Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Research Article

Canadian Journal of Kidney Health and Disease
Volume 5: 1–8

DOI: 10.1177/2054358118789158
journals.sagepub.com/home/cjk
SAGE

Effect of Rosuvastatin on Acute Kidney Injury in Sepsis-Associated Acute Respiratory Distress Syndrome

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Abstract

Background: Acute kidney injury (AKI) commonly occurs in patients with sepsis and acute respiratory distress syndrome (ARDS).

Objective: To investigate whether statin treatment is protective against AKI in sepsis-associated ARDS.

Design: Secondary analysis of data from Statins for Acutely Injured Lungs in Sepsis (SAILS), a randomized controlled trial that tested the impact of rosuvastatin therapy on mortality in patients with sepsis-associated ARDS.

Setting: 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.

Patients: 644 of 745 participants in SAILS who had available baseline serum creatinine data and who were not on chronic dialysis.

Measurements: Our primary outcome was AKI defined using the Kidney Disease Improving Global Outcomes creatinine criteria. Randomization to rosuvastatin vs placebo was the primary predictor. Additional covariates include demographics, ARDS etiology, and severity of illness.

Methods: We used multivariable logistic regression to analyze AKI outcomes in 511 individuals without AKI at randomization, and 93 with stage 1 AKI at randomization.

Results: Among individuals without AKI at randomization, rosuvastatin treatment did not change the risk of AKI (adjusted odds ratio: 0.99, 95% confidence interval [CI]: 0.67-1.44). Among those with preexisting stage 1 AKI, rosuvastatin treatment was associated with an increased risk of worsening AKI (adjusted odds ratio: 3.06, 95% CI: 1.14-8.22). When serum creatinine was adjusted for cumulative fluid balance among those with preexisting stage 1 AKI, rosuvastatin was no longer associated worsening AKI (adjusted odds ratio: 1.85, 95% CI: 0.70-4.84).

Limitations: Sample size, lack of urine output data, and prehospitalization baseline creatinine.

Conclusion: Treatment with rosuvastatin in patients with sepsis-associated ARDS did not protect against de novo AKI or worsening of preexisting AKI.

Abrégé

Contexte: L'insuffisance rénale aiguë (IRA) survient fréquemment chez les patients atteints d'une septicémie et du syndrome de détresse respiratoire aiguë (SDRA).

Objectif de l'étude: Déterminer si un traitement aux statines offre une protection contre l'IRA chez les patients atteints d'un SDRA associé à une septicémie.

Type d'étude: Il s'agit d'une analyse secondaire des données de l'étude SAILS (*Statins for Acutely Injured Lungs in Sepsis*), un essai contrôlé à répartition aléatoire qui se penchait sur l'effet d'un traitement à la rosuvastatine sur le taux de mortalité des patients atteints d'un SDRA associé à une septicémie.

Cadre de l'étude: Les données proviennent de 44 centres hospitaliers du réseau *National Heart, Lung, and Blood Institute ARDS Clinical Trials Network*.

Patients: Les 644 participants à l'essai SAILS (sur un total de 745) non dialysés à vie et pour qui on disposait de valeurs initiales de créatinine sérique.

Mesures: La principale mesure observée était une atteinte d'IRA, définie selon les critères liés aux valeurs de la créatinine avancées par la fondation *Kidney Disease : Improving Global Outcomes*. Le facteur prédictif essentiel était la répartition aléatoire

