Citation:

http://www.thelancet.com/journals/lanres
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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Word Count (excluding abstract, references, acknowledgements, and legends): 3,739
Abstract

Background: Delirium commonly occurs in mechanically ventilated patients and is associated with cognitive impairment lasting at least 1 year after hospital discharge. Pre-clinical studies and observational research in the intensive care unit (ICU) have suggested that use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may be associated with reduced delirium. These findings require further evaluation via randomized controlled trials to assess whether the pleiotropic effects of statins may reduce delirium in the ICU and decrease subsequent cognitive impairment.

Methods: Within the multi-center randomized trial of rosuvastatin vs. placebo in patients with sepsis-associated acute respiratory distress syndrome (ARDS) completed by the ARDS Network (SAILS trial), we conducted an ancillary study evaluating rosuvastatin’s effects on daily delirium status (primary endpoint) in the ICU and cognitive function at 6 and 12 month follow-up. In the SAILS trial, patients were randomized in permuted blocks of 8 and stratified by study hospital, with those in the rosuvastatin group receiving a 40-mg loading dose and daily 20-mg dose until the earliest of 3 days after ICU discharge, study day 28, or death. Delirium was evaluated using the validated Confusion Assessment Method for the ICU, and a battery of validated tests evaluated the following aspects of cognitive function: executive function; language; verbal reasoning and concept formation; and working, immediate, and delayed memory. Patients were characterized as having cognitive impairment if 1 of these domains was ≥2 standard deviations below population norms or at least 2 domains were ≥1.5 standard deviations below norms. Analysis of the primary outcome was by intention to treat. This trial is registered with ClinicalTrials.gov (NCT00979121 and NCT00719446).
**Findings:** Of 272 patients evaluated daily for delirium, 195 (72%) ever had delirium. In consenting survivors, 37% and 29% had cognitive impairment at 6 and 12 months, respectively. There was no significant effect of randomization to rosuvastatin versus placebo on delirium, with a hazard ratio (95% confidence interval) for daily delirium status of 1.14 (0.92 – 1.41, p=0.22).

**Interpretation:** Delirium occurred in the vast majority of patients with sepsis-associated ARDS, with cognitive impairment over 1-year follow-up occurring in approximately 1 in 3 survivors. Despite encouraging pre-clinical and observational studies demonstrating that statins were associated with reduced daily delirium in the ICU, this trial demonstrates no benefit of rosuvastatin in reducing delirium in the ICU or cognitive impairment during 12-month follow-up. Hence, there is continued need to evaluate interventions aimed at attenuating ICU and post-ICU cognitive impairments commonly observed in this population.

**Funding:** National Heart, Lung and Blood Institute funded this follow-up study (N01HR56170, R01HL091760 and 3R01HL091760-02S1),) and the SAILS trial (contracts HHSN268200536165C to HHSN268200536176C and HHSN268200536179C), along with support from the Johns Hopkins Institute for Clinical and Translational Research (ICTR) (UL1 TR 000424-06). Additionally, the SAILS trial was supported by the Investigator-Sponsored Study Program of AstraZeneca.

**Keywords:** Respiratory distress syndrome, adult; sepsis; Hydroxymethylglutaryl-CoA reductase inhibitors; rosuvastatin; delirium; cognition; double-blind method; treatment outcome
Research in Context

Evidence before this study

Animal research and human observational studies have shown indirect evidence of potential beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for delirium and cognition.\(^\text{(15-18)}\) In critically ill patients, two large observational studies found strong associations of statin use with reduced daily odds of delirium in the intensive care unit (ICU).\(^\text{(19,20)}\) We searched PubMed, Embase and Cochrane on June 30, 2015, with no language or date limitations, for any randomized trials evaluating statins in critically ill patients. We did not find any completed randomized 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

This ancillary study of a multi-centered, randomized, double-blinded, placebo-controlled trial evaluating the effect of a statin (in this case, rosuvastatin) vs. placebo is novel in evaluating effects on delirium in the ICU and cognitive function at 6- and 12-month follow-up. This study, conducted in patients with sepsis-associated acute respiratory distress syndrome, found that delirium occurred in 72% of patients and that cognitive impairment, over 1-year follow-up, occurred in approximately 1 in 3 survivors.

Implications of all the available evidence

Despite preliminary evidence in animal studies and in two rigorous, observational ICU studies of statins, this ancillary study demonstrated no benefit of randomization to rosuvastatin in reducing delirium in the ICU or cognitive impairment at 6- and 12-month follow-up. There is continued need to evaluate interventions aimed at attenuating ICU and post-ICU cognitive impairments commonly observed in this population.
**Introduction**

Critically ill patients are at high risk for delirium, occurring in up to 80% of mechanically ventilated patients.\(^{(1)}\) In such patients, a longer duration of delirium is associated with impaired cognitive function, lasting \(\geq 12\) months after discharge.\(^{(1)}\) Such cognitive impairment reduces quality of life and return to work, while increasing institutionalization and healthcare costs.\(^{(2;3)}\)

Despite the importance of this neurocognitive morbidity, there are limited pharmacological interventions to reduce delirium and long-term cognitive impairment.\(^{(4)}\)

Both animal and human data offer indirect evidence that neuroinflammation, with associated oxidative damage and apoptosis, is an important part of the pathophysiology of delirium in the ICU and subsequent long-term cognitive impairment.\(^{(5-8)}\)

Severe sepsis is a prototype of systemic inflammation, including neuroinflammation.\(^{(9)}\)

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, commonly known as statins, have pleiotropic properties, including relatively fast-acting anti-inflammatory effects, and may improve neuronal function via effects on neurotransmitters and endothelial function.\(^{(10-15)}\)

An animal model of sepsis demonstrated that 48 hours of statin therapy reduced systemic inflammation, decreased oxidative damage in the brain, and protected against cognitive impairment assessed 2 weeks later.\(^{(16)}\)

Studies in other fields have found a protective association of statins with delirium.\(^{(17;18)}\)

Moreover, two large, rigorously designed, observational studies in critically ill patients provide preliminary data showing strong and consistent associations of statin use with reduced daily odds of delirium in the ICU, particularly in septic patients early in their ICU stay.\(^{(19;20)}\)

This potential benefit is hypothesized 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 the ICU and cognitive function after critical illness via randomized trials.\(^{(8;19-22)}\)
A randomized controlled trial appropriate for evaluating the effect of statins in critically ill septic patients is the large, multi-centered trial known as Statins for Acutely Injured Lungs from Sepsis (SAILS), conducted by the ARDS Network (ARDSNet), which evaluated the short-term effects of rosuvastatin versus placebo on mortality and ventilator-free days.\(^{(23)}\) In conjunction with the SAILS trial, we conducted an ancillary study to assess if rosuvastatin reduced delirium in the ICU and improved cognitive function at 6- and 12-month follow-up.

