Correspondence

Authors' response to commentaries on rosuvastatin for delirium and cognitive impairment in sepsis-associated acute respiratory distress syndrome

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We are encouraged by the interest (1,2) in our publication that evaluated the effect of rosuvastatin *vs.* placebo on delirium in the intensive care unit (ICU) and subsequent cognitive impairment (3). We appreciate the critique of our publication by Pourafkari *et al.* (2). Pourafkari *et al.* commented about our study being underpowered for secondary analyses of cognitive impairment at 6- and 12-month follow-up. We reported a 2% absolute reduction in the proportion of patients with cognitive impairment for rosuvastatin *vs.* placebo at 6-month follow-up (36% *vs.* 38%). This 2% reduction was not statistically significant (treatment effect 0.93; 95% CI: 0.39–2.22; P=0.87), which may be due to the study being underpowered (i.e., too few patients to detect such a small effect). However, the subsequent comparison of cognitive impairment at 12-month (30% *vs.* 28% for rosuvastatin *vs.* placebo, respectively) and the vast majority of the individual standardized tests used to evaluate cognitive impairment favored placebo relative to rosuvastatin. Hence, to be convinced that the lack of statistical significance at 6 months was attributable to the trial's sample size, we would have expected non-significant results consistently favoring rosuvastatin, which was not the case.

Another comment by Pourafkari *et al* focused on our study not adjusting for unmeasured confounders. We have less concern for unmeasured confounders affecting our analysis of delirium (the primary outcome) due to the randomized treatment assignment utilized in the trial. Additionally, descriptions of risk factors for delirium were similar between treatment groups (see the first appendix table of our original paper). Lastly, as part of our *a priori* analyses plan, we used multiple imputations for missing delirium data, and demonstrated consistent results with the primary analysis, suggesting less concern for any differential missingness of data between treatment groups after randomization.

Pourafkari *et al*. also indicated concern for elimination of "higher risk" patients in our cohort. Mechanically ventilated patients are at high risk for delirium (4), and indeed, a large proportion of patients (72%) in our cohort had delirium. Furthermore, as part of our *post-hoc* analyses (3), we adjusted for known baseline risk factors for delirium and there was

no qualitative change in our results.

Finally, we want to clarify a comment made by Pourafkari *et al.* regarding exclusion of patients who are comatose (Richmond-Agitation Sedation Scores of –4 or –5). In our methods section, we report that the individual ICU days during which patients were comatose were excluded from analysis since delirium status cannot be evaluated when a patient is comatose (3). Only these specific ICU days, rather than all patients ever having coma, were excluded. We have further expanded on this issue in our recent commentary regarding use of joint modelling statistical methods for evaluating delirium in the ICU (5). Our recent commentary highlights that this statistical method has the advantage of only evaluating for delirium on days when patients are at risk for delirium (i.e., not on days with coma) (5).

In addition to delirium and cognitive outcomes, our study evaluated rosuvastatin's effects on an extensive set of physical outcomes (including both patient-reported outcomes and performance-based measures) and mental health outcomes, finding no significant effect of rosuvastatin *vs.* placebo (6). Lange and Maier (1) commented that a strength of our study is the rigorous assessment of outcomes using standardized neuropsychological instruments, which have been validated in ICU populations. As new studies are designed to evaluate statins for delirium in the ICU, it is important to develop a core outcomes set (COS) to facilitate comparison of studies and synthesis of findings (7), as Lange and Maier highlighted in their commentary (1). A proposal for developing such a COS is currently registered with the Core Outcome Measures in Effectiveness Trials (COMET) website (8). Moreover, we have an ongoing National Heart, Lung, and Blood Institute-funded project (grant #R24HL111895, www.improveLTO.com) that includes one specific aim focused on creating a COS for post-discharge outcomes in studies of acute respiratory failure survivors (9,10). The methodology used in this project (as outlined in the appendix of our recent publication (11), as well as the resulting COS, may be helpful in considering recommendations for post-discharge outcomes measures in a delirium COS.

In addition to creating a delirium COS, we believe that use of appropriate statistical methods for evaluating delirium outcomes in studies of critically ill patients is another important methodological issue. For example, the use of joint modelling statistical methods allows for recurring events (e.g., daily delirium status) and accounts for terminating events that preclude further assessment of the events (e.g., death in the ICU) (5). A delirium COS and use of appropriate statistical methods are both important next steps in advancing methodology for clinical trials aimed at evaluating interventions to prevent and treat delirium in critically ill patients.

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Footnote

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