des sujets (traitement à la rosuvastatine ou par placébo). Les caractéristiques sociodémographiques des patients, l'étiologie du SDRA et la gravité de l'atteinte constituaient les covariables additionnelles colligées.
Méthodologie: La survenue d'une IRA a été analysée par régression logistique multivariée chez deux sous-groupes : 511 patients qui ne présentaient initialement aucun signe clinique d'IRA et 93 patients initialement atteints d'IRA de stade 1.
Résultats: Chez les sujets non atteints d'IRA au moment de la répartition, le traitement à la rosuvastatine n'a eu aucun effet sur le risque de survenue d'IRA (rapport de cotes corrigé : 0,99; IC 95 % : 0,67-1,44). Chez les sujets initialement atteints d'IRA de stade 1, le traitement à la rosuvastatine a été associé à un risque plus élevé d'aggravation de l'atteinte existante (rapport de cotes corrigé : 3,06; IC 95 % : 1,14-8,22). Cependant, chez ces mêmes sujets, lorsque la créatinine sérique a été ajustée selon le bilan hydrique cumulatif, l'effet néfaste de la rosuvastatine n'a plus été observé (rapport de cotes corrigé : 1,85; IC 95 % : 0,70-4,84).
Limites: La taille de l'échantillon ainsi que l'absence de certaines données (concernant notamment la créatinine préhospitalisation et la diurèse) limitent les constats de notre étude.
Conclusion: Un traitement par rosuvastatine n'a eu aucun effet protecteur contre le développement ou l'aggravation d'une IRA chez des patients atteints du SDRA associé à une septicémie.

Keywords
AKI, acute renal failure, statin, sepsis, ARDS

Received March 27, 2018. Accepted for publication June 6, 2018.

What was known before

Statins have been shown to prevent septic and ischemic acute kidney injury (AKI) in some animal models, and recent human data—including randomized trials—suggest potential benefit in prevention of contrast-induced AKI. However, it is not known whether statin therapy may be protective against sepsis-associated AKI in critically ill patients with acute respiratory distress syndrome (ARDS).

What this adds

Using data from Statins for Acutely Injured Lungs in Sepsis (SAILS), we found that administration of rosuvastatin did not prevent new-onset AKI and did not prevent worsening of existing AKI, after taking into account demographics, ARDS etiology, and severity of illness.

Introduction

Acute kidney injury (AKI) is a common and serious complication in patients with sepsis. Among critically ill patients, sepsis is estimated to be the primary trigger for ~40% to 50% of AKI cases.[1] Sepsis-associated AKI is associated with mortality of up to 50% to 60%, with a graded association between AKI severity and death.[2] There are limited therapeutic options in treating sepsis-associated AKI besides supportive care, including renal replacement therapies when indicated.

Statins have been shown to prevent septic and ischemic AKI in mouse models[3-5] and have been proposed as a novel treatment for AKI. Recent human studies have primarily focused on the effect of statin therapy on preventing AKI in patients undergoing coronary angiography[6] and cardiac surgery.[7] In this study, we sought to investigate the effect of statin therapy on sepsis-associated AKI in critically ill patients with the acute respiratory distress syndrome (ARDS).

Methods

Study Design and Population

We analyzed data from the Statins for Acutely Injured Lungs in Sepsis (SAILS) study from the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.[8] SAILS was a multicenter, prospective, randomized controlled,

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double-blinded trial evaluating the effect of rosuvastatin therapy in critically ill patients with sepsis-associated ARDS. In total, 745 participants were enrolled from 44 hospitals from 2010 to 2013. The original SAILS design, protocol, and primary results have been described and published.[8] Patients were eligible if they were receiving mechanical ventilation meeting the American/European Consensus Conference definition for Acute Lung Injury[9] and had evidence of a known or suspected infection at study entry. Patients were randomized to placebo vs rosuvastatin 40 mg at the time of enrollment followed by 20 mg daily until the third day after intensive care unit discharge, study day 28, hospital discharge, or death. Rosuvastatin dose was reduced to 10 mg for patients with creatinine level ≥2.8 mg/dL (while not on dialysis). The primary predictor for the current analysis is rosuvastatin treatment as specified in the original trial in an intention-to-treat design.

The institutional review boards at each participating institution reviewed and approved the study protocol; informed consent was obtained from all patients or their health care surrogates.