**Methods**

This ancillary study of the SAILS trial is part of the NIH-funded ARDSNet Long-Term Outcomes Study (ALTOS) that included prospective evaluation of daily delirium status in the ICU (primary outcome) and cognitive function at 6- and 12-month follow-up (secondary outcomes). Initially, daily delirium status in the ICU and cognitive assessments were conducted only for patients recruited from 12 of 37 hospitals participating in the SAILS trial. Based on new data demonstrating that statin use was associated with reduced odds of delirium in the ICU,\(^{(24)}\) the ARDS Network amended the SAILS protocol, expanding assessment of daily delirium status in the ICU and cognitive outcomes at 6 and 12 month follow-up to 23 additional hospitals. Institutional review boards at each participating site approved this study, with informed consent obtained from each patient or their proxy (when the patient was incapable of consent).

**Study Procedures and Eligible Patients**

Details of the SAILS eligibility criteria and study intervention have been reported previously,\(^{(23)}\) and are briefly summarized herein. From March 18, 2010 to September 30, 2013, patients were randomized (with concealed allocation) in permuted blocks of 8, with stratification by hospital study site, via a web-based system to receive daily enteral rosuvastatin...
(a 40-mg loading dose and daily 20-mg dose) or a similar-appearing placebo, administered from the time of randomization until the earliest of death, 3 days after ICU discharge, or study day 28.(23) SAILS was stopped early due to futility, after recruiting 745 of its 1000 patient sample size, with no significant differences in short-term mortality, ventilator-free days, and ICU-free days. The first 75 patients in the current analysis were co-enrolled in ARDSNet’s prior 1000-patient EDEN study, a randomized trial of initial trophic vs. full enteral feeding for up to 6 days after ARDS, that demonstrated no significant difference in short-term outcomes,(23) or 6- and 12-month cognitive function.(25;26) All SAILS patients were managed with simplified protocols for lung protective ventilation, ventilator weaning, and fluid and hemodynamic management.(27;28)

For evaluation of SAILS survivors’ cognitive function at 6 and 12 month follow-up, the following additional exclusion criteria were applied: <18 years old, non-English speaking, homeless or pre-existing cognitive impairment (evaluated based on patients’ status prior to hospitalization using medical record review and/or interview with the patient and/or proxy). Patient loss during 6- and 12-month follow-up was minimized through established cohort retention methods.(29-35)

**Primary Outcome: Daily Delirium Status in the ICU**

Daily delirium status in the ICU was evaluated by research or clinical personnel, blinded to treatment allocation, using the validated and reliable Confusion Assessment Method for the ICU (CAM-ICU).(36-38) As per CAM-ICU methodology,(36) patients who were non-responsive to verbal stimulation (e.g., Richmond Agitation Sedation Scale (RASS)(39) score of -4 or -5), referred to hereafter as “coma,” were excluded from delirium assessment for that day.
**Secondary Outcomes: Cognitive Function at 6 and 12 month follow-up**

At 6 and 12 month follow-up, occurring from 2010 to late 2014, research personnel, blinded to treatment allocation, completed a battery of reliable and valid, standardized tests evaluating the cognitive domains of greatest relevance in ARDS survivors.(26;40) This test battery was validated for administration via phone or in-person assessment,(40) with approximately 40% of assessments done in-person and 60% by phone in each of the rosuvastatin and placebo groups. Based on this test battery, a binary assessment of overall “cognitive impairment” was conservatively defined, as in prior research,(26) as having either 1 cognitive test score ≥2 standard deviations (SD) below population norms (i.e. bottom 2.5%) or at least 2 test scores ≥1.5 SD below norms (i.e. bottom 6.7%).(41) Additionally, individual results on specific cognitive tests are presented as both continuous scores and binary outcomes (≥1.5 SD below norm). The following cognitive domains were evaluated in the test battery: (1) executive function, evaluated via the Hayling Sentence Completion Test scaled score (range: 1 to 10; higher is better);(42) (2) language, evaluated via a Verbal Fluency Test total score (higher score is better);(43) (3) verbal reasoning and concept formation, evaluated via the Similarities age-adjusted scaled score (range: 1 to 19; higher is better) from the Wechsler Adult Intelligence Scale-Third Edition;(44;45) and (4) attention and working memory evaluated via the Digit Span age-adjusted scaled score (range: 1 to 19; higher is better) from the Wechsler Adult Intelligence Scale-Third Edition(44;45) (5) immediate and delayed memory, evaluated via the Logical Memory I and II age-adjusted scaled scores (range: 1 to 19; higher is better) from the Wechsler Memory Scale-Third Edition;(44;45)

**Statistical analysis**

Descriptive statistics were used to compare patient and intensive care data across the two treatment groups. The primary outcome, daily delirium status up to 28 days after randomization,
was compared across treatment groups using a joint survival model that allowed for recurrent events (i.e., the repeated within-subject daily delirium status) and for a terminating event (death or ICU discharge).(46) The recurrent event model included a main effect of treatment only, quantified as the relative hazard of delirium on any day in the ICU comparing rosuvastatin vs. placebo groups. The terminating event model included two main effects: randomized treatment group and the type of terminating event (death or ICU 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 the ICU at 28 days were administratively censored.

The primary analysis was performed on the available data using the intention-to-treat principle, with patients contributing to the model on days when the CAM-ICU was administered and delirium was able to be assessed (i.e. no coma). The joint survival model used in the primary analysis is valid under the missing at random assumption, with missingness as follows: CAM-ICU never available for 3 (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. A sensitivity analysis was performed 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 prior day.

Continuous and binary secondary outcomes were compared at 6 and 12 months using linear or logistic random intercept regression models, respectively, that included the main effect of time only. Treatment effects were estimated separately at 6 and 12 months using the same models with addition of an effect of treatment group and its interaction with time. Sensitivity analyses
included repeating the statistical analyses of the 6 and 12 outcomes for only the cohort of patients with both delirium and cognitive impairment data.

Pre-specified sub-group analyses were performed for the primary and secondary analyses to evaluate if the treatment effect differed based on 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 the ICU on treatment on study day 7 (reflecting more prolonged exposure to rosuvastatin). Post-hoc analyses completed for both the primary and secondary outcomes including adjusting for potential clustering of patient outcomes within hospitals and the adjusting for known risk factors for delirium. (47;48)

The sample size for these analyses was based on the available patients at the participating sites during the eligible enrollment period, as described above. All analyses were conducted according to an *a priori* written statistical analysis plan, and performed using R version 3.1.3 and SAS version 9.3 statistical software. The primary analysis was conducted using the “frailtypack” package within R and secondary analyses were conducted using Proc Mixed and Proc NLMixed(49) within SAS. A two sided P<0.05 was considered significant.

This trial is registered with ClinicalTrials.gov (NCT00979121 and NCT00719446).

