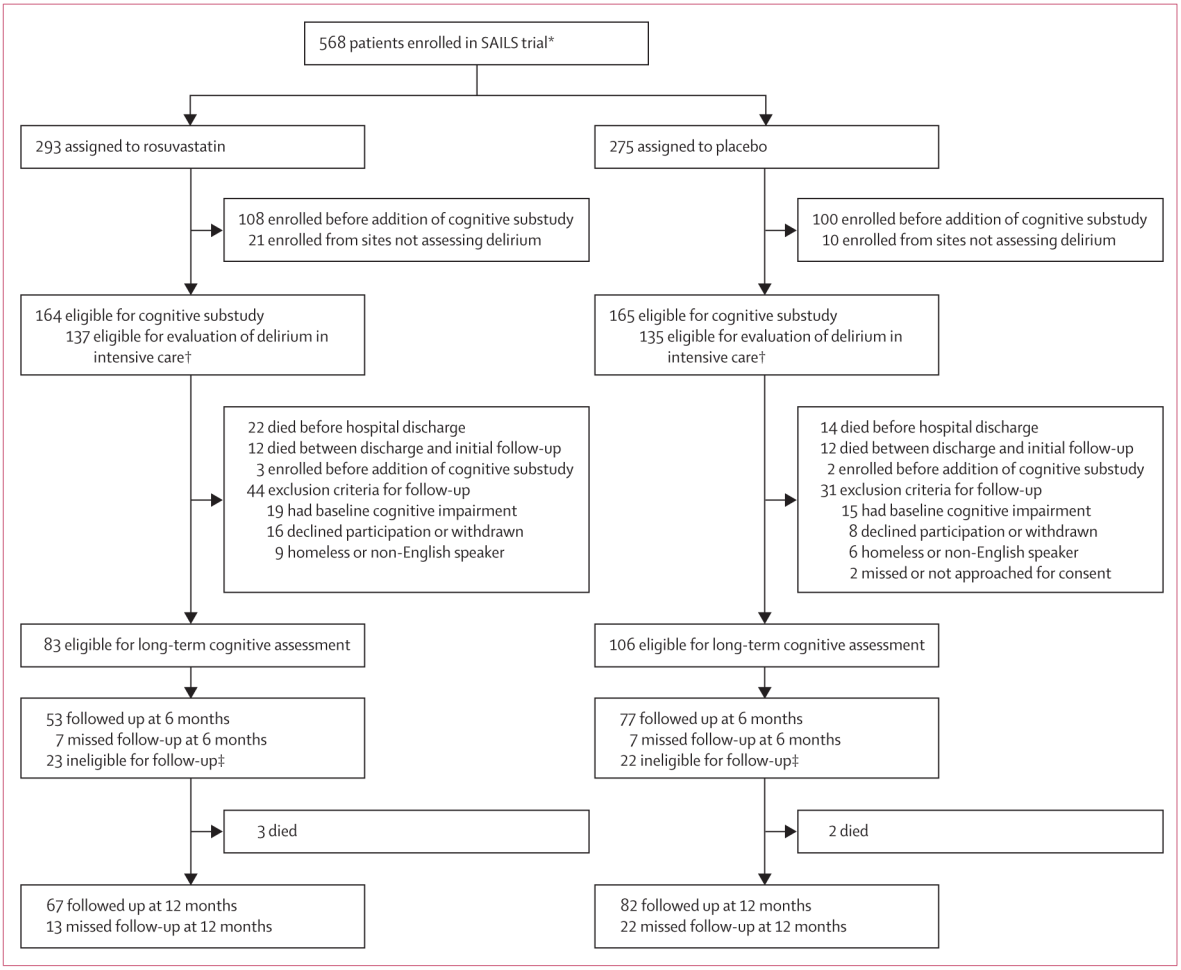

Figure 1. Trial profile

*Less than the 745 patients in the SAILS trial because two sites did not participate and there was a temporary cessation of recruitment into this ancillary study. †57 (17%) of 329 patients were excluded from assessment of delirium, but still eligible for follow-up at 6 months and 12 months: 46 (14%) were in intensive care before the protocol revision expanding assessment of delirium and cognitive status to other hospitals, eight (2%) were at sites not participating in delirium assessment, and three (1%) had missed delirium assessment. ‡Because of the timing of approval by the institutional review boards for this ancillary study, but patients later provided consent and were eligible for follow-up at 12 months.

