Association of Statin Use with Risk and Outcome of Acute Kidney Injury in Community-Acquired Pneumonia

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Summary

Background and objectives Sepsis is a leading cause of AKI. Animal studies suggest that the pleiotropic effect of statins attenuates the risk for AKI and decreases mortality. This study examined whether statin use was associated with a lower risk for pneumonia-induced AKI and 1-year and cause-specific mortality in patients with AKI.

Design, setting, participants, & measurements Multicenter, prospective cohort study of 1836 patients hospitalized with community-acquired pneumonia.

Results Baseline characteristics differed among statin users and nonusers. Of the 413 patients (22.5%) who received a statin before hospitalization, statin treatment, when adjusted for differences in age, severity of pneumonia, admission from nursing home, health insurance, and propensity for statin use, did not reduce the risk for AKI (odds ratio [OR], 1.32 [95% confidence interval (CI), 1.02–1.69]; P=0.05). Of patients with AKI (n=631), statin use was associated with a lower risk for death at 1 year (27.8% versus 38.8%; P=0.01), which was not significant when adjusted for differences in age, severity of pneumonia and AKI, use of mechanical ventilation, and propensity score (OR, 0.72 [95% CI, 0.50–1.06]; P=0.09). Among patients with AKI, cardiovascular disease accounted for one third of all deaths.

Conclusions In a large cohort of patients hospitalized with pneumonia, statins did not reduce the risk for AKI. Among patients with AKI, statin use was not associated with lower risk for death at 1 year. The higher risk for AKI observed among statin users may be due to indication bias.

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Introduction

Sepsis, an immune response to infection, is a leading cause of AKI (1–5). Among patients hospitalized with community-acquired pneumonia (CAP), a leading infectious cause of hospitalization in developed countries, more than one third develop AKI (1). Regardless of severity, patients with AKI incur a higher short-term risk for death than do patients without AKI (1,4,6). Survivors of AKI also incur a long-term risk for death that has been attributed to cardiovascular disease (7–9). Regrettably, however, there is no specific intervention aside from supportive care to prevent AKI or improve outcomes from AKI.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are widely prescribed lipid-lowering medications that have become a cornerstone of primary and secondary prevention of cardiovascular disease (10,11). Statins have many pleiotrophic effects (12–14), and although some studies suggest that these pleiotrophic effects may decrease the risk for severe sepsis (*i.e.*, sepsis with coexisting severe acute organ dysfunction) (15), other studies have shown no benefit (16). Our prior work suggests that statins do not decrease the risk for severe sepsis or death in patients with CAP (17). Nevertheless, we found that AKI was a common complication of CAP that was associated with long-term mortality (1). Experimental evidence in animals suggests that statins attenuate the risk for sepsis-induced AKI, reduce mortality because of attenuation of the systemic inflammatory response, and reduce renal vascular permeability and renal tubular hypoxic injury (18). Whether statin modulates the risk for sepsis-induced AKI and long-term mortality associated with AKI in humans is unknown.

This large, multicenter, prospective, observational inception cohort study of patients hospitalized with CAP (the Genetic and Inflammatory Markers of Sepsis [GenIMS] study) used the highly sensitive and widely validated Risk, Injury, Failure, Loss and End-stage (RIFLE) renal disease criteria to define AKI. The objectives of our study were two-fold. First, we examined whether statin use was associated with a lower risk for AKI compared with those never exposed to statins. Second, we examined the hospital course and risk for

death at 1 year in patients with AKI who received statin therapy compared with those never exposed to a statin. We also examined cause-specific mortality among patients with AKI.

Materials and Methods

Study Design and Selection of Participants

The GenIMS study enrolled patients with CAP presenting to the emergency departments of 28 teaching and nonteaching hospitals in the United States (19). Eligible patients were ≥18 years of age and had a clinical and radiologic diagnosis of CAP according to the criteria of Fine *et al.* (20). The institutional review boards at all participating sites approved the study, and we obtained written informed consent from all participants or their proxies. To examine the association between statin use and outcomes, we used two different comparison cohorts (17). We first compared patients who had prehospital statin use (prehospital cohort), defined as a history of statin use in the week before CAP hospitalization, with patients who did not have prehospital statin use. We then compared prehospital statin users whose statin therapy was continued in the hospital (continued-use cohort) with those who had no prehospital statin use or did not continued statin use in the hospital.

Methods of Data Collection

We prospectively collected outpatient statin use by structured patient interview or review of medication history. Patients were classified as statin users if they were taking statins in the week before hospitalization for CAP. Subsequent continued inpatient statin use was determined using medical record abstraction. We prospectively ascertained comorbid conditions using the Charlson Comorbidity Index (21) and the history of CKD; we assessed severity of illness using the Acute Physiology and Chronic Health Evaluation III score (22) and the Pneumonia Severity Index (20). We defined severe sepsis as infection plus acute organ dysfunction (23). We defined acute organ dysfunction as a new Sequential Organ Failure Assessment score of ≥3 in any of six organ systems (24).