Main Analysis

For the present analysis, we excluded 15 patients who were on chronic dialysis prior to the study and 86 patients with a missing creatinine measurement in the first 7 days after randomization. The remaining population was divided into those without AKI at the time of randomization and those with preexisting AKI at the time of randomization. AKI was defined using the Kidney Disease Improving Global Outcomes (KDIGO) creatinine-based criteria.[10] The primary outcome for those without AKI at randomization was the development of de novo AKI within 7 days after randomization. De novo AKI is defined as an increase in creatinine by ≥0.3 mg/dL within 48 hours or an increase of creatinine by ≥50% from baseline over the first 7 days (with baseline creatinine defined as the lowest creatinine within 96 hours prior to randomization). The primary outcome for those with preexisting stage 1 AKI was the development of worsening (stage 2 or 3) AKI stage, including receipt of dialysis. Participants with preexisting stage 2/3 AKI were not included in regression analyses. Figure 1 illustrates the derivation of our analytic cohort.

We used multivariable logistic regression to determine the association between rosuvastatin and AKI outcomes. We a priori decided to adjust for age, sex, race, ethnicity, ARDS etiology (primary respiratory defined as pneumonia or aspiration, vs nonrespiratory etiology), and severity of illness defined using Acute Physiology, Age, Chronic Health Evaluation (APACHE) III scores.

We additionally performed exploratory analysis comparing peak serum creatine kinase (CK) levels between rosuvastatin and control groups, separately for those with and without preexisting AKI. The incidence of serum CK levels above 10 times the upper limit of normal were also compared between rosuvastatin and control groups, to mirror analysis performed in the original SAILS publication.[8]

All data were prospectively collected during the original trial. Analysis was conducted using STATA 14.1/SE (College Station, Texas).

Fluid-Adjusted Analysis

Prior data from the ARDS Network have shown that fluid balance can confound AKI ascertainment.[11] Correction of creatinine for fluid balance may reassign patients from AKI to non-AKI groups and vice versa. Therefore, we replicated previously published methodology[11,12] to adjust serum creatinine for volume of distribution. We first estimated the volume of distribution for creatinine on the day of randomization as the total body water (TBW), equaling 60% of body weight on randomization.[13] We then calculated the on-study cumulative fluid balance using 24-hour fluid intake/output recorded. The final fluid-adjusted creatinine[11] is equal to the measured creatinine × (1 + [on-study cumulative fluid balance/TBW]). Patients are then reclassified as AKI or no AKI using fluid-adjusted creatinines, and the primary analysis was repeated using these fluid-adjusted values.

Results

Among 644 participants in our analytic cohort, 511 (79%) had no AKI, 93 (14%) had stage 1 AKI, and 40 (6%) had stage 2 or stage 3 AKI before randomization (Figure 1). Our cohort had similar characteristics as the original trial participants (Table 1). The median age was 55 (interquartile range [IQR]: 42-66), 51% were female, 14% were African American, and 12% were of Hispanic ethnicity. Mean baseline creatinine for both rosuvastatin and placebo groups were 1.2 mg/dL.

Effect of Rosuvastatin on De Novo AKI

Among the 511 participants without preexisting AKI at randomization, 200 (39%) developed stage 1 or greater AKI after randomization. There were no significant differences in risk of AKI between the rosuvastatin and control groups. Further analysis using fluid-adjusted creatinines to ascertain AKI also showed no difference in AKI risk between the rosuvastatin and control groups (Table 2).

Effect of Rosuvastatin on Preexisting Stage 1 AKI

Among the 93 participants with preexisting stage 1 AKI at randomization, 49 (53%) progressed to stage 2 or higher AKI after randomization (Table 2). In our primary analysis, the rosuvastatin group had a 3-fold higher adjusted odds of worsening AKI ($P = .03$). However, this association was no