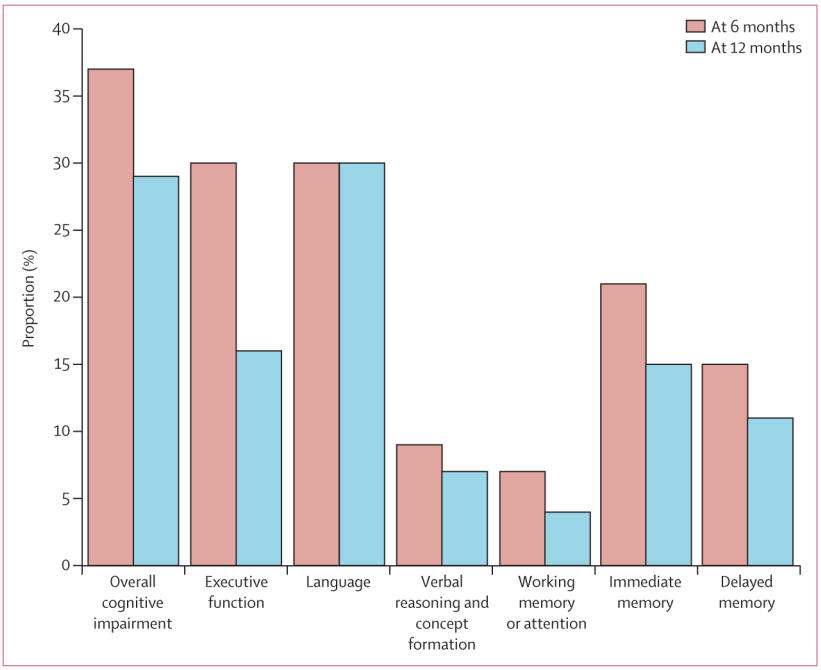

Figure 2.
Proportion of patients with cognitive impairment

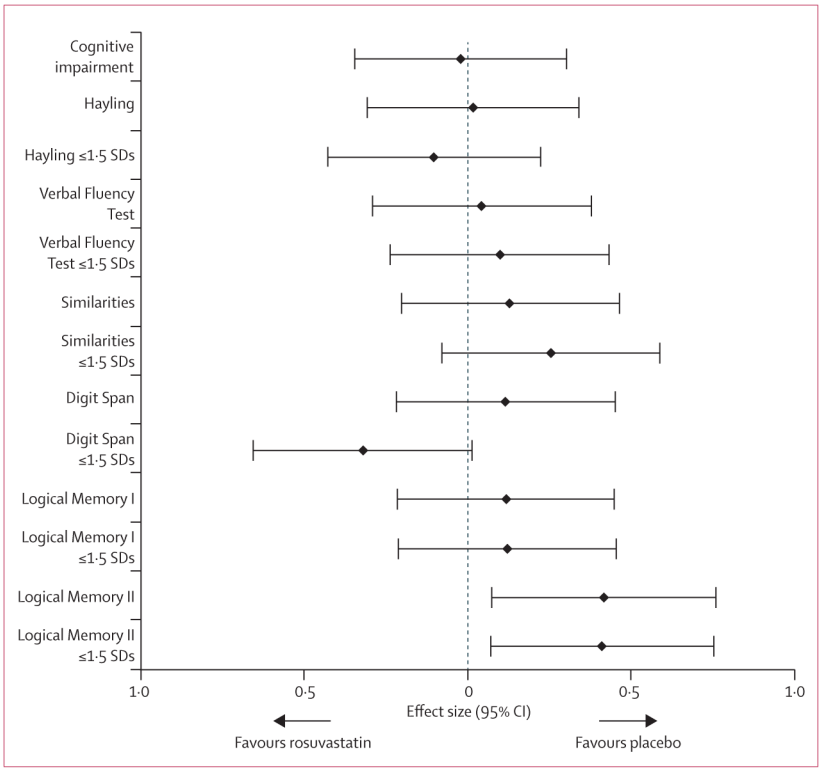

Figure 3. Treatment effect at 6 months

The effect size is the treatment effect (difference in means or proportions) divided by the pooled standard deviation from the rosuvastatin and placebo groups.[50,51]

