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Prehospital Statin and Aspirin Use and the Prevalence of Severe Sepsis and ALI/ARDS

Hollis Ray O'Neal Jr, MD, MSc¹, Tatasuki Koyama, PhD², Elizabeth A S Koehler, MS², Edward Siew, MD, MSCI³, Blake R Curtis, BS⁴, Richard D Fremont, MD⁵, Addison K May, MD⁶, Gordon R Bernard, MD⁴, and Lorraine B Ware, MD⁴

¹ Louisiana State University Health Sciences Center, Department of Medicine, Section of Pulmonary & Critical Care Medicine, Baton Rouge, LA, United States

² Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, United States

³ Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

⁴ Division of Allergy, Pulmonary & Critical Care Medicine, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, United States

⁵ Department of Medicine, Meharry Medical College, Nashville, TN

⁶ Department of Surgery, Vanderbilt University School of Medicine, Nashville, TN

Abstract

Objectives—To determine if prehospital statin use is associated with a lower risk of sepsis, ALI/ARDS, and mortality in critically ill patients. We also investigated the effect of combined prehospital use of both statins and aspirin.

Design—Cross-sectional analysis of a prospective cohort

Patients—575 critically ill patients admitted to the medical or surgical ICU of an academic tertiary-care hospital

Measurements and Main Results—Of 575 patients, 149 (26%) were on statin therapy prior to hospitalization. A multivariable analysis including age, gender, current tobacco use, prehospital aspirin use, race, and APACHE II score revealed that patients on statin therapy prior to hospitalization were less likely to have or develop severe sepsis (OR 0.62, 95% CI 0.40 to 0.96) or ALI/ARDS (OR 0.60, 95% CI 0.36 to 0.99) during the first four ICU days. In-hospital mortality for patients with and without prehospital statin use (OR 1.06, 95% CI 0.62 to 1.83) was similar. Patients who had prehospital use of both statins and aspirin had the lowest rates of severe sepsis, ALI/ARDS and mortality.

Conclusions—Prehospital use of statins may be protective against the sepsis and ALI. This effect may be potentiated by prehospital aspirin use.

Corresponding Author: Hollis R. O'Neal Jr., MD, MSc, Section of Pulmonary and Critical Care Medicine, Department of Medicine: Earl K. Long Medical Center, Louisiana State University, 5825 Airline Highway, Baton Rouge, LA 70805, Phone: (225) 358-1065, Fax: (225) 358-1076, honeal@lsuhsc.edu.

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Keywords

Acute Lung Injury; Acute Respiratory Distress Syndrome; Severe Sepsis; Sepsis; Statin; Aspirin; Inflammation

Introduction

Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS) are common causes of acute respiratory failure with estimated incidences in the U.S. of 78.9 and 58.7 cases per 100,000 person-years, respectively[1]. The mortality of these conditions approaches 40 percent.[1] Despite advances in critical care since the initial description of these syndromes [2], low tidal volume ventilation remains the only specific therapy that has been proven to reduce mortality.[3]

Severe sepsis, the most common cause of ALI/ARDS, is also a common condition with high mortality and limited proven, specific therapies.[4] Since both sepsis and lung injury are prevalent, have a high mortality and limited treatment options, primary prevention may be the best way to combat these syndromes.

Despite differences in affected organ systems and clinical presentation, sepsis and acute lung injury syndromes have similar underlying mechanisms, as they both are characterized by inflammation and endothelial dysfunction.[5–7] Although the role of the inflammatory cascade in the pathophysiology of these syndromes is well described, [5–7] clinical trials investigating the use of anti-inflammatory agents in the treatment of both ALI/ARDS[8–10] and sepsis[11, 12] have been disappointing.

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have a desirable effect on the lipid profile of most individuals. These medications have proven to be effective in both primary [13] and secondary [14] prevention of cardiovascular disease – effects that appear to be independent of effects on the lipid profile.[15] In addition to inhibition of cholesterol synthesis, statins have immunomodulatory and anti-inflammatory effects in a variety of human conditions.[16–20] Because of these pleiotropic effects, statins have been studied as preventive therapy for noncardiovascular conditions such as cancer[21, 22] and venothromboembolism [23] with promising results. Furthermore, several observational studies have suggested that statin therapy may prevent progression to severe sepsis [24] and reduce mortality in patients with infections or bacteremia [25, 26]. Recent data reveal that preadmission statin use may reduce the risk of death among patients admitted to the Intensive Care Unit (ICU)[27]. In addition to beneficial effects in sepsis, animal models suggest that statins may have similar protective effects in ALI/ARDS [28]; however, an observational study did not find that statin therapy altered the course of patients with ALI/ARDS[29].