**Role of the Funding Source**

All researchers are independent of the funding bodies. The funding bodies had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the manuscript for publication.
DMN and EC had full access to all the outcomes data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Results**

Participating hospitals recruited 329 SAILS patients, of which 164 (50%) were randomized to rosuvastatin. Of these 329 patients, 275 (84%) were enrolled at a hospital that performed delirium outcome assessments. Of these 275 patients, 3 (1%) were excluded due to missing delirium assessment data (2 patients from rosuvastatin group and 1 from placebo), leaving 137 (50%) and 135 (50%) randomized to rosuvastatin and placebo, respectively, for analysis of the primary outcome of delirium in the ICU (Figure 1). For the secondary outcomes related to 6- and 12-month cognitive function, among the 329 SAILS patients, 60 (18%) died prior to 6-month follow-up (34 [20%] in rosuvastatin and 26 [16%] in placebo group, p=0.45), 75 (23%) met ALTOS exclusion criteria, and 5 (1.5%) were enrolled prior to starting the ALTOS study, leaving 189 eligible patients, of which 83 (44%) and 106 (56%) were randomized to rosuvastatin and placebo, respectively (Figure 1).

**Patient characteristics**

Baseline patient and ICU characteristics were similar between the rosuvastatin versus placebo groups across the patient cohorts evaluated in this analysis (Table 1 and Appendix Table 1). In the overall cohort of 329 patients, characteristics included a mean (SD) age of 52 (16) years, 51% (167/329) women, 82% (270/329) living independently at home, and 70% (229/326) having Pa02/Fi02 ratio ≤200 and 40% (130/329) having shock. Moreover, during their ICU stay, 53% (174/327) of patients received vasopressors, 30% (100/329) received corticosteroids and 15% (48/329) required hemodialysis, with a mean (SD) duration of mechanical ventilation and
hospital stay of 10 (10) and 21 (13) days, respectively. As also observed in SAILS,(23) the statin group had worse renal and hepatic organ-failure free days (Table 1). In the cohort evaluated for 6- and 12-month cognitive impairment, the average (SD) years of education was 13 (2.3) vs. 13 (2.6) in the rosuvastatin vs. placebo groups. During follow-up, of 174 patients, 3 (<2%) had a stroke, 6 (<4%) had any hospitalization for neurologic cause, and 26 (15%) commenced any type of psychiatric medication.

**Delirium in the ICU and Cognitive Impairment at 6 and 12 Months**

Of the 272 patients evaluated daily for delirium in the ICU, 195 (72%) ever had delirium, with a mean (SD) of 32% (30%) of daily patient assessments being delirium and 14% (21%) being coma. Of 192 delirious patients with coincident RASS sedation assessments, 10 (5%) had exclusively hyperactive (RASS >0), 112 (58%) exclusively hypoactive (RASS ≤0), and 70 (37%) mixed delirium during their ICU stay. At 6- and 12-month follow-up, respectively, 37% (48/130) and 29% (43/148) of evaluated survivors had evidence of overall cognitive impairment (as defined in Methods), without significant improvement over time (p=0.17) (Table 2). At 6-month follow-up, the domains of cognition most commonly impaired were (Figure 2): executive function (30%, 39 of 128 patients), verbal fluency (30%, 38 of 128), immediate memory (21%, 26 of 126) and delayed memory (15%, 19 of 123), with only executive function demonstrating significant improvement at 12 month follow-up (30% [39/128] vs. 16% [23/148] impaired at 6 vs. 12 months, p=0.003).

**Comparison of Rosuvastatin versus Placebo**

For rosuvastatin vs. placebo groups, patients had similar mean (SD) proportions of assessments with delirium (34% (30%) vs. 31% (29%), p =0.39) and coma (13% (20%) vs. 15% (22%), p=0.34). For the primary outcome of daily delirium status in the ICU, there was no significant
effect of rosuvastatin versus placebo, with a hazard ratio for delirium (95% confidence interval) of 1.14 (0.92 – 1.41, p=0.22). The results of the primary analysis were consistent after multiple imputation for missing delirium status. There was no patient subgroup identified which demonstrated a significant benefit of rosuvastatin vs. placebo for reducing delirium.

For each of the secondary outcomes of cognitive function at 6- and 12-month follow-up, there was no significant beneficial effect of rosuvastatin vs. placebo (Figure 3 shows 6-month results). There were significant associations between randomization to rosuvastatin and worse delayed memory, with a worse mean (SD) continuous score (Logical Memory II test score: 7.9 (3.3) vs. 8.8 (2.7), p=0.017) and a greater percentage of patients with impaired delayed memory (24% vs. 10%, p=0.050) (Table 3).

Across the subgroup analyses, there were no significant effects of rosuvastatin vs. placebo, except as reported herein. For the subgroup of patients in the ICU at day 7 or longer, at 6-month follow-up, those receiving rosuvastatin vs. placebo had higher odds of impairment in language (evaluated via verbal fluency test), and lower (i.e., worse) scaled scores for both immediate and delayed memory (Logical Memory I and II tests). These differences were not significant at 12-months, with the exception of delayed memory in which the rosuvastatin vs. placebo group had higher (i.e., better) scaled scores.

Post-hoc analyses of primary and secondary outcomes accounting for clustering of patient outcomes within hospitals (Appendix Table 2) and adjusting for known delirium risk factors (Appendix Table 3) did not materially change the results for the primary outcome. 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 (i.e., worse) in rosuvastatin vs. placebo (-1.43 [-267, -0.18], p=0.025) at 6 month follow-up only (Appendix Table 3).

As reported previously,(23) evaluation of adverse events in the SAILS trial demonstrated no significant difference in rosuvastatin vs. placebo in the occurrence of elevated creatine kinase levels (16 vs. 13, p=0.65) and alanine aminotransferase levels (10 vs. 12, p=0.39), but there were significantly more patients with elevated aspartate aminotransferase levels (16 vs. 2 patients, p<0.001). Additionally, hyperthermia, a serious adverse event, occurred in three patients in the rosuvastatin group.

**Discussion**

In this ancillary study of the randomized, double-blinded, placebo-controlled SAILS trial of rosuvastatin versus placebo for sepsis-associated ARDS, 72% of patients ever had delirium in the ICU and approximately one-third had cognitive impairment at 6- and 12-month follow-up, with executive function being the only cognitive domain demonstrating significant improvement over time. Despite indirect evidence from pre-clinical studies and results from two observational ICU studies of statin use, this trial demonstrated no benefit of randomization to rosuvastatin in reducing delirium in the ICU or cognitive impairment at 6- and 12-month follow-up.

**Comparison with Other Studies**

The 72% delirium prevalence in this study is similar to the 77% reported in a prior 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 in delirium that evaluated all consecutive patients admitted to a single ICU in which only 42% of patients were mechanically ventilated,(20) and lower than the pooled prevalence in a recent
meta-analyses of critically ill patients. The prevalence of cognitive impairment at 6- and 12-month follow-up in this report was very similar to a separate patient cohort from ARDSNet’s EDEN trial that used an identical cognitive test battery and definition of cognitive impairment. This prevalence was also very similar to a two-site cohort of patients with respiratory failure or shock evaluated at 3- and 12-month follow-up, using a different cognitive testing battery.