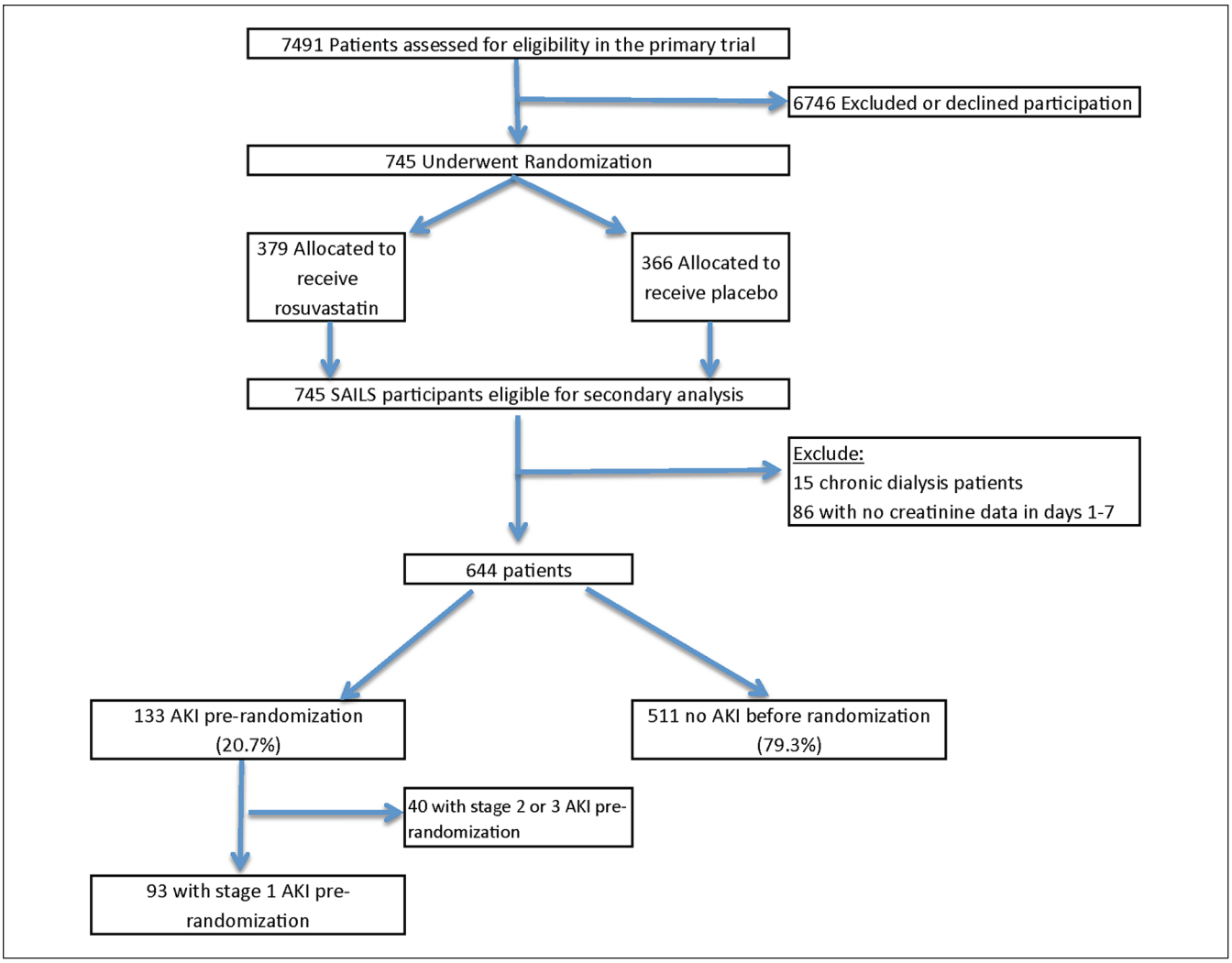

Figure 1. Screening, randomization, and derivation of analytic cohort.

longer significant in our secondary analysis when creatinine levels were adjusted for fluid balance (adjusted odds ratio: 1.85, 95% confidence interval [CI]: 0.70-4.84, $P = .21$). We found that there was a trend toward higher prevalence of vasopressor use before randomization in the placebo group (81%) compared with the rosuvastatin group (62%, $P = .06$) which was associated with higher mean fluid balance at randomization (+ 4.3 L in the placebo group vs + 2.5 L in the rosuvastatin group, $P = .02$).