Aspirin, through its antiplatelet effects, is the cornerstone in both the prevention and treatment of cardiovascular and cerebrovascular disease and is commonly taken in conjunction with statins for primary or secondary prevention of atherosclerotic coronary artery disease. The effect of platelets in the pathogenesis of acute lung injury and sepsis has been studied for decades [30, 31]. Platelets are known to play an important role in mediating an animal model of sepsis-induced lung injury [32]. Platelet inhibition with aspirin attenuates the development of transfusion-related lung injury in an animal model[33]. Because of important differences in platelet/neutrophil interactions between animal models and human lung biology, the role of platelets in clinical ALI/ARDS cannot reliably be extrapolated[34]. Although preadmission aspirin use appeared to have no effect on mortality

in a cohort of patients with pneumonia[35], the effect of anti-platelet therapy with aspirin on the development of acute lung injury syndromes has not been investigated; furthermore, prior clinical studies of statins and sepsis or ALI/ARDS did not consider the potential confounding effects of aspirin use. We performed a cross-sectional analysis of a prospectively collected cohort to test the hypothesis that prehospital use of statins is associated with lower risk of the development of severe sepsis and ALI/ARDS, as well as lower mortality, in critically ill patients. We also examined the association of aspirin use with the development of these clinical syndromes.

Materials and Methods

Study Design

We constructed our study population using data obtained from the first 1004 patients who were prospectively enrolled, between January 23, 2006 and April 1, 2008, in the Validating Acute Lung Injury Markers for Diagnosis (VALID) study. The VALID study was designed to develop and validate plasma biomarkers for use in diagnosis and prognosis of ALI/ARDS. The study protocol was approved by the Vanderbilt University Institutional Review Board, and written informed consent was obtained from the patient or their surrogate at the time of enrollment when possible. Because the study carried minimal risk to the study participants, a waiver of informed consent was granted by the Institutional Review Board.

Patients eligible for the VALID study were those aged 18 or greater admitted to the Medical, Surgical, Cardiovascular and Trauma ICU's who remained in the ICU at least 2 days. Patients were excluded from enrollment into VALID if they were under 18 years of age, were in any other hospital ICU greater than 3 days prior to enrollment, had cardiac arrest prior to enrollment, died or were discharged from the ICU within 48 hours, or if transfer orders were written or anticipated to be written less than four hours from screening and enrollment. Patients were also excluded from VALID if they were admitted to the ICU for an uncomplicated overdose, routine postoperative admission after cardiothoracic surgery or if they had a history of severe chronic lung disease such as severe asthma, chronic obstructive pulmonary disease (COPD) or pulmonary fibrosis.

Upon enrollment into VALID, plasma and urine were collected. Clinical data, including demographics, medical history, hemodynamics, ventilator parameters, medications with dosages (including prehospital medications), and laboratory values were extracted from the medical record. Although data on the specific type of statin used were collected, for the purpose of multivariable analysis, patients on any type of prehospital statin therapy were grouped as "statin users". Severe sepsis was diagnosed by published consensus definitions[36] using clinical data from the time of enrollment and for each of the three following days. ALI/ARDS was diagnosed in a similar manner, using published consensus definitions.[37] All chest radiographs during the first four ICU days were reviewed by at least two investigators to reach consensus on the presence or absence of bilateral pulmonary infiltrates consistent with ALI/ARDS. Adjudication of the diagnoses of severe sepsis and ALI/ARDS was made by review of all pertinent clinical data and chest radiographic findings by at least two investigators for each enrolled patient. Additional clinical data were collected upon enrollment and daily for the next 72 hours to determine if the patient developed organ failures[38], severe sepsis[36], or ALI/ARDS[37]. Neither the diagnosis of severe sepsis nor that of ALI/ARDS was dependent upon the assessment of the treating clinicians. Outcome data were also collected, including need for dialysis, duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, and hospital mortality.