Outcome Ascertainment

Definition of AKI. The risk for incident cases of AKI was ascertained using the maximum RIFLE stages, as proposed by the Acute Dialysis Quality Initiative (25). Patients were classified as having developed AKI if they met any Risk, Injury, or Failure stages at any time during hospitalization. The RIFLE stage was determined on the basis of the worse of serial serum creatinine or urine output. For patients with no known premorbid creatinine and no known medical history of CKD, we estimated premorbid creatinine using the Modification of Diet in Renal Disease equation (26). We then selected the lower creatinine value from either the hospital admission creatinine or the estimated creatinine as the baseline value (27).

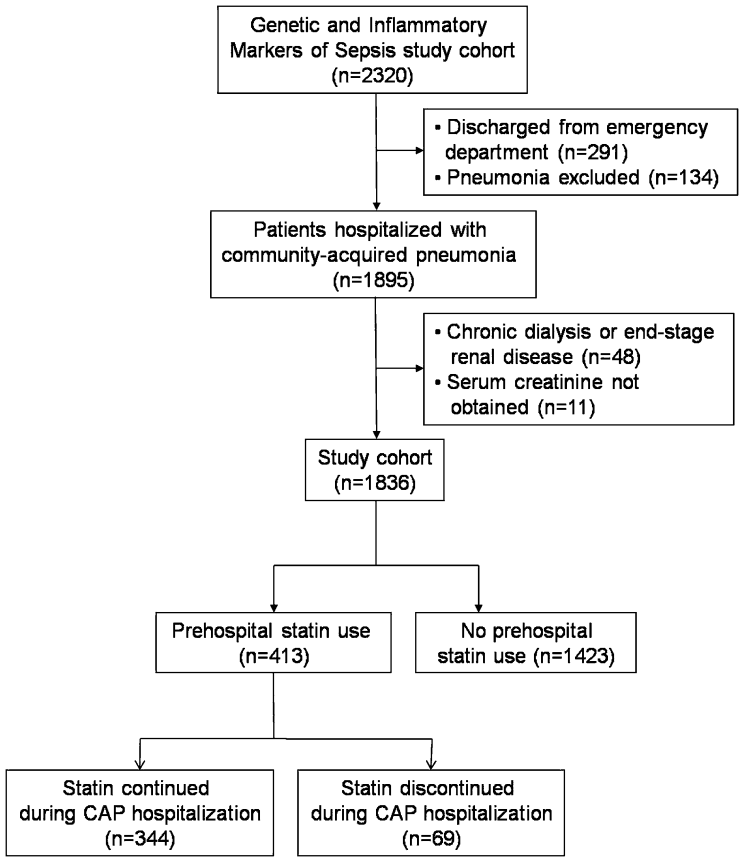

Figure 1. | **Patient disposition for the Genetic and Inflammatory Markers of Sepsis study cohort.** CAP, community-acquired pneumonia.

Table 1. Baseline characteristics of patients with and without statin use

Characteristic	Prehospital Statin Use[a] (*n*=413)	No Prehospital Statin Use[b] (*n*=1423)	*P* Value	Continued Statin Use[c] (*n*=344)	No Continued Statin Use[d] (*n*=1492)	*P* Value
Demographic						
mean age (yr)	72.4±11	66.8±17.8	<0.001	72.8±10.6	66.9±17.6	<0.001
male gender	227 (54.9)	727 (51.1)	0.16	192 (55.8)	762 (51)	0.11
race						
white	368 (89.1)	1125 (79)	<0.001	315 (91.5)	1178 (78.9)	<0.001
black	36 (8.7)	242 (17)		22 (6.4)	256 (17.1)	
other	9 (2.1)	56 (3.9)		7 (2)	58 (3.8)	
admitted from nursing home	12 (2.91)	103 (7.24)	0.001	8 (2.33)	107 (7.1)	0.001
Charlson Comorbidity Index[e]						
mean score	2.16±2.0	1.78±2.2	<0.001	2.2±2.0	1.7±2.2	<0.001
patients with score > 0	344 (83.2)	978 (68.7)	<0.001	293 (85.1)	1029 (68.9)	<0.001
CKD	9 (2.1)	24 (1.6)	0.50	6 (1.74)	27 (1.81)	0.93
cardiovascular disease	189 (54.1)	278 (21.9)	<0.001	166 (57)	301 (22.6)	<0.001
chronic respiratory disease	158 (38.2)	545 (38.3)	0.98	137 (39.8)	566 (37.9)	0.51
diabetes	125 (30.2)	236 (16.5)	<0.001	105 (30.5)	256 (17.1)	<0.001
cirrhosis	0	4 (0.8)	0.29	0	4 (0.2)	0.73
mean baseline creatinine level (mg/dl)	0.91±0.1	0.89±0.2	0.05	0.90±0.1	0.89±0.2	0.08
Healthy user indicators						
health insurance	410 (99.2)	1344 (94.4)	<0.001	343 (99.7)	1411 (94.5)	<0.001
lives at home	383 (92.7)	1249 (87.7)	0.005	322 (93.6)	1310 (87.8)	0.002
ambulating independently	279 (67.5)	872 (61.2)	0.02	238 (69.1)	913 (61.1)	0.006
previous smoker	204 (49.3)	577 (40.5)	0.001	179 (52)	602 (40.3)	<0.001
current smoker	68 (16.4)	374 (26.2)	<0.001	51 (14.8)	391 (26.2)	<0.001
pneumococcal vaccine	209 (50.6)	496 (34.8)	<0.001	179 (52)	526 (35.2)	<0.001
influenza vaccine in the prior 8 months	207 (50.1)	523 (36.7)	<0.001	176 (51.1)	554 (37.1)	<0.001
long-term aspirin use	223 (54)	406 (28.5)	<0.001	192 (55.8)	437 (29.2)	<0.001
long-term anticoagulant use	103 (24.9)	194 (13.6)	<0.001	87 (25.2)	210 (14)	<0.001
Severity of illness on day 1						
mean Pneumonia Severity Index score[f]	93.4±25.7	86.2±33.6	<0.001	93.2±25.1	86.6±33.5	<0.001
mean Pneumonia Severity Index score without age	38.8±27.3	36.4±30.8	0.007	38.5±27	36.6±30.7	0.02
Pneumonia Severity Index class						
I or II	53 (12.8)	353 (24.8)	<0.001	40 (11.6)	366 (24.5)	<0.001
III	72 (17.4)	310 (21.7)		62 (18)	320 (21.4)	
IV	201 (48.6)	485 (34)		173 (50.2)	513 (34.3)	
V	87 (21)	275 (19.3)		69 (20)	293 (19.6)	
mean APACHE III score[g]	40.3±12.3	40.2±14.3	0.59	40.1±12.1	40.3±14.3	0.83
mean SOFA score[h]	2.3±1.8	2.3±1.9	0.37	2.3±1.8	2.3±1.9	0.57
severe sepsis[i]	54 (13)	213 (14.9)	0.33	105 (30.5)	467 (31.3)	0.77
Treatments administered						