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Table 1

Baseline characteristics and intensive care data

	Eligible for delirium or cognitive assessment		With data for delirium		Eligible for cognitive assessment	
	Rosuvastatin group (n=164)	**Placebo group (n=165)**	**Rosuvastatin group (n=137)**	**Placebo group (n=135)**	**Rosuvastatin group (n= 83)**	**Placebo group (n=106)**
Baseline characteristics						
Age (years)	52 (18)	53 (15)	52 (18)	52 (16)	49 (16)	52 (14)
Women	82 (50%)	85 (52%)	65 (47%)	70 (52%)	44 (53%)	56 (53%)
White	142 (88%)	137 (85%)	120 (90%)	116 (87%)	68 (83%)	92 (88%)
Education (years)*	..	..	..	..	13 (2·2)	13 (2·6)
Previous residence						
Home independently	138 (84%)	132 (80%)	113 (82%)	108 (80%)	76 (92%)	90 (85%)
Home with help	18 (11%)	19 (12%)	16 (12%)	17 (13%)	5 (6%)	9 (8%)
Health-care facility	7 (4%)	14 (8%)	7 (5%)	10 (7%)	2 (2%)	7 (7%)
Other	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Body-mass index (kg/m^2)	32 (10)	31 (11)	32 (9)	31 (11)	33 (11)	32 (10)
Diabetes	31 (19%)	40 (24%)	26 (19%)	32 (24%)	16 (19%)	28 (26%)
Previous stroke with sequelae	1 (1%)	3 (2%)	1 (1%)	2 (1%)	0 (0%)	2 (2%)
Used statins before admission	21 (13%)	30 (18%)	19 (14%)	26 (19%)	7 (9%)	16 (15%)
Baseline intensive care data						
APACHE III score	90 (27)	89 (28)	91 (27)	90 (28)	85 (27)	87 (28)
PaO_2:FiO_2 ratio	168 (69)	172 (68)	171 (70)	171 (68)	172 (71)	164 (65)
Patients with PaO_2:FiO_2 ratio ≤200	117 (72%)	112 (68%)	96 (71%)	93 (69%)	58 (70%)	79 (75%)
Baseline shock	64 (39%)	65 (39%)	52 (38%)	55 (41%)	34 (41%)	41 (39%)
Primary lung injury						
Pneumonia	108 (66%)	118 (72%)	88 (65%)	97 (72%)	53 (64%)†	81 (77%)†
Non-pulmonary infection	34 (21%)	32 (20%)	28 (21%)	26 (19%)	21 (25%)†	18 (17%)†
Aspiration	14 (9%)	9 (5%)	13 (10%)	8 (6%)	9 (11%)†	3 (3%)†
Other	7 (5%)	5 (3%)	7 (6%)	4 (3%)	0 (0%)†	3 (3%)†

	Eligible for delirium or cognitive assessment		With data for delirium		Eligible for cognitive assessment	
	Rosuvastatin group (n=164)	Placebo group (n=165)	Rosuvastatin group (n=137)	Placebo group (n=135)	Rosuvastatin group (n= 83)	Placebo group (n=106)
Daily intensive care data						
Any dialysis in hospital	26 (16%)	22 (13%)	24 (18%)	20 (15%)	13 (16%)	9 (8%)
Any vasopressor use‡	86 (53%)	88 (53%)	70 (52%)	76 (56%)	42 (51%)	53 (50%)
Proportion of days per patient, if any	39 (25)	40 (27)	41 (24)	39 (27)	37 (26)	36 (20)
Any corticosteroids‡	47 (29%)	53 (32%)	38 (28%)	43 (32%)	26 (31%)	33 (31%)
Proportion of days per patient, if any	67 (33)	67 (33)	67 (33)	65 (34)	56 (33)	72 (33)
Organ failure-free days to day 14						
Cardiovascular	10 (4)	10 (4)	9 (4)	10 (4)	11 (3)	11 (4)
Renal	11 (5)†	12 (4)†	11 (5)†	12 (4)†	12 (5)	13 (3)
Hepatic	12 (4)	13 (3)	12 (4)†	13 (3)†	13 (3)	13 (3)
Coagulation	12 (4)	12 (4)	12 (4)	12 (4)	13 (3)	13 (2)
Duration of mechanical ventilation (days)	10 (9)	10 (11)	11 (10)	11 (12)	9 (7)	10 (10)
Length of stay in intensive care (days)	14 (9)	13 (8)	14 (10)	13 (9)	13 (9)	12 (7)
Length of stay in hospital (days)	21 (13)	21 (13)	22 (13)	22 (14)	21 (14)	20 (12)

Data are mean (SD) or n (%) unless stated otherwise. Unknown or missing data for eligible cohort versus delirium assessment cohort versus cognitive assessment cohort: race 6 *vs* 5 *vs* 3; used statins before admission 4 *vs* 1 *vs* 4; APACHE III score 18 *vs* 15 *vs* 8. PaO_2:FiO_2 3 *vs* 2 *vs* 1; primary lung injury 2 *vs* 1 *vs* 1; vasopressor use 2 *vs* 2 *vs* 1; duration of mechanical ventilation 2 *vs* 0 *vs* 2; length of stay in intensive care 9 *vs* 6 *vs* 6; length of stay in hospital 2 *vs* 2 *vs* 1. APACHE III=Acute Physiology And Chronic Health Evaluation III. PaO_2=partial pressure of oxygen in arterial blood. FiO_2=fraction of inspired oxygen.

*Data collected only for patients eligible for cognitive follow-up.

†p<0·05 for rosuvastatin group versus placebo group.