The findings that rosuvastatin did not improve delirium in the ICU conflicts with two rigorously designed observational studies, mentioned above, with these prior results demonstrating strong and consistent associations of statin use with reduced daily delirium in the ICU, particularly for septic patients early in their ICU stay. The high overall prevalence of delirium in our study or heterogeneity in baseline risk for delirium within our study cohort may have affected study results. Additionally, differences in findings compared to the observational studies may reflect unmeasured confounders biasing the prior studies—a limitation minimized with the randomized, double-blinded design of our study. Such a difference in findings was also observed in evaluating statins’ effect on short-term mortality and other infection-related complications in patients with infection and sepsis, whereby prior observational studies reported improved outcomes that were not replicated in the SAILS randomized trial. However, as discussed subsequently, these differing results also may have arisen because of the greater lipophilic properties (and hence, greater crossing of the blood brain barrier and tissue penetration) of simvastatin, used in 78% and 88% of patients in the 2 prior observational studies, versus rosuvastatin used in SAILS. Additionally, a prior observational study suggested that inflammation (measured by C-reactive protein (CRP)) may be a potential mediator of the beneficial association between statins and delirium, but in the
present study, no differences were found in CRP levels in rosuvastatin vs. placebo groups (except on study day 9). In patients taking statins at baseline and randomized to placebo, there may be concern regarding rebound inflammation after cessation of statins. However, such a concern may be less likely given similar CRP levels between treatment groups in this study; however, such data on baseline status use were only recorded in a subset of patients, preventing full evaluation of this issue.

Notably, the associations between randomization to rosuvastatin vs. placebo and worse delayed memory (in our original analysis) and worse verbal reasoning and concept formation (in our post-hoc adjusted sensitivity analysis) at 6-month follow-up, were part of multiple secondary analyses. These analyses were intended to be hypotheses-generating for future research.

The methods and results from this ancillary study may help inform future randomized trials in this field. Future trials could evaluate more lipophilic statins to more fully understand the potential effect of statins on delirium. In addition, such trials should include secondary outcomes measures to understand any benefits of reduced delirium, such as reduced length of stay and post-discharge cognitive impairment, as evaluated in this study. Moreover, this study and prior research may help inform development of a minimum set of outcome measures (i.e., a “core outcome set” (57)) for trials evaluating delirium in critically ill patients (see http://www.comet-initiative.org/studies/details/796). Such a core outcome set would be recommended for use in all trials in this field to facilitate comparison and synthesis of results across studies. Moreover, consideration of appropriate statistical methods to evaluate the effect of ICU-based interventions on the duration of delirium (when assessable – i.e. when patient is not in comatose state), accounting for the competing risks of death and ICU discharge, are important and the methodology in this study provides one example to consider. Lastly, future trials must consider
striking a balance within the spectrum of efficacy versus effectiveness research in deciding about standardizing potentially important co-interventions (e.g. sedation) versus allowing routine practice to be used during the conduct of the trial.

Strengths and Limitations

This study has several strengths, including being an ancillary study embedded within a multi-centered, randomized, double-blinded, placebo-controlled trial, and longitudinal detailed assessments of cognitive function at 6- and 12-month follow-up. However, there are also potential limitations. First, the primary outcome of delirium, assessed using the CAM-ICU screening instrument performed by trained research and clinical staff, was subject to both missing data and possible measurement error. However, the randomized nature of this study (with stratification by hospital site) and the statistical methods (including sensitivity analyses using multiple imputation of missing data) help reduce such concern. Second, rosuvastatin (compared to atorvastatin and simvastatin) has less antibacterial effects(58) and tissue penetration (given its lower lipophilic property). Hence, we cannot conclude that a different statin medication would not be beneficial. Experts have suggested that randomized trials of delirium evaluate both statins with higher and lower lipophilic properties given uncertainty regarding effects on neuroinflammation.(8) However, notably, both a lipophilic (i.e., simvastatin) and non-lipophilic (i.e., rosuvastatin) statin have been evaluated in large randomized trials of ARDS patients with similar findings of no beneficial effects on mortality and ventilator-free days.(23;59) The SAILS trial selected rosuvastatin based on its relative superiority in terms of bioavailability, risk of hepatic dysfunction, and drug-drug interactions.(23) Third, relatively young ARDS patients with sepsis were enrolled; hence, these results may not generalize to other populations of critically ill patients. Fourth, there was no validated screening instrument used for
excluding patients with pre-existing cognitive impairment from cognitive assessments at 6 and 12 month follow-up. However, the randomized comparison of rosuvastatin vs. placebo, the relatively high exclusion rate for baseline cognitive impairment (11% in our study versus 6% in a prior ICU study using a validated cognitive screening instrument(1)), and the comparable rates of actual cognitive impairment(1,26,60) all provide reassurance regarding this issue. Lastly, the study may have been underpowered to detect the a priori hypothesis of superiority of rosuvastatin vs. placebo given that the sample size was dependent on the parent trial without any a priori sample size calculation. However, the results of the trial do not support the superiority hypothesis and the confidence interval of the treatment effect in this ancillary study are valuable in offering a range of plausible values for treatment effects, as supported by the available data.(61)

**Conclusions**

This ancillary study of the SAILS randomized, double-blinded trial of rosuvastatin versus placebo for sepsis-associated ARDS demonstrated that delirium in the ICU occurred in the vast majority of patients and cognitive impairment occurred in approximately one-third of survivors lasting for at least 1 year after ARDS. Despite encouraging pre-clinical and observational studies demonstrating that statins were associated with reduced daily delirium in the ICU, this trial demonstrates no benefit of rosuvastatin in reducing delirium in the ICU or cognitive impairment during 12-month follow-up. Hence, there is continued need to evaluate interventions aimed at attenuating ICU and post-ICU cognitive impairments commonly observed in this population.
**Declaration of interests**
The authors report no conflicts of interest.

**Acknowledgements**
We thank all patients and their proxies who participated in the study. We acknowledge our dedicated research staff, including the following who assisted with data collection, management and manuscript preparation: Ellen Caldwell, MS; Ashlee Case, MS; Lin Chen, BS; Caroline Chessare, BA; Nancy Ciesla, DPT, MS; Lori-Ann Flores, BSN; Stephanie Gundel, BS; Mohamed Hashem, MD; Melissa McCullough, BS; Jessica McCurley, MS; Mardee Merrill, BS; Mariela Pinedo, BS; Kyle Schneck, MA; Stacey Schoonmaker, BA; Kristin Sepulveda, BA; Marcella Rose Shrout, MA; Elizabeth Vayda, MS; and Cassie Wicken, BA.

DMN, EC, and ROH contributed to conception and design of the manuscript. DMN, EC, VDD CLH, AWW, JCJ, PEM, PAM-T, EWE, and ROH contributed to analysis and interpretation of data. DMN drafted the manuscript and all other authors critically revised it for important intellectual content. All authors gave final approval of the manuscript version to be published.