Table 1. (Continued)

Characteristic	Prehospital Statin Use[a] (*n*=413)	No Prehospital Statin Use[b] (*n*=1423)	*P* Value	Continued Statin Use[c] (*n*=344)	No Continued Statin Use[d] (*n*=1492)	*P* Value
antibiotic use in the last week	66 (15.9)	257 (18)	0.33	59 (17.1)	264 (17.6)	0.60
received antibiotics according to ATS guidelines	338 (81.8)	1128 (79.2)	0.25	281 (81.6)	1185 (79.4)	0.34
Hospital characteristics						
admitted to teaching hospital	207 (50.1)	770 (54.1)	0.15	171 (49.7)	806 (54)	0.14
bed group						
<100	8 (1.9)	28 (1.9)	0.22	8 (2.3)	28 (1.8)	0.37
100–249	158 (38.2)	620 (43.5)		132 (38.3)	646 (43.3)	
250–499	173 (41.8)	562 (39.4)		144 (41.8)	591 (39.6)	
≥500	74 (17.9)	213 (14.9)		60 (17.4)	227 (15.2)	

Values expressed with a plus/minus sign are the mean ± SD. Unless otherwise noted, other values are number (percentage) of patients. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ATS, American Thoracic Society.

[a]Patients who were taking a statin medication as an outpatient in the 7 days before hospitalization for community-acquired pneumonia (CAP).

[b]Patients who were not taking a statin medication as an outpatient in the 7 days before CAP hospitalization.

[c]Patients who were taking a statin medication as an outpatient in the 7 days before hospitalization for CAP and in whom statins were continued during hospital stay.

[d]Patients who were not taking a statin medication as an outpatient in the 7 days before CAP hospitalization or patients in whom statin medications were never continued during hospital stay.

[e]According to the method of Charlson *et al*. (21).

[f]Measured according to criteria by Fine *et al*. (20) in the emergency department in 1546 (84.2%) patients. There were no significant differences between patients who did and did not have a Pneumonia Severity Index measured.

[g]Assessed on first hospital day regardless of whether patient was admitted to an intensive care unit (22).

[h]Assessed on the first day of hospital admission according to the method of Vincent *et al*. (24).

[i]Defined as sepsis plus acute organ dysfunction according to 2001 international consensus criteria for severe sepsis (23).

Patients were classified as stage Risk if serum creatinine was 1.5 times the baseline creatinine or urine output was <0.5 ml/kg per hour for 6 hours; stage Injury if serum creatinine was twice the baseline or urine output was <0.5 ml/kg per hour for 12 hours; and stage Failure if serum creatinine was thrice the baseline or creatinine level was ≥4 mg/dl with an acute increase of >0.5 mg/dl, urine output was <0.3 ml/kg per hour for 24 hours, or anuria was noted for 12 hours (25).

All-Cause and Cause-Specific Mortality. Study coordinators ascertained death in the hospital. We ascertained all-cause and cause-specific postdischarge mortality using a National Death Index (NDI) search and NDI-coded causes of death. The reliability of NDI for epidemiologic studies has been previously validated (28).

Statistical Analyses

We conducted univariate comparisons of baseline characteristics between statin users and nonusers using chi-squared tests, *t* tests, Fisher exact tests, or their nonparametric equivalents, as appropriate. We assessed 1-year mortality in patients with AKI by comparing Kaplan-Meier failure plots using log-rank tests. We adjusted for potential confounders by fitting multivariable models using generalized estimating equations (GEEs) (29) and obtained odds ratios (ORs) and associated 95% confidence intervals (CIs). The reported significance levels (*P* values) were obtained from a type 3 contrast and are more accurate than those obtained from the GEE model. These significance levels, although close to those obtained from the GEE model, tend to be conservative. Four categories of potential confounders were considered: demographic characteristics and comorbid conditions; baseline creatinine; severity of pneumonia; and healthy user indicators (health insurance, residence at home, functional status, former smoker, and influenza and pneumococcal vaccination).

