POINT:
Should Patients Receiving Statins Prior to ICU Admission Be Continued on Statin Therapy? Yes

Alexander H. Flannery, PharmD, BCPS; Lexington, KY; Peter S. Kruger, MBBS, PhD; Brisbane, QLD, Australia

ABBREVIATIONS: ACS = acute coronary syndrome; ALT = alanine aminotransferase; ARDSNet = ARDS Clinical Trial Network; AST = aspartate aminotransferase

With the release of updated guidelines for the treatment of cholesterol, an additional 13 million Americans may be eligible for or prescribed statin therapy, possibly bringing the overall total to 56 million. Already, as many as 30% of acute hospital admissions are prescribed statins. More patients than ever before are likely to present to the hospital receiving statins prior to admission, making the decision to continue a patient’s home statin regimen an almost daily occurrence for practicing critical care physicians. Unintentional discontinuation of medications for chronic disease is a risk with hospitalization and an even greater risk with ICU admission. As such, the clinical question related to continued statin therapy in the ICU provides an opportunity to influence both short- and long-term outcomes from critical illness.

The best-known mechanism of action for statins involves inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase. The inhibition of mevalonate synthesis explains the primary effect of statins to reduce cholesterol levels, but it also offers an explanation of the pleiotropic effects of statins that are perhaps independent of cholesterol. Inhibition of mevalonate synthesis may inhibit the activation of guanosine triphosphate-binding proteins, thereby reducing the activation of transcription factors and resulting in the pleiotropic (ie, antiinflammatory, antioxidant, immune modulation, antithrombotic, protection of endothelial function) effects of statins.

Acute discontinuation of statin therapy has been postulated to influence outcomes in a variety of illnesses, although much of this is only supported by observational data. For patients with acute coronary syndrome, withdrawal of preexisting statin therapy has been associated with a worse outcome. Data for this analysis were from a study where clinical decisions regarding statin use were not part of the original study protocol. Although this creates a potential bias that usual medications, including statin therapy, were ceased in more unwell patients, it is interesting that the cessation of prior statin use was associated with a worse outcome than no prior use or continued use. Additionally, a small randomized trial of patients with stroke suggested an improved outcome when prior statin therapy was continued. Statin withdrawal has also been associated with an increased risk for adverse cardiovascular events following vascular surgery.

The most extensive body of literature on the role of statins in critical care has focused on patients with sepsis. Although the benefits of de novo statin therapy for treating sepsis in the ICU remain investigational, the number of reports describing a beneficial effect of continuing a patient's statin prescription continues to emerge. A 2006 retrospective cohort study using multivariate regression analysis suggested that continued use of a patient's outpatient statin therapy is an independent predictor of hospital mortality. A similar suggestion of mortality benefit was described in candidemia.

In a nested cohort study within two randomized controlled trials, statin use in the ICU, most of which was continued from the patient’s outpatient regimen, was associated with a reduction in hospital mortality, particularly for doses of atorvastatin or simvastatin ≥ 40 mg. In a 6-year French cohort study investigating prior
statin therapy on the impact of ventilator-associated pneumonia, statin continuation after ICU admission was an independent predictor of 30-day mortality.12 Although a similar retrospective analysis has demonstrated that the benefits of continuing statin therapy in the ICU disappear after propensity matching and multivariate adjustment, there still appears to be a trend toward benefit in this analysis, with statistical significance limited by small sample size.13

Perhaps the two most intriguing and conflicting studies are the randomized controlled trials investigating this clinical issue. In a phase 2 multicenter, prospective, randomized, double-blind, placebo-controlled trial, subjects were stratified by site as well as by prior statin use to atorvastatin 20 mg daily or matching placebo.14 Although de novo statin therapy was not associated with either attenuation of infection or improved survival, benefits were observed in the prior statin user group. Prior statin users were noted to have lower levels of IL-6 at baseline. Additionally, prior statin users randomized to continued statin therapy in the ICU demonstrated a lower 28-day mortality than those who discontinued statin therapy upon ICU admission.15

In a prospective, randomized, double-blind, placebo-controlled trial, 150 patients on prior statin therapy hospitalized for infection were randomized to atorvastatin 20 mg or placebo.3 No significant differences were found between the two study groups over time in any of the outcomes, including levels of IL-6 and C-reactive protein, degree of organ failure, and mortality. Of note, only 16% of the cohort required ICU care, and the overall cohort had a low mortality of 6.6% compared with the previously mentioned study whose patients were critically ill with APACHE (Acute Physiology and Chronic Health Evaluation) II scores ranging from 21.2 to 25.6.14 It is possible that the pleiotropic effects of statins may not be fully appreciated unless marked systemic inflammation is present, potentially explaining the lack of benefit observed in general ward patients compared with more unwell patients.