The following authors reported National Institutes of Health grants during the conduct of the study: DMN, PAM-T, CLH, and AWW. CLH reported grants from the Patient Centered Outcomes Research Institute. ROH reported an honorarium from Michigan Hospital Association.
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**Figure 1. Enrollment and Follow-up**

*This sample size of 568 is less than the 745 patient sample in the SAILS trial due to 2 sites not participating and a temporary cessation of recruitment into this ancillary study.*

**Of 329 patients, 57 (17%) were excluded for delirium evaluation, but still eligible for 6 and 12 month cognitive follow-up, due to: 46 (14%) were in the ICU prior to the protocol revision expanding evaluation of delirium and cognitive status to other hospitals, 8 (2%) were at study sites not participating in delirium assessment, and 3 (1%) had missed delirium assessment.*
*** These patients were ineligible for assessment at 6-months due to the timing of IRB approval for this ancillary study, but were consented and eligible for the 12 month assessment.
Patients were evaluated on the following aspects of cognitive function (test used): executive function (Hayling Sentence Completion), language (Verbal Fluency Test), verbal reasoning and concept formation (Similarities), and memory--working/attention (Digit Span), memory--immediate (Logical Memory I), and memory--delayed (Logical Memory II). Patients were characterized as having Overall Cognitive Impairment if 1 of these domains was \( \geq 2 \) standard deviations below population norms (i.e. bottom 2.5%) or at least 2 domains \( \geq 1.5 \) standard deviations below norms (i.e. bottom 6.7%). For each domain, we present proportion of patients with scores score \( \geq 1.5 \) standard deviations below norm (i.e. bottom 6.7%).
This figure illustrates the treatment effect, presented as an effect size with 95% confidence interval for rosvastatin versus placebo. Effect size was calculated as the treatment effect (Table 3, difference in means or proportions) divided by the pooled standard deviation from the rosvastatin and placebo groups. (62;63)
## Table 1. Baseline Characteristics and Intensive Care Data*

<table>
<thead>
<tr>
<th></th>
<th>Eligible for delirium and/or cognitive assessment**</th>
<th>With Delirium Data**</th>
<th>Eligible for Cognitive Assessment**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuva-statin (n= 164)</td>
<td>Placebo (n= 165)</td>
<td>Rosuva-statin (n= 137)</td>
</tr>
<tr>
<td><strong>Baseline patient data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>52 (18)</td>
<td>53 (15)</td>
<td>52 (18)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>82 (50)</td>
<td>85 (52)</td>
<td>65 (47)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>142 (88)</td>
<td>137 (85)</td>
<td>120 (90)</td>
</tr>
<tr>
<td>Prior Residence, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home independently</td>
<td>138 (84)</td>
<td>132 (80)</td>
<td>113 (82)</td>
</tr>
<tr>
<td>Home with help</td>
<td>18 (11)</td>
<td>19 (12)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Healthcare facility</td>
<td>7 (4)</td>
<td>14 (8)</td>
<td>7 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32 (10)</td>
<td>31 (11)</td>
<td>32 (9)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>31 (19)</td>
<td>40 (24)</td>
<td>26 (19)</td>
</tr>
<tr>
<td>Prior stroke with sequelae, No. (%)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Baseline intensive care data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE III score</td>
<td>90 (27)</td>
<td>89 (28)</td>
<td>91 (27)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio</td>
<td>168 (69)</td>
<td>172 (68)</td>
<td>171 (70)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio ≤200, No. (%)</td>
<td>117 (72)</td>
<td>112 (68)</td>
<td>96 (71)</td>
</tr>
<tr>
<td>Baseline Shock, No. (%)</td>
<td>64 (39)</td>
<td>65 (39)</td>
<td>52 (38)</td>
</tr>
<tr>
<td>Primary lung injury risk factor, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>108 (66)</td>
<td>118 (72)</td>
<td>88 (65)</td>
</tr>
<tr>
<td>Non-pulmonary infection</td>
<td>34 (21)</td>
<td>32 (20)</td>
<td>28 (21)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>14 (9)</td>
<td>9 (5)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5)</td>
<td>5 (3)</td>
<td>7 (6)</td>
</tr>
<tr>
<td><strong>Daily intensive care data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any dialysis in hospital, No. (%)</td>
<td>26 (16)</td>
<td>22 (13)</td>
<td>24 (18)</td>
</tr>
<tr>
<td>Any vasopressor use, No. (%)†</td>
<td>86 (53)</td>
<td>88 (53)</td>
<td>70 (52)</td>
</tr>
<tr>
<td>Proportion of days per patient, if any</td>
<td>39 (25)</td>
<td>40 (27)</td>
<td>41 (24)</td>
</tr>
<tr>
<td>Any corticosteroids, No. (%)†</td>
<td>47 (29)</td>
<td>53 (32)</td>
<td>38 (28)</td>
</tr>
<tr>
<td>Proportion of days per patient, if any</td>
<td>67 (33)</td>
<td>67 (33)</td>
<td>67 (33)</td>
</tr>
<tr>
<td>Organ failure-free days to day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>10 (4)</td>
<td>10 (4)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Renal</td>
<td>11 (5)‡</td>
<td>12 (4)‡</td>
<td>11 (5)‡</td>
</tr>
<tr>
<td>Hepatic</td>
<td>12 (4)</td>
<td>13 (3)</td>
<td>12 (4)‡</td>
</tr>
<tr>
<td>Coagulation</td>
<td>12 (4)</td>
<td>12 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days</td>
<td>10 (9)</td>
<td>10 (11)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>ICU length of stay</td>
<td>14 (9)</td>
<td>13 (8)</td>
<td>14 (10)</td>
</tr>
<tr>
<td>Hospital length of stay</td>
<td>21 (13)</td>
<td>21 (13)</td>
<td>22 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE III=acute physiology and chronic health evaluation III; PaO2=partial pressure of oxygen in arterial blood; FiO2=fraction of inspired oxygen; ICU=Intensive Care Unit.

*Proportions might not add to 100% because of rounding. Unknown or missing data for eligible cohort, delirium assessment cohort, and cognitive assessment cohort, respectively: race=6, 5, 3; APACHE III score=18, 15, 8; PaO2/FiO2=3, 2, 1; primary lung injury=2, 1, 1; vasopressor use=2, 2, 1; duration of mechanical ventilation=2, 0, 2; ICU length of stay=9, 6, 6; hospital length of stay=2, 2, 1.
** Statin use prior to hospital admission was available for a subset of patients. In this subset, the number and percentage of patients randomized to rosuvastatin vs. placebo for the each of the 3 cohorts described in the columns of this Table (i.e., the “delirium and/or cognitive assessment” cohort, the “delirium data” cohort, and the “cognitive assessment” cohort) are: 21 (13%) vs 30 (18%) [missing data in N=4], 19 (14%) vs 26 (19%) [missing N=1], and 7 (9%) vs 16 (15%) [missing N=4], respectively.