To account for differential likelihood of receiving a statin, we constructed a propensity score for prehospital or continued in-hospital statin use (30). We calculated a propensity score as the estimated probability from logistic regression of a patient's being assigned to a statin. We first fit a series of logistic regression models with hospital as a clustering variable using GEE. For inclusion in the model, the following variables were considered: age, Charlson Comorbidity Index score, history of diabetes, insurance status, use of aspirin and anticoagulants, pre-existing cardiovascular disease, prior functional status, whether patient was admitted from home, current smoking status, and white or black

race. Initially, a series of models were fit that included each variable separately, and the receiver-operating characteristic (ROC) curves for model prediction was computed. We took the three variables associated with the largest area under the ROC curve and fit three different sets of two-variable models. Each two-variable combination was considered for all possible combinations of these covariates. Using the ROC as the criterion, we then selected multiple two-variable models that served as the basis for the set of three-variable models. This process continued until the addition of new variables to the model resulted in little change in the ROC. The final model included age, history of diabetes and cardiovascular disease, aspirin and anticoagulant use, functional status, and living arrangement before hospitalization. The propensity scores were then used as a covariate in the multivariable GEE models. All analyses were performed using SAS 9.0 (SAS Institute, Cary, NC) and Stata 9.0 (Stata Corp, College Station, TX), and statistical significance was assumed at $P<0.05$.

Results

Baseline Characteristics of Study Participants by Statin Use

Of the 2320 patients enrolled in the study, 1836 patients formed the study cohort (Figure 1); premorbid baseline creatinine was estimated in 1745 patients. Of the 91 patients with known baseline creatinine, we found moderate agreement between premorbid creatinine and the estimated

Table 2. Baseline characteristics of prehospital and continued statin use compared with no continued statin use

Characteristic	Prehospital and Continued Statin Use[a] (n=344)	Prehospital but No Continued Statin Use[b] (n=69)	P Value
Demographics			
mean age (yr)	72.8±10.6	70.1±12.4	0.16
male gender	192 (55.8)	35 (50.7)	0.43
white race	315 (91.5)	53 (76.8)	0.001
admitted from nursing home	8 (2.3)	4 (5.8)	0.11
Charlson Comorbidity Index			
mean score	2.2±2	2±2	0.23
patients with score > 0	293 (85.1)	51 (73.9)	0.02
CKD	6 (1.7)	3 (4.3)	0.17
cardiovascular disease	166 (57)	23 (39.6)	0.01
chronic respiratory disease	137 (39.8)	21 (30.4)	0.14
diabetes	105 (30.5)	20 (28.9)	0.80
cirrhosis	115 (33.4)	20 (28.9)	0.43
mean baseline creatinine (mg/dl)	0.90±0.1	0.94±0.3	0.99
Healthy user indicators			
health insurance	343 (99.7)	67 (97.1)	0.02
lives at home	322 (93.6)	61 (88.4)	0.12
ambulating independently	238 (69.1)	41 (59.4)	0.11
previous smoker	179 (52)	25 (36.2)	0.01
current smoker	51 (14.8)	17 (24.6)	0.12
pneumococcal vaccine	179 (52)	30 (43.4)	0.19
influenza vaccine in the prior 8 months	176 (51.1)	31 (44.9)	0.34
long-term aspirin use	192 (55.8)	31 (44.9)	0.09
long-term anticoagulant use	87 (25.2)	16 (23.1)	0.71
Severity of illness on day 1			
mean Pneumonia Severity Index score	106.5±29.6	105.1±33.6	0.89
mean APACHE III score	40.1±12.1	41.4±13.5	0.54
mean SOFA score	2.34±1.81	2.44±1.81	0.62
severe sepsis	42 (12.2)	12 (17.4)	0.24
Treatments administered			
antibiotic use in the last week	59 (17.1)	7 (10.1)	0.14
received antibiotics according to ATS guidelines	281 (81.7)	57 (82.6)	0.85

Values expressed with a plus/minus sign are the mean ± SD. Unless otherwise noted, other values are number (percentage) of patients. APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ATS, American Thoracic Society.

[a]Patients who were taking a statin medication as an outpatient in the 7 days before hospitalization for community-acquired pneumonia (CAP) and in whom the medication was continued during hospital stay.

[b]Patients who were taking a statin medication as an outpatient in the 7 days before CAP hospitalization and in whom the medication was not continued during hospital stay

creatinine to classify patients with AKI (Cohen $\kappa = 0.70$ [95% CI, 0.52–0.87]; $P<0.001$). Of the 1836 patients, 413 (22.5%) were receiving treatment with a statin before hospitalization (prehospital statin use cohort). Of patients who received a prehospital statin, therapy was continued in 344 patients (83.3%) (continued statin use cohort).