Serum CK Levels

Table 3 shows the baseline and peak serum CK levels by subgroups and by placebo vs rosuvastatin treatment. Notably, among patients with preexisting stage 1 AKI at randomization, there was higher crude incidence of peak CK above 10 times the upper limit of normal for those treated with rosuvastatin (20%) vs those treated with placebo (8%; $P = .09$).

Discussion

In this analysis of patients with sepsis-associated ARDS enrolled in a randomized clinical trial, we found that rosuvastatin treatment did not protect against de novo AKI or worsening of existing mild AKI. To our knowledge, this is the first study to examine the effect of statin therapy in sepsis-associated AKI in humans. Our study adds to an emerging body of literature exploring whether statins may offer a renoprotective benefits.

Statins are potent lipid-lowering agents that are effective in preventing and treating coronary artery disease. The potentially nephroprotective effect of statin therapy is rooted in the "pleiotropic" effects including enhancement of nitric oxide production along with anti-inflammatory and antioxidant properties.[14] Yet the benefits of statins on kidney disease remain controversial. A recent meta-analysis of more than 50 randomized controlled trials (RCTs) in which statins were given for at least 6 months concluded that statin therapy did

Table 1. Baseline Characteristics of Study Participants.

Prerandomization characteristics	All (n = 644)	Placebo (n = 315)	Rosuvastatin (n = 329)	*P*
Age	54.2 (16.4)	54.1 (15.8)	54.4 (17.0)	.82
Median (IQR)	55 (42-66)	55 (43-65)	55 (42-67)	
Female	329 (51%)	164 (52%)	165 (50%)	.63
Race				.68
White	515 (80%)	254 (81%)	261 (79%)	
African American	88 (14%)	42 (13%)	46 (14%)	
Other	20 (3%)	10 (3%)	10 (3%)	
Unknown	21 (3%)	9 (3%)	12 (4%)	
Hispanic ethnicity	76 (12%)	34 (11%)	42 (13%)	.77
Weight (kg)	87.7 (30.9)	86.6 (31.3)	88.8 (30.5)	.39
Median (IQR)	82 (68-100)	80 (66-100)	84 (69-100)	
ARDS etiology				
Direct (pneumonia or aspiration)	509 (79%)	247 (78%)	262 (80%)	.43
APACHE III score (n = 613)	93.2 (27.8)	94.7 (27.1)	91.7 (28.4)	.18
Baseline creatinine (mg/dL) (n = 640)	1.2 (0.9)	1.2 (0.9)	1.2 (0.9)	.62
Median (IQR)	0.9 (0.7-1.4)	1.0 (0.6-1.5)	0.9 (0.7-1.4)	
AKI before randomization	133 (20%)	58 (18%)	75 (23%)	.17
AKI requiring dialysis	37 (6%)	20 (6%)	17 (5%)	.52

Note. IQR = interquartile range; ARDS = acute respiratory distress syndrome; AKI = acute kidney injury

Table 2. Effect of Rosuvastatin on Acute Kidney Injury Outcomes.