†Data presented as overall average for each patient’s mean value of available daily data. Corticosteroids data available until earlier of 48 hours after cessation of mechanical ventilation or day 7. Vasopressor data available until earlier of death, study hospital discharge or day 14. Proportions calculated among days in intensive care unit in which medication data were available. Days without organ failure until day 14 calculated as previously published.

‡p<0.05 when comparing patient characteristics in rosuvastatin vs. placebo group.
<table>
<thead>
<tr>
<th>Table 2. Cognitive Function Status at 6 and 12 Month Follow-Up&lt;sup&gt;a&lt;/sup&gt;</th>
<th>6 Months (n=130)</th>
<th>12 Month (n=149)</th>
<th>Difference (CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Impairment, No. (%)</td>
<td>48 (37)</td>
<td>43 (29)</td>
<td>-8 (-19, 3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Executive function: Hayling Sentence Completion score</td>
<td>4.4 (2.0)</td>
<td>5.1 (1.6)</td>
<td>0.8 (0.5, 1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>39 (30)</td>
<td>23 (16)</td>
<td>-15 (-25, -5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Language: Verbal Fluency score</td>
<td>32 (12)</td>
<td>32 (12)</td>
<td>1 (-1, 2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>38 (30)</td>
<td>41 (30)</td>
<td>0 (-11, 11)</td>
<td>0.99</td>
</tr>
<tr>
<td>Verbal reasoning &amp; concept formation: Similarities score</td>
<td>9.8 (3.3)</td>
<td>10.1 (3.2)</td>
<td>0.5 (0.1, 0.9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>12 (9)</td>
<td>10 (7)</td>
<td>-2 (-19, 15)</td>
<td>0.80</td>
</tr>
<tr>
<td>Memory (working)/attention: Digit Span score</td>
<td>9.4 (2.5)</td>
<td>9.4 (2.7)</td>
<td>0.0 (-0.4, 0.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>9 (7)</td>
<td>6 (4)</td>
<td>-3 (-58, 52)</td>
<td>0.92</td>
</tr>
<tr>
<td>Memory (immediate): Logical Memory I score</td>
<td>8.7 (3.3)</td>
<td>8.9 (3.2)</td>
<td>0.2 (-0.3, 0.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>26 (21)</td>
<td>21 (15)</td>
<td>-6 (-32, 21)</td>
<td>0.68</td>
</tr>
<tr>
<td>Memory (delayed): Logical Memory II score</td>
<td>8.5 (3.0)</td>
<td>8.8 (2.8)</td>
<td>0.3 (-0.1, 0.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Score ≤1.5 SD, No. (%)</td>
<td>19 (15)</td>
<td>15 (11)</td>
<td>-4 (-20, 13)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval

<sup>a</sup>Mean values (SD) are presented unless otherwise indicated. Details of test scoring: Hayling age-adjusted score (1-10, higher score is better); Verbal Fluency Test (higher score is better); and Similarities, Digit Span, and Logical Memory I and II age-adjusted scores (1-19, higher score is better). Number of unknown or missing data for assessments performed at 6 and 12 months, respectively, are: Cognitive impairment 0, 1; Hayling 2, 1; Verbal Fluency Test 2, 11; Similarities 2, 9; Digit Span 2, 10; Logical Memory I 4, 9; Logical Memory II 7, 14

<sup>b</sup>Calculations from linear or logistic regression models with random intercept and an indicator for time (12 vs 6 month follow-up). “Difference” represents the difference between 12 and 6 months in mean score for continuous measures or in proportion for binary measures.
<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=53)</th>
<th>Placebo (n=77)</th>
<th>Treatment Effect (CI)(^b)</th>
<th>P-Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Impairment, No. (%)</td>
<td>19 (36)</td>
<td>29 (38)</td>
<td>0.93 (0.39, 2.22)</td>
<td>0.87</td>
</tr>
<tr>
<td>Executive function: Hayling Sentence Completion score ≤ 1.5 SD, No. (%)</td>
<td>4.5 (1.8)</td>
<td>4.4 (2.1)</td>
<td>0.0 (-0.6, 0.6)</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>14 (26)</td>
<td>25 (33)</td>
<td>0.74 (0.31, 1.80)</td>
<td>0.51</td>
</tr>
<tr>
<td>Language: Verbal Fluency score</td>
<td>31 (13)</td>
<td>32 (11)</td>
<td>-1 (-4, 3)</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>18 (35)</td>
<td>20 (26)</td>
<td>1.44 (0.54, 3.80)</td>
<td>0.46</td>
</tr>
<tr>
<td>Verbal reasoning &amp; concept formation: Similarities score ≤ 1.5 SD, No. (%)</td>
<td>9.7 (3.8)</td>
<td>9.9 (3.0)</td>
<td>-0.4 (-1.5, 0.7)</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>7 (13)</td>
<td>5 (7)</td>
<td>2.29 (0.60, 8.77)</td>
<td>0.23</td>
</tr>
<tr>
<td>Memory (working)/attention: Digit Span score ≤ 1.5 SD, No. (%)</td>
<td>9.2 (2.5)</td>
<td>9.5 (2.6)</td>
<td>-0.3 (-1.2, 0.6)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>1 (2)</td>
<td>8 (11)</td>
<td>0.17 (0.02, 1.52)</td>
<td>0.11</td>
</tr>
<tr>
<td>Memory (immediate): Logical Memory I score ≤ 1.5 SD, No. (%)</td>
<td>8.6 (3.4)</td>
<td>8.9 (3.3)</td>
<td>-0.4 (-1.5, 0.7)</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>12 (24)</td>
<td>14 (18)</td>
<td>1.37 (0.50, 3.76)</td>
<td>0.54</td>
</tr>
<tr>
<td>Memory (delayed): Logical Memory II score ≤ 1.5 SD, No. (%)</td>
<td>7.9 (3.3)</td>
<td>8.8 (2.7)</td>
<td>-1.2 (-2.2, -0.2)</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>12 (24)</td>
<td>7 (10)</td>
<td>3.06 (1.00, 9.37)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval;

\(^a\) Mean values (SD) are presented unless otherwise indicated. Details of test scoring: Hayling age-adjusted score (1-10, higher score is better); Verbal Fluency Test (higher score is better); and for Similarities, Digit Span, and Logical Memory I and II age-adjusted scores (1-19, higher score is better). Number of unknown or missing data for assessments performed at 6 months, by rosuvastatin and placebo groups, respectively: Cognitive impairment 0, 0; Hayling 0, 2; Verbal Fluency Test 1, 1; Similarities 1, 1; Digit Span 1, 1; Logical Memory I 3, 1; Logical Memory II 3, 4

\(^b\) Calculated from linear or logistic regression models with random intercept and an indicator for treatment (rosuvastatin vs. placebo), time (12 vs. 6 month follow-up) and the interaction of treatment group and time. The treatment effect represents 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).
Appendix

Rosuvastatin for Delirium and Cognitive Impairment in Sepsis-Associated Acute Respiratory Distress Syndrome: An Ancillary Study to a Randomized Controlled Trial