Table 1 shows the baseline characteristics of patients with and those without prehospital statin treatment and those in whom statins were continued during hospitalization compared with those without continued statin use. The mean age of the cohort was 68.1 years. Patients receiving treatment with statins were older and predominantly of white race. Statin users were more likely to have at least one chronic health condition based on their Charlson Comorbidity Index score. In particular, as one might expect, there were a higher prevalence of cardiovascular disease and diabetes and increased use of antiplatelet and anticoagulant medications. Nevertheless, statin users were healthy because they were more likely to have health insurance, to be admitted from home, and to have independent mobility; were less likely to smoke; and were up to date with their vaccination.

Although the prevalence of CKD was similar (prehospital statin versus no statin, 2.1% versus 1.6%; $P=0.50$), statin users had a higher baseline creatinine than nonusers (mean serum creatinine ± SD, 0.91±0.1 versus 0.89±0.2 mg/dl; $P=0.05$); this difference was not clinically significant. Statin users had more severe pneumonia, as evidenced by higher Pneumonia Severity Index score than that in patients unexposed to statins. Table 2 shows the baseline characteristics of statin users stratified by whether their statins were continued in the hospital. Those whose statin was not continued ($n=69$) were more likely to be of nonwhite race and to have less comorbidity (including a lower prevalence of cardiovascular disease) and were less likely to have health insurance; they were otherwise similar to patients in whom statins were continued during CAP hospitalization.

Association between Statin Use and Risk for AKI

Overall, 34.4% ($n=631$) of patients developed AKI. In univariate analysis, more patients with prehospital statin use developed AKI than those without statin use (unadjusted OR, 1.57 [95% CI, 1.25–1.98]) (Table 3). Similar risk for AKI was present among those with continued in-hospital statin use. However, the severity of AKI was highly variable (Table 3). We found no difference in the risk for AKI among patients in whom statins were continued during hospitalization and those in whom statins were discontinued during hospitalization.

When adjusted for differences in age, severity of pneumonia, admission from nursing home, and health insurance, statin use was associated with increased risk for AKI in those with prehospital statin use (OR, 1.39 [95% CI, 1.09–1.77]; $P=0.02$) and continued statin use (OR, 1.32 [95% CI, 1.02–1.71]; $P=0.04$) (Figure 2). After adjustment for propensity for statin use (including age, history of diabetes and cardiovascular disease, aspirin and anticoagulant use, functional status, and living arrangement before hospitalization), however, this higher risk remained significant among patients with prehospital statin use (OR, 1.32 [95% CI, 1.02–1.69]; $P=0.05$) but not in those with continued statin use (OR, 1.26 [95% CI, 0.95–1.66]; $P=0.11$).

Although the risk for AKI varied depending on the method used to determine baseline renal function (Supplemental Table A), we found no association between statin use and risk for AKI among the subgroup of patients ($n=91$) with known baseline creatinine, patients who were assigned day 1 creatinine as a baseline ($n=598$), and patients in whom baseline creatinine was estimated using the Modification of Diet in

Table 3. Association between statin use and risk and severity of acute kidney injury

Characteristic	Prehospital Statin Use	No Prehospital Statin Use	*P* Value	Continued Statin Use	No Continued Statin Use	*P* Value
Risk for AKI						
all patients[a] ($n=1836$)	176 (42.6)	455 (32)	<0.001	144 (41.9)	487 (32.6)	0.001
subgroup with cardiovascular disease[b] ($n=467$)	86 (45.5)	121 (43.5)	0.67	73 (44)	134 (44.5)	0.91
subgroup without cardiovascular disease[c] ($n=1151$)	59 (37)	275 (27.7)	0.01	46 (36.8)	288 (28)	0.04
Severity of AKI[d]						
risk	79 (45)	228 (50.1)	0.01	68 (47.2)	239 (49.1)	0.02
injury	51 (29)	84 (18.5)		42 (29.2)	93 (19.1)	
failure	46 (26.1)	143 (31.4)		34 (23.6)	155 (31.8)	

Unless otherwise stated, data are number (percentage) of patients. AKI, acute kidney injury.
[a]Patients were classified as having developed AKI within the entire cohort of 1836 patients if they met any of the Risk, Injury, or Failure stages at any time during hospitalization as proposed by the Acute Dialysis Quality Initiative (25).
[b]Subgroup of 467 patients who had a history of pre-existing cardiovascular disease before hospitalization for community-acquired pneumonia (CAP).
[c]Subgroup of 1151 patients with no history of pre-existing cardiovascular disease before CAP hospitalization.
[d]For severity of AKI, 1836 patients within the entire cohort were classified according to the maximum Risk, Injury, or Failure reached during the entire hospitalization as proposed by the Acute Dialysis Quality Initiative (25).