Outcome: de novo AKI in patients without preexisting AKI (n = 511)	Placebo (n = 257)	Rosuvastatin (n = 254)	*P*
Developed AKI	103 (40%)	97 (38%)	.66
Stage 1 (% out of all AKI)	44 (42.7%)	34 (35.1%)	
Stage 2	11 (10.7%)	12 (12.4%)	
Stage 3 without dialysis	32 (31.1%)	35 (36.1%)	
Stage 3 with dialysis	16 (15.5%)	16 (16.5%)	
Logistic regression analysis		OR (95% CI)	
Crude	Reference	0.92 (0.65-1.32)	.66
Multivariable[a]	Reference	0.99 (0.67-1.44)	.94
Fluid-adjusted analysis		OR (95% CI)	
Crude	Reference	0.84 (0.59-1.21)	.35
Multivariable[a]	Reference	0.92 (0.63-1.34)	.64
Outcome: worsened AKI in patients with preexisting stage 1 AKI (n = 93)	**Placebo (n = 39)**	**Rosuvastatin (n = 54)**	***P***
Developed ≥ stage 2 AKI post randomization	16 (41%)	33 (61%)	.06
Logistic regression analysis		OR (95% CI)	
Crude	Reference	2.26 (0.97-5.24)	.06
Multivariable[a]	Reference	3.06 (1.14-8.22)	.03
Fluid-adjusted analysis		OR (95% CI)	
Crude	Reference	1.41 (0.61-3.27)	.42
Multivariable[a]	Reference	1.85 (0.70-4.84)	.21

Note. AKI = acute kidney injury; OR = odds ratio; CI = confidence interval.
[a]Multivariable analyses were adjusted for age, sex, race, ethnicity, ARDS etiology (primary respiratory etiology defined as either pneumonia or aspiration, vs nonrespiratory etiology), and severity of illness defined by APACHE III scores.

not reduce the risk for kidney failure events (defined as end-stage renal disease, doubling of serum creatinine, or >25% or 50% decrease in estimated glomerular filtration rate [eGFR] depending on the study) among adults not already receiving

Table 3. Serum CK Levels.

Subgroup without preexisting AKI at randomization (n = 511)	Placebo (n = 257)	Rosuvastatin (n = 254)	*P*
Baseline CK[a]	201 ± 291	212 ± 405	.73
Peak CK[a]	477 ± 1463	1070 ± 10141	.33
Peak CK > 10 times upper limit of normal	11 (4.3%)	15 (5.9%)	.40
Subgroup with preexisting stage 1 AKI at randomization (n = 93)	**Placebo (n = 39)**	**Rosuvastatin (n = 54)**	***P***
Baseline CK[a]	389 ± 918	237 ± 566	0.33
Peak CK[a]	754 ± 1676	3119 ± 15,474	0.35
Peak CK > 10 times upper limit of normal	3 (8%)	11 (20%)	0.09

Note. CK = creatine kinase.
[a]Expressed as mean ± standard deviation, in U/L.

dialysis, but that statin therapy may modestly reduce proteinuria and rate of eGFR decline.[15]

The potential role of *short-term* statin administration on AKI prevention has been investigated more recently in human studies. Several recent RCTs found that short-term precontrast statin administration may be protective against contrast-associated AKI (CA-AKI).[6,16-18] The largest of these studies randomized nearly 3000 patients in China with type 2 diabetes or mild to moderate chronic kidney disease undergoing coronary or peripheral arterial angiography to a 5-day course of rosuvastatin vs no statin and found the incidence of CA-AKI to be significantly lower in the rosuvastatin group (2.3% vs 3.9%, $P = .01$).[16] However, more studies are needed to replicate the effect sizes seen in recent studies and to determine the best groups to target for CA-AKI. In the cardiac surgery setting, recent large RCTs found that statin administration did not protect against postoperative AKI,[7,19] while a possibility of renal harm was suggested by some data.[7,20]

Our analysis did not demonstrate any renal benefit with rosuvastatin in patients with sepsis and ARDS. Rather, our primary analysis showed that rosuvastatin treatment may in fact be harmful in patients with preexisting AKI, though this finding may be confounded by prerandomization differences in fluid balance and vasopressor use between the groups. We had only a modest number of patients with preexisting AKI at randomization, which limited our power to detect potential harm or benefit. In the original SAILS study, enrollment was stopped early due to futility after 745 participants (out of planned 1000) for lack of benefit with regard to in-hospital mortality.[8] Interestingly, in the original SAILS study, the rosuvastatin group had slightly fewer days free of renal failure (mean 10.1 days in the rosuvastatin arm vs 11.0 days in placebo arm, $P = .01$).[8] However, renal failure was defined fairly crudely as serum creatinine level of at least 2.0 mg/dL in the original study, while our current analysis used a more updated consensus definition of AKI and incorporated both de novo AKI as well as worsening serum creatinine in those with preexisting AKI as outcomes. Therefore, we believe that a potentially detrimental renal effect of rosuvastatin—in the setting of sepsis—cannot be ruled out.