‡Data are overall mean of each patient's mean value of available daily data; data for corticosteroids available until 48 h after cessation of mechanical ventilation or day 7, whichever came first; data for vasopressor available until death, discharge from study hospital, or day 14, whichever came first; proportions calculated among days in intensive care on which drug data were available; days without organ failure until day 14 calculated as previously described.[23]

Table 2

Cognitive Function Status at 6 months and 12 months

	At 6 months (n=130)	At 12 months (n=149)	Difference (95% CI)	p value
Cognitive impairment	48/130 (37%)	43/148 (29%)	−8 (−19 to 3)	0·17
Executive function (mean Hayling Sentence Completion score, SD)	4·4 (2·0)	5·1 (1·6)	0·8 (0·5 to 1·0)	<0·0001
Patients with score ≤1·5 SD	39/128 (30%)	23/148 (16%)	−15 (−25 to −5)	0·003
Language (mean Verbal Fluency score, SD)	32 (12)	32 (12)	1 (−1 to 2)	0·26
Patients with score ≤1·5 SD	38/128 (30%)	41/138 (30%)	0 (−11 to 11)	0·99
Verbal reasoning and concept formation (mean Similarities score, SD)	9·8 (3·3)	10·1 (3·2)	0·5 (0·1 to 0·9)	0·010
Patients with score ≤1·5 SD	12/128 (9%)	10/140 (7%)	−2 (−19 to 15)	0·80
Working memory and attention (mean Digit Span score, SD)	9·4 (2·5)	9·4 (2·7)	0·0 (−0·4 to 0·4)	0·99
Patients with score ≤1·5 SD	9/128 (7%)	6/139 (4%)	−3 (−58 to 52)	0·92
Immediate memory (mean Logical Memory I score, SD)	8·7 (3·3)	8·9 (3·2)	0·2 (−0·3 to 0·7)	0·46
Patients with score ≤1·5 SD	26/126 (21%)	21/140 (15%)	−6 (−32 to 21)	0·68
Delayed memory (mean Logical Memory II score, SD)	8·5 (3·0)	8·8 (2·8)	0·3 (−0·1 to 0·8)	0·13
Patients with score ≤1·5 SD	19/123 (15%)	15/135 (11%)	−4 (−20 to 13)	0·64

Data are n/N (%) unless stated otherwise. Differences were calculated from linear or logistic regression models with random intercept and an indicator for time (12 months *vs* 6 months).

Table 3

Cognitive impairment at 6 months by treatment group

	Rosuvastatin group (n=53)	Placebo group (n=77)	Treatment effect (95% CI)	p value
Cognitive impairment	19/53 (36%)	29/77 (38%)	0·93 (0·39 to 2·22)	0·87
Executive function (mean Hayling Sentence Completion score, SD)	4·5 (1·8)	4·4 (2·1)	0·0 (−0·6 to 0·6)	0·92
Patients with score ≤1·5 SD	14/53 (26%)	25/75 (33%)	0·74 (0·31 to 1·80)	0·51
Language (mean Verbal Fluency score, SD)	31 (13)	32 (11)	−1 (−4 to 3)	0·80
Patients with score ≤1·5 SD	18/52 (35%)	20/76 (26%)	1·44 (0·54 to 3·80)	0·46
Verbal reasoning and concept formation (mean Similarities score, SD)	9·7 (3·8)	9·9 (3·0)	−0·4 (−1·5 to 0·7)	0·44
Patients with score ≤1·5 SD	7/52 (13%)	5/76 (7%)	2·29 (0·60 to 8·77)	0·23
Working memory and attention (mean Digit Span score, SD)	9·2 (2·5)	9·5 (2·6)	−0·3 (−1·2 to 0·6)	0·49
Patients with score ≤1·5 SD	1/52 (2%)	8/76 (11%)	0·17 (0·02 to 1·52)	0·11
Immediate memory (mean Logical Memory I score, SD)	8·6 (3·4)	8·9 (3·3)	−0·4 (−1·5 to 0·7)	0·49
Patients with score ≤1·5 SD	12/50 (24%)	14/76 (18%)	1·37 (0·50 to 3·76)	0·54
Delayed memory (mean Logical Memory II score, SD)	7·9 (3·3)	8·8 (2·7)	−1·2 (−2·2 to −0·2)	0·017
Patients with score ≤1·5 SD	12/50 (24%)	7/73 (10%)	3·06 (1·00 to 9·37)	0·050

Data are n/N (%), unless stated otherwise. Treatment effects were calculated from linear or logistic regression models with a random intercept and an indicator for treatment (rosuvastatin *vs* placebo), time (12 months *vs* 6 months), and the interaction of treatment group and time. The treatment effect is the mean difference in score for continuous measures (whereby a positive value represents better cognitive performance in the rosuvastatin group) and the odds ratio for binary measures (whereby a value >1 indicates worse cognitive performance in the rosuvastatin group).