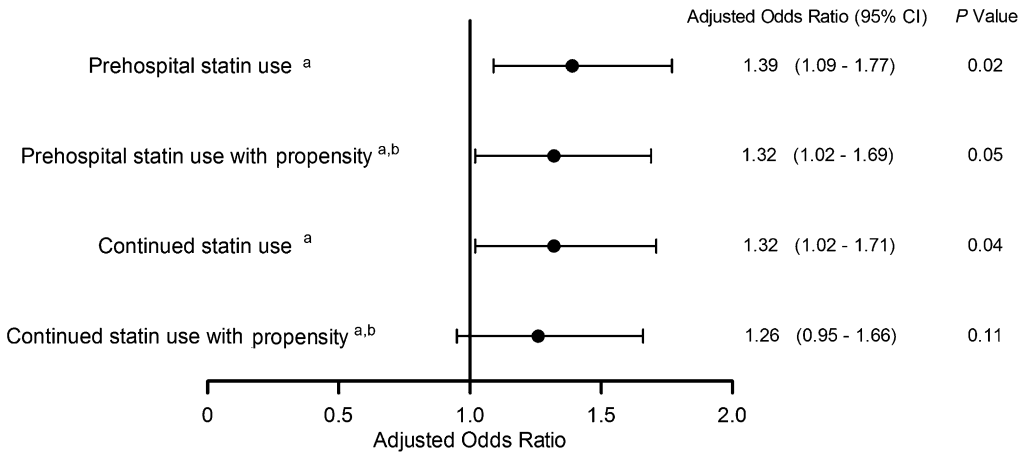

Figure 2. | Adjusted odds ratio plot showing association between statin use and the risk for acute kidney injury in the prehospital and continued statin use cohorts. [a]Odds ratios adjusted for differences in age, pneumonia severity index, admission from extended-care facility, and health insurance. [b]Variables included in the propensity score were age, history of diabetes, history of cardiovascular disease, long-term aspirin use, long-term anticoagulation use, functional status, and living arrangement before hospitalization for community-acquired pneumonia.

Renal Disease equation (Supplemental Table B), and when hospital admission creatinine was used as a baseline (Supplemental Table C).

Of the subgroup of patients with preexisting cardiovascular disease (n=467), the risk for AKI was similar among those with and without statin exposure (Table 3). Of those without cardiovascular disease (n=1151), statin users incurred a higher risk for AKI (prehospital use, 36.8% versus 27.7%, P=0.01; continued use, 36.8% versus 28%, P=0.04). However, this higher risk with statin use among patients without cardiovascular disease was explained by differences in age and severity of pneumonia (adjusted OR with prehospital statin use, 1.28 [95% CI, 0.94–1.74], P=0.12; OR with continued statin use, 1.22 [95% CI, 0.83–1.80], P=0.31) such that statin exposure was not associated with increased risk for AKI.

Association between Statin Use and Hospital Course and Outcome in Patients with AKI

Table 4 shows hospital course and outcomes in patients with AKI by statin use. Of patients who developed AKI, statin exposure was associated with a lower risk for severe

Table 4. Hospital course and outcomes in patients with acute kidney injury by statin use

Characteristic[a]	All Patients With AKI (n=631)	AKI With Prehospital Statin Use (n=176)	AKI Without Prehospital Statin Use (n=455)	P Value	AKI With Continued Statin Use (n=144)	AKI Without Continued Statin Use (n=487)	P Value
Developed severe sepsis	329 (52.1)	76 (43.1)	253 (55.6)	0.005	62 (43)	267 (54.8)	0.01
ICU admission	245 (38.8)	62 (35.23)	183 (40.2)	0.24	47 (32.6)	198 (40.6)	0.08
Mechanical ventilation	116 (18.3)	25 (14.2)	91 (20)	0.09	17 (11.8)	99 (20.3)	0.02
Median length of hospital stay (d) (IQR)	8 (5–12)	7 (5–11)	8 (5–13)	0.12	7 (5–11)	8 (5–12)	0.35
RRT during CAP hospitalization	16 (2.5)	5 (2.8)	11 (2.4)	0.76	2 (1.4)	14 (2.9)	0.32
RRT at 1 yr among survivors	8 (2)	0	8 (2.8)	0.11	0	8 (2.7)	0.12
1-yr mortality	229 (36.2)	52 (29.5)	177 (38.9)	0.02	40 (27.8)	189 (38.8)	0.01

Unless otherwise stated, data are the number (percentage) of patients. AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range; CAP, community-acquired pneumonia; RRT, renal replacement therapy.
[a]Hospital course and outcome in the entire cohort of 631 patients with community-acquired pneumonia who developed acute kidney injury, by statin use.

sepsis. Although a third of patients with AKI were admitted to the intensive care unit, overall intensive care use was similar. However, statins were less likely to be continued in patients who received mechanical ventilation. Overall, 2.5% of patients with AKI received renal replacement therapy during hospitalization. At 1 year, 2% of survivors of AKI were still receiving long-term renal replacement therapy. However, we found no difference in the risk for renal replacement therapy by statin use.

At 1 year, patients receiving statin treatment were less likely to die (Table 4 and Figure 3). When adjusted for differences in age, severity of pneumonia and AKI, use of mechanical ventilation, and health insurance, statin use was marginally associated with lower risk for death at 1 year (OR with prehospital statin use, 0.73 [95% CI, 0.52–1.03], P=0.07; OR with continued statin use, 0.69 [95% CI, 0.48–1.00], P=0.05) (Figure 4). This protective effect of statin was attenuated and no longer significant when adjusted for differences in propensity for statin use (OR with prehospital statin , 0.77 [95% CI, 0.53–1.11], P=0.16; OR with continued statin use, 0.72 [95% CI, 0.50–1.06], P=0.09). In the subgroup of patients with and without pre-existing cardiovascular disease and in those without AKI, we found no difference in the risk for death at 1 year by statin use (data not shown).