Dale M. Needham, MD1,2,3 - Professor
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Victor D. Dinglas, MPH1,2
Catherine L. Hough, MD5
Amy W. Wozniak, MS1,4
James C. Jackson, PsyD6
Peter E. Morris, MD7 - Professor
Pedro A. Mendez-Tellez, MD1,8
E. Wesley Ely, MD6,9 - Professor
Ramona O. Hopkins, PhD10,11,12 - Professor

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7 Division of Pulmonary, Critical Care & Sleep Medicine, University of Kentucky, Lexington, KY, USA
8 Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
9 Geriatric Research, Education and Clinical Center Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN, USA
10 Department of Medicine, Pulmonary and Critical Care Division, Intermountain Medical Center, Murray, Utah, USA
11 Psychology Department and Neuroscience Center, Brigham Young University, Provo, Utah, USA
12 Center for Humanizing Critical Care, Intermountain Health Care, Murray, Utah, USA
### Table 1. Additional data on delirium risk factors in rosuvastatin vs. placebo groups

<table>
<thead>
<tr>
<th>Baseline Data</th>
<th>Eligible for Delirium and/or Cognitive Assessment</th>
<th>With Delirium Data</th>
<th>Eligible for Cognitive Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rosuvastatin (n=164)</td>
<td>Placebo (n=165)</td>
<td>Rosuvastatin (n=137)</td>
</tr>
<tr>
<td>Dementia/cognitive impairment, n (%)</td>
<td>21 (13)</td>
<td>18 (11)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>83 (51)</td>
<td>80 (48)</td>
<td>67 (49)</td>
</tr>
<tr>
<td>Visual impairment†, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hearing impairment†, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Depression†, n (%)</td>
<td>15 (35)</td>
<td>16 (30)</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Alcohol dependence‡, n (%)</td>
<td>17 (12)</td>
<td>12 (9)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>History of smoking†††, n (%)</td>
<td>89 (59)</td>
<td>85 (57)</td>
<td>73 (58)</td>
</tr>
<tr>
<td>Medical ICU admission, n (%)</td>
<td>116 (71)</td>
<td>102 (62)</td>
<td>96 (70)</td>
</tr>
<tr>
<td>Urgent admission, n (%)</td>
<td>161 (98)</td>
<td>164 (99)</td>
<td>134 (98)</td>
</tr>
<tr>
<td>Emergent surgery, n (%)</td>
<td>15 (9)</td>
<td>14 (8)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Trauma as ARDS risk factor, n (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Serum blood urea nitrogen, mg/dL‡</td>
<td>26 (21)</td>
<td>27 (20)</td>
<td>27 (22)</td>
</tr>
<tr>
<td>Serum albumin, g/dL‡</td>
<td>2.3 (0.6)</td>
<td>2.3 (0.6)</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>Metabolic acidosis‡, n (%)</td>
<td>62 (42)</td>
<td>65 (41)</td>
<td>48 (39)</td>
</tr>
<tr>
<td>Corticosteroid use on day one, n (%)</td>
<td>35 (23)</td>
<td>35 (22)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>Lowest mean arterial pressure at randomization</td>
<td>59 (11)</td>
<td>60 (11)</td>
<td>59 (12)</td>
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</tbody>
</table>

#### Daily ICU Data

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=106)</th>
<th>Placebo (n=106)</th>
<th>Rosuvastatin (n=105)</th>
<th>Placebo (n=105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU length of stay, days</td>
<td>14 (9)</td>
<td>13 (8)</td>
<td>14 (10)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Comatose, percent ICU days</td>
<td>11 (18)</td>
<td>12 (20)</td>
<td>11 (17)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>Mechanical ventilation, percent ICU days</td>
<td>72 (20)</td>
<td>71 (19)</td>
<td>72 (20)</td>
<td>72 (19)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.5 (1.2)</td>
<td>1.3 (1)</td>
<td>1.5 (1.2)</td>
<td>1.3 (1)</td>
</tr>
<tr>
<td>PaO2§, mm Hg for Days 1-4</td>
<td>90 (32)</td>
<td>90 (26)</td>
<td>90 (35)</td>
<td>91 (28)</td>
</tr>
<tr>
<td>PaO2§, mm Hg, all available data</td>
<td>91 (32)</td>
<td>91 (26)</td>
<td>91 (34)</td>
<td>91 (27)</td>
</tr>
<tr>
<td>Mean daily midazolam-equivalent dose, mg³</td>
<td>15 (21)</td>
<td>22 (31)</td>
<td>13 (20)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Mean daily morphine-equivalent dose, mg⁴</td>
<td>58 (58)</td>
<td>57 (66)</td>
<td>59 (61)</td>
<td>60 (69)</td>
</tr>
<tr>
<td>Mean daily dexmedetomidine dose, μg⁵</td>
<td>648 (539)</td>
<td>401 (418)</td>
<td>648 (539)</td>
<td>429 (427)</td>
</tr>
<tr>
<td>Mean daily propofol dose, mg⁶</td>
<td>1237 (1618)</td>
<td>1074 (1319)</td>
<td>1188 (1682)</td>
<td>930 (1318)</td>
</tr>
</tbody>
</table>

### Abbreviations:
- APACHE III=Acute Physiology and Chronic Health Evaluation III; ICU=intensive care unit; ARDS=acute respiratory distress syndrome; PaO2=partial pressure of oxygen in arterial blood
- *The additional variables included in eTable 1 were based on prior publications.(1-3) In this cohort, 213 patients had all of the required data for the E-Pre-Deliric ICU delirium prediction model.(2) Comparing patients in the rosuvastatin vs. placebo, there was a 43% vs. 42% (p=0.576) predicted incidence of delirium, demonstrating similar balance of delirium risk between the two groups.
- **Proportions might not add to 100% because of rounding. Unknown or missing data for eligible cohort, delirium assessment cohort, and cognitive assessment cohort, respectively: trauma as ARDS risk factor=2, 1, 1; metabolic acidosis= 17, 13, 10; blood urea nitrogen=1, 1, 0; alcohol dependence=47, 40, 27; smoking=30, 26, 14; albumin=53, 46, 33; corticosteroid= 19, 17, 15; mean arterial pressure=5, 4, 4; percent days comatose=32, 2, 32; percent days mechanically ventilated = 11, 8, 6; percent organ failure-free days=2, 2, 1; creatinine=2, 2, 1; PaO2 days 1-4 = 79, 76, 38; PaO2 all days = 75, 72, 36.
- †Data available for a subset of patients. Sample sizes for eligible cohort, delirium assessment cohort, and cognitive assessment cohort, respectively (rosuvastatin vs. placebo): 97 (43 vs. 54), 85 (38 vs. 47), and 87 (36 vs. 51).
- ‡Defined as Alcohol Use Disorder Identification Test score is ≥14
- §If ever smoked >100 cigarettes in lifetime.
- ††Worst value within first 24 hours of randomization
- †‡pH <7.35 with bicarbonate <24mmol/L
- #Unless otherwise specified, data are presented as overall average for each patient’s mean value of available daily data.
- ▲Blood gas measurement closest to 8AM
- ○Using standard conversion factors(4;5)
Table 2. 6-Month Results by Treatment Group,\textsuperscript{a} Adjusted for Clustering by Hospital Study Site