The mechanism for possible deleterious renal effect of statins is unclear. As the kidneys are responsible for excreting 10% of rosuvastatin (vs 90% eliminated in feces),[21] it is plausible that patients with preexisting AKI were at higher risk of any potentially nephrotoxic effect due to higher circulating levels of rosuvastatin. AKI associated with statin administration is most commonly caused by rhabdomyolysis leading to acute tubular necrosis (often in the setting of concurrent use of fibrates or other interacting medications, which were exclusion criteria in the original SAILS study). Interestingly, in our exploratory analysis examining serum CK levels, we found higher peak CK levels in those treated with rosuvastatin compared with placebo, though these differences did not reach statistical significance. Among those with preexisting stage 1 AKI at randomization, rosuvastatin treatment is crudely associated with a nearly 3-fold increased odds of having peak CK above 10 times upper limit of normal, though this association again did not reach statistical significance, likely owing to the small sample of patients with preexisting AKI available for analysis. Based on our data, we cannot definitively conclude, nor rule out, that rhabdomyolysis (or subclinical levels of rhabdomyolysis) played a role in the association between rosuvastatin and worsening of AKI. There is indeed additional recent literature suggesting acute nephrotoxicity associated with high-potency statins,[22,23] with one case report of suspected direct tubular toxicity associated with high-dose rosuvastatin.[22]

Our study has the following limitations. First, we did not use urine output to define AKI,[24] and creatinine measurements were not obtained daily for the entire 28-day treatment period. Second, no prehospitalization serum creatinine values were available. However, as part of the study protocol, all creatinine values from the 96 hours prior to randomization were systematically collected, and we used the lowest creatinine in the prerandomization period as reference. In addition, our current analysis may have been underpowered to detect significant differences in AKI outcomes, given our

fixed sample size from the original SAILS trial. For example, we had an 80% power to detect a 12% difference in rate of de novo AKI among the 511 patients without preexisting AKI, and therefore a smaller effect size of rosuvastatin on AKI risk would not have been identified. Finally, given the requirement for sepsis-associated ARDS, the SAILS participants are critically ill with a mean APACHE III score of 93. Therefore, the results here may not be generalizable to all cases of sepsis-induced AKI. Nevertheless, this study is strengthened by randomized and protocoled exposure to rosuvastatin, and its completeness of prospectively collected data including severity of illness, fluid balance, vasopressor use, and preenrollment creatinine values. We also performed a thorough analysis adjusting serum creatinine for cumulative fluid balance, as fluid overload is common in this population and is known to influence AKI ascertainment.

Conclusions

In conclusion, we demonstrated that rosuvastatin treatment in critically ill patients with sepsis and ARDS did not prevent de novo AKI and did not prevent worsening of AKI in those with preexisting mild AKI. While statins have been proposed to be renoprotective in other settings, our study showed no renal benefit in sepsis-associated AKI, and potential harm of statin administration on exacerbating preexisting mild AKI cannot be ruled out.

Ethics Approval and Consent to Participate

Institutional Review Boards at each participating institution reviewed and approved the study protocol; informed consent was obtained from all patients or their health care surrogates.

Consent for Publication

All authors consent for publication.

Availability of Data and Materials

No.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The original SAILS study was supported by a grant from the National Heart, Lung, and Blood Institute (NHLBI) (HHSN268200 536165C-536179C), and the Investigator-Sponsored Study Program of AstraZeneca. R.K.H. was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (K23DK100468, R03DK111881). K.D.L. was supported by a grant from the NIDDK (K24DK113381). The funding sources had no role in the study design, study conduct, data analysis, or data interpretation.

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