Among patients with AKI who died within the subsequent year (36.3%, n=229), cardiovascular disease accounted for a third of all deaths (36.6%), followed by cancer (18%). Infection (16.3%), respiratory disease (11%), renal failure and metabolic complications (7.2%), and other causes (10.8%) accounted for the remaining deaths. Cardiovascular causes of death included atherosclerotic cardiovascular disease, acute myocardial infarction, ischemic heart disease, congestive heart failure, and cerebrovascular accident.

Discussion

In a large, multicenter, prospective cohort study of patients hospitalized with CAP, we found significant differences in baseline characteristics among statin users and nonusers. After adjusting for these differences, we found that statin use was not associated with a lower risk for AKI. On the contrary,

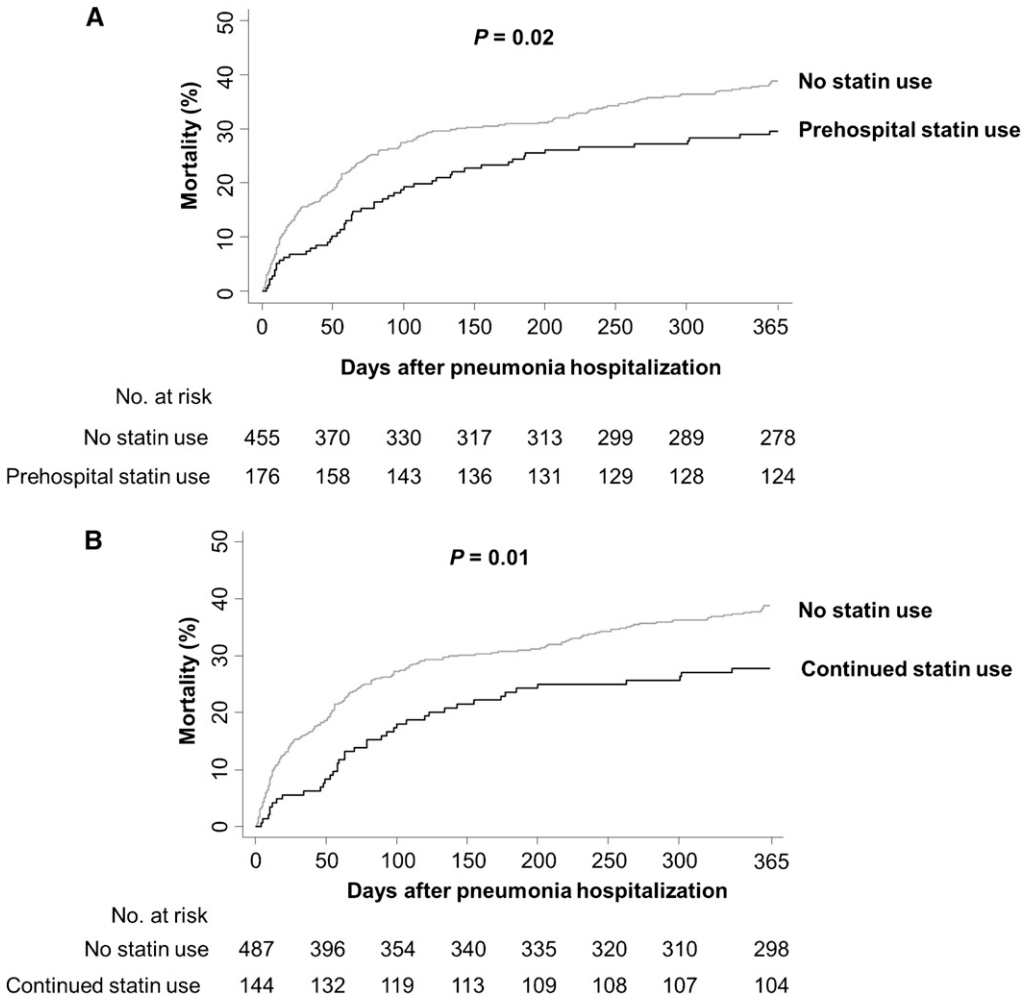

Figure 3. | **Association between statin use and 1-year mortality among patients with acute kidney injury.** The Kaplan-Meier failure plots for probability of death at 1 year was lower among patients with acute kidney injury who received treatment with a statin than those who never received a statin medication before pneumonia hospitalization. (A) Prehospital statin use cohort (log-rank P=0.02). (B) Continued statin use (log-rank P=0.01) cohort.