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=53)</th>
<th>Placebo (n=77)</th>
<th>Treatment Effect (CI)\textsuperscript{b}</th>
<th>P-Value\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Impairment, n (%)</td>
<td>19 (36)</td>
<td>29 (38)</td>
<td>1 (0, 2)</td>
<td>0.82</td>
</tr>
<tr>
<td>Executive function: Hayling Sentence Completion score</td>
<td>4.5 (1.8)</td>
<td>4.4 (2.1)</td>
<td>0.0 (-0.6, 0.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>14 (26)</td>
<td>25 (33)</td>
<td>1 (0, 2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Language: Verbal Fluency score</td>
<td>31.4 (12.9)</td>
<td>32.2 (11.4)</td>
<td>-0.4 (-4.2, 3.4)</td>
<td>0.84</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>18 (35)</td>
<td>20 (26)</td>
<td>1 (1, 4)</td>
<td>0.51</td>
</tr>
<tr>
<td>Verbal reasoning &amp; concept formation: Similarities score</td>
<td>9.7 (3.8)</td>
<td>9.9 (2.9)</td>
<td>-0.4 (-1.5, 0.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>7 (13)</td>
<td>5 (7)</td>
<td>2 (1, 9)</td>
<td>0.23</td>
</tr>
<tr>
<td>Memory (working)/attention: Digit Span score</td>
<td>9.2 (2.5)</td>
<td>9.5 (2.6)</td>
<td>-0.3 (-1.2, 0.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>1 (2)</td>
<td>8 (11)</td>
<td>0 (0, 2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Memory (immediate): Logical Memory I score</td>
<td>8.6 (3.4)</td>
<td>8.8 (3.3)</td>
<td>-0.3 (-1.4, 0.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>12 (24)</td>
<td>14 (18)</td>
<td>1 (0, 4)</td>
<td>0.55</td>
</tr>
<tr>
<td>Memory (delayed): Logical Memory II score</td>
<td>7.9 (3.3)</td>
<td>8.8 (2.7)</td>
<td>-1.2 (-2.1, -0.2)</td>
<td>0.019</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>12 (24)</td>
<td>7 (10)</td>
<td>3 (1, 9)</td>
<td>0.050</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; 95% CI, 95% confidence interval

\textsuperscript{a} Mean values (SD) are presented unless otherwise indicated. Details of test scoring: Hayling age-adjusted score (1-10, higher score is better); Verbal Fluency Test (higher score is better); and for Similarities, Digit Span, and Logical Memory I and II age-adjusted scores (1-19, higher score is better). Number of unknown or missing data for assessments performed at 6 months, by rosuvastatin and placebo groups, respectively: Cognitive impairment 0, 0; Hayling 0, 2; Verbal Fluency Test 1, 1; Similarities 1, 1; Digit Span 1, 1; Logical Memory I 3, 1; Logical Memory II 3, 4

\textsuperscript{b} Calculated from linear or logistic regression models with random intercepts for both hospital study site and patient and an indicator for treatment (rosuvastatin vs. placebo), time (12 vs. 6 month follow-up) and the interaction of treatment group and time. The treatment effect represents 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).
Table 3. 6-Month Results by Treatment Group, a Adjusted for Baseline Covariates b

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin  (n=36)</th>
<th>Placebo  (n=54)</th>
<th>Treatment Effect (CI)c</th>
<th>P-Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Impairment, n (%)</td>
<td>11 (31)</td>
<td>18 (33)</td>
<td>1.09 (0.32, 3.72)</td>
<td>0.89</td>
</tr>
<tr>
<td>Executive function: Hayling Sentence Completion score</td>
<td>4.4 (1.8)</td>
<td>4.3 (2.1)</td>
<td>-0.1 (-0.9, 0.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>8 (22)</td>
<td>19 (37)</td>
<td>0 (0, 2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Language: Verbal Fluency score</td>
<td>32 (15)</td>
<td>34 (11)</td>
<td>-2 (-7, 2)</td>
<td>0.33</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>13 (37)</td>
<td>11 (20)</td>
<td>3 (1, 15)</td>
<td>0.09</td>
</tr>
<tr>
<td>Verbal reasoning &amp; concept formation: Similarities score</td>
<td>9.4 (3.6)</td>
<td>10.2 (2.9)</td>
<td>-1.4 (-2.7, -0.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>4 (11)</td>
<td>1 (2)</td>
<td>N/A^d</td>
<td></td>
</tr>
<tr>
<td>Memory (working)/attention: Digit Span score</td>
<td>9.0 (2.6)</td>
<td>9.5 (2.5)</td>
<td>-0.7 (-1.7, 0.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>1 (3)</td>
<td>5 (9)</td>
<td>N/A^d</td>
<td></td>
</tr>
<tr>
<td>Memory (immediate): Logical Memory I score</td>
<td>8.4 (3.3)</td>
<td>8.8 (3.1)</td>
<td>-0.8 (-2.1, 0.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>8 (24)</td>
<td>8 (15)</td>
<td>N/A^d</td>
<td></td>
</tr>
<tr>
<td>Memory (delayed): Logical Memory II score</td>
<td>7.6 (3.3)</td>
<td>8.9 (2.7)</td>
<td>-1.8 (-3.0, -0.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Score ≤1.5 SD, n (%)</td>
<td>9 (26)</td>
<td>4 (8)</td>
<td>7 (1, 33)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**Abbreviations:** SD, standard deviation; 95% CI, 95% confidence interval

a Mean values (SD) are presented unless otherwise indicated. Details of test scoring: Hayling age-adjusted score (1-10, higher score is better); Verbal Fluency Test (higher score is better); and for Similarities, Digit Span, and Logical Memory I and II age-adjusted scores (1-19, higher score is better). Number of unknown or missing data for assessments performed at 6 months, by rosuvastatin and placebo groups, respectively: Cognitive impairment 0, 0; Hayling 0, 2; Verbal Fluency Test 1, 0; Similarities 1, 0; Digit Span 1, 0; Logical Memory I 2, 0; Logical Memory II 2, 3

b Adjusted for: Acute Physiology and Chronic Health Evaluation III, age, cognitive impairment/dementia, hypertension, alcohol abuse, smoking, admission category, urgent admission, emergency surgery, metabolic acidosis, serum blood urea nitrogen, mean arterial pressure, and steroid use

c Calculated from linear or logistic regression models with random intercept for patient and an indicator for treatment (rosuvastatin vs. placebo), time (12 vs. 6 month follow-up), the interaction of treatment group and time, and all adjustment variables described above. The treatment effect represents 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).

d The model did not converge
Reference List