Continued statin use in the ICU may have other benefits due to its association with reductions in delirium. Statins may alter the neuroinflammatory process, which is hypothesized to contribute to ICU delirium. For every day that statin use is continued in the ICU, the odds of the patient being delirium and coma free increase by 39%.15 A recent multicenter, prospective cohort study revealed that the probability of delirium increases the longer a patient remains off his or her home statin regimen.16

The prospective studies evaluating statin use for a variety of ICU conditions have vigilantly screened for adverse effects, such as elevation in hepatocellular enzyme and creatine kinase levels. With one exception, they have consistently found no significant differences compared with placebo.13,14,17-19 Combined, this represents safety data on statin use in the ICU for almost 800 patients. The exception is the recently completed study of rosuvastatin in ARDS.19 Although no differences were found between the rosuvastatin and placebo groups in significant elevation of creatine kinase or alanine aminotransferase levels, the protocol was amended during the study for closer aspartate aminotransferase monitoring. Elevated aspartate aminotransferase levels were subsequently found to be more common in patients receiving rosuvastatin than in those receiving placebo, although the numbers were small. The clinical significance of this finding remains unclear and stands in contrast to the multiple studies that failed to suggest any safety concerns with statin use in the ICU. Although drug levels of statins in the critically ill have been reported in some but not all cases to be well in excess of healthy volunteers, this finding has not led to an overt suggestion that statin use in the ICU is unsafe.13,19,20 It remains unknown whether these elevated concentrations explain the improved outcomes in patients on continued statin therapy in the ICU.14 Statins take 7 to 14 days to reach peak antiinflammatory effects, potentially explaining why there appears to be a larger benefit for continuing as opposed to de novo statin therapy.5

Limited information exists regarding the current state of practice of continuing a patient’s home statin therapy upon ICU admission. In a 2012 international survey of physicians in Australia, New Zealand, and the United Kingdom, 77.4% of physicians responded that they would restart a patient’s statin therapy during ICU admission, even if no new cardiac indications were present.21

Further randomized trials are needed to confirm the risk-benefit ratio of continuing statin therapy in the ICU. The suggestion of benefit across a variety of outcomes without an apparent increase in adverse effects and the low cost of therapy favor continuation while more definitive evidence is gathered.

References


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**COUNTERPOINT:**
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Joel D. Mermis, MD; Steven Q. Simpson, MD, FCCP; Kansas City, KS

For every patient admitted to an ICU, providers must make crucial decisions regarding which medications to use to enhance the patient's likelihood of survival and long-term recovery. Sometimes the decision is only regarding which medications to initiate in the ICU. However, we often must decide which outpatient medications are crucial or desirable to continue in the ICU and which are either not helpful or detrimental to the patient's current condition. Among the most common drugs that force this decision are the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, commonly known as statins. Statins are the best selling and most widely used agents in the history of the pharmaceutical industry, and many patients admitted to the ICU with a critical illness have been taking these drugs as outpatients.¹

We believe that for most critical illnesses, there is insufficient evidence to warrant continuation of treatment with statins in the ICU setting. To address this issue as a risk analysis proposition, we pose a series of important questions.

**Is This Drug Effective in the Setting of This Patient's Critical Illness?**

Statins exhibit numerous properties in vitro and in animal experiments that suggest a role for the drugs in the treatment or prevention of critical illnesses.² They alter synthesis and release of inflammatory cytokines through several mechanisms, alter leukocyte rolling and adhesion, inhibit inducible nitric oxide synthase, and inhibit microvascular clotting. It is mechanistically

**AFFILIATIONS:** From the Division of Pulmonary and Critical Care Medicine, University of Kansas School of Medicine.

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**CORRESPONDENCE TO:** Steven Q. Simpson, MD, FCCP, Division of Pulmonary and Critical Care Medicine, University of Kansas School of Medicine, 3901 Rainbow Blvd, Mail Stop 3007, Kansas City, KS 66160; e-mail: simpson3@kumc.edu

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