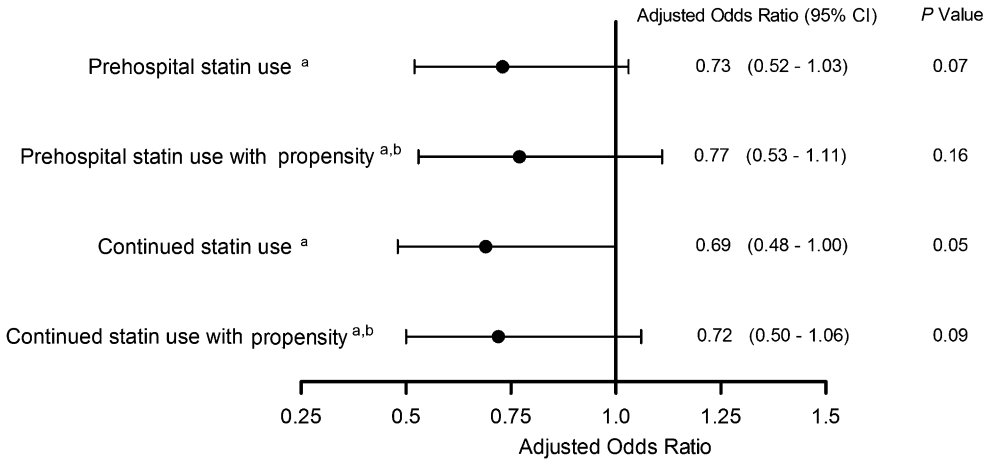

Figure 4. | Multivariable analysis of association between statin use and 1-year mortality in patients with acute kidney injury. Adjusted odds ratios showing no association between statin use and risk for death at 1 year in patients with AKI after community-acquired pneumonia among prehospital and continued statin use cohorts. [a]Odds ratios adjusted for age; pneumonia severity index; severity of acute kidney injury using the Risk, Injury, Failure, Loss and End-stage kidney disease (RIFLE) criteria; and use of mechanical ventilation and health insurance. [b]Variables included in the propensity score were age, history of diabetes, history of cardiovascular disease, long-term aspirin use, long-term anticoagulation use, functional status, and living arrangement before hospitalization for community-acquired pneumonia.

statin use was marginally associated with increased risk for AKI, although this effect was no longer evident after controlling for indication bias. We also did not find an association between statin use and 1-year mortality in patients with AKI. However, we did find that cardiovascular disease accounted for one third of all deaths among patients who died in the year after AKI. This study is, to our knowledge, the first large-scale investigation of the association between statin use and the development of AKI or outcomes of AKI in patients with sepsis.

The reason statin users appeared to have a higher risk for AKI, we believe, lies in the potential source of confounding by indication for statin use. For instance, as one might expect, there was a greater prevalence of diabetes and cardiovascular disease among statin users, which are clinical indications for statin use but are also well known risk factors for AKI. Because statin use is a surrogate for underlying cardiovascular disease, it is likely to have confounded the assessment of association between statins and risk for AKI. We accounted for indication bias by propensity models. However, we found that although the higher risk for AKI was attenuated, there was nevertheless a persistent trend with statin use, especially among those without a history of cardiovascular disease. This may be residual confounding by unmeasured risk factors for AKI.

We also found that the protective effect of statin on mortality was attenuated when adjusted for severity of pneumonia and healthy user effect. The healthy user effect occurs when adherence to a treatment is a surrogate marker for engaging in a broad spectrum of health-promoting behaviors that are themselves linked to the outcome of interest. Indeed, statin users in our study were universally more likely to have healthy user indicators, such as being insured, living at home, being of good functional status, receiving vaccinations, taking a daily aspirin, and quitting smoking, findings supported by other work in this area (16,31,32). Nevertheless, despite accounting for healthy user effect, we found a trend toward mortality benefit among continued users. However, despite being the largest study of AKI in the setting of CAP, this study was still underpowered to detect small but clinically meaningful benefit of statin use. Given that sepsis is a leading cause of AKI (2,4,33) and that there are no specific therapies to improve outcomes from AKI, our findings may warrant further evaluation in larger studies. Because several statin trials are underway or are being planned in various patient population, our study is likely to inform such trial design.

This study has important limitations. First, because the study was observational, our findings are hypothesis generating and cannot prove cause and effect. Second, as a result of small sample size, the precision of estimates of the effect of statins on mortality in patients with AKI could have been biased because of unmeasured confounders. Furthermore, we could only explore the association of statins in general and were unable to determine differences with particular statin agents or doses or assess dose responsiveness.

Third, we could not control for fluid, hemodynamic, and other concurrent interventions that could have influenced course of AKI and outcomes. Fourth, we did not ascertain postdischarge statin use that could have potentially affected long-term mortality in patients with AKI. Fifth, any putative association between statin use and outcomes might be due to chance alone given numerous statistical analyses. Finally, because most of our patients had health insurance (a surrogate for healthy-user effect), we were unable to assess the influence of statins in other populations in the United States, who might not have access to insurance and thus statin use.

Strengths of this study include its prospective nature and the fact that it was specifically designed to explore risk factors for the development of AKI and risk for death at 1 year. We used detailed, prospectively collected information about baseline medical conditions and socioeconomic and functional status to build the propensity scores, and we used a highly sensitive definition for AKI. Such granularity was uncommon in previous studies of statins and studies of

patients with AKI receiving statins, especially those based on administrative datasets (34). We recruited patients at multiple centers so that we could study many participants and determine that our findings were consistent across centers; this suggests that our findings are robust and probably generalizable to patients with CAP elsewhere.

In conclusion, we found no evidence of a protective effect for statin use on the risk for AKI. Thus, we believe statins are unlikely to be useful in the prevention of pneumonia-induced AKI. The slightly increased risk for AKI associated with statin use may be due to residual confounding resulting from indication bias and to unmeasured risk factors for AKI. Among patients with AKI, although a third of deaths were due to cardiovascular disease, statin use was not associated with a lower risk for death at 1 year. However, we were unable to conclusively exclude a small beneficial effect of statins on mortality. This question may warrant further evaluation in larger observational or interventional studies.

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Disclosures

None.

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