Inclusion/Exclusion Criteria

The first 1004 patients enrolled into the VALID study were considered for inclusion into the cohort. To enrich the cohort for patients likely to be diagnosed with severe sepsis or ALI/ARDS, we excluded patients admitted to the Trauma ICU. To avoid the confounding effects of cardiovascular disease which might be associated both with higher rates of statin use and fewer diagnoses of ALI/ARDS and sepsis, we excluded patients admitted to the Cardiovascular ICU and patients admitted to any ICU with an acute cardiac diagnosis. Finally, because statin use was exceedingly rare in patients less than 40 years of age, only patients 40 years or older were included.

Statistical Analysis

Univariable analyses were conducted using Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for categorical variables. Median values with lower and upper quartiles are reported for continuous variables, and frequencies with proportions are reported for categorical variables. Logistic regression models were developed for the rates of severe sepsis, ALI/ARDS, and death. The explanatory variables of interest were specified before data exploration. Interactions with the main variable (statin use) and other variables were investigated in an exploratory fashion; however, no compelling effects were found, and interaction terms were not considered in the models. The proportions of patients with outcomes of interest are compared based on statin and aspirin use with a Cochran-Armitage test for trend. PASW Statistics (formerly SPSS, version 18.0) was used for database management, and R 2.9.1 [39] was used for statistical analysis; a two-sided significance level of 0.05 was used for statistical inference.

Results

Clinical Characteristics

The final population included 575 patients, 149 of whom used any statin medication prior to hospitalization (Figure 1). Table 1 includes a comparison of baseline characteristics. Overall, the group of prehospital statin users was older, heavier, had higher serum creatinine levels and was more likely to be diabetic, findings consistent with clinical indications for these medications and previously published reports assessing statins as prevention for sepsis and infectious-related complications[24, 25, 40]. A significantly higher percentage of prehospital statin nonusers were Caucasian. Additionally, there was an association between prehospital statin use and prehospital aspirin use. There was no difference in severity of illness (as measured by APACHE II score), gender or tobacco use, presence of malignancy, or illicit drug use between statin users or nonusers.

Specific prehospital statin medications used are listed in Table 1. In the majority of prehospital statin users (92/149, 61.7%), statins were not administered during the first four ICU days. Conversely, statin therapy was initiated in 13 (3.1%) of the 426 patients without known prehospital statin use. This resulted in 70 patients with in-hospital statin use during the first four ICU days. As the preferred statin on the hospital formulary is simvastatin, all but three patients (two with atorvastatin, one with pravastatin) received this medication while in the hospital.

Severe Sepsis and ALI/ARDS

Of the 575 patients included in the final analysis, 119 (20.7%) had ALI/ARDS at the time of enrollment. At the time of enrollment, 25/149 (16.8%) of statin users were diagnosed with ALI/ARDS compared to 94/426 (22.1%) of statin nonusers ($p = .20$). Furthermore, 278 (48.3%) subjects had severe sepsis at the time of enrollment. At the time of enrollment, 61/149 (40.9%) of statin users were diagnosed with severe sepsis compared to 217/426

(50.9%) of statin nonusers ($p = .04$). In total during next three ICU days, an additional 20 patients met diagnostic criteria for severe sepsis and an additional 33 patients met diagnostic criteria for ALI/ARDS (Table 2). For the purpose of analysis, all patients who met diagnostic criteria during the first 4 days in the ICU for severe sepsis [298 (51.8%)] or ALI/ARDS [152 (26.4%)] were considered to be cases. Prehospital statin use was associated with a significantly higher rate of having a diagnosis of severe sepsis (43.0% vs 54.9%, $p = .01$) or ALI/ARDS (19.4% vs 28.9%, $p = .03$) during the first 4 ICU days in a univariable analysis (Table 3). Additionally, we performed a univariable analysis to explore the effect of Type 2 statins (Atorvastatin, Fluvastatin) versus Type 1 statins (Lovastatin, Pravastatin, Simvastatin) on the diagnoses of severe sepsis and ALI/ARDS. There was a trend that patients taking Type 2 statins were less likely to have the diagnosis of severe sepsis than those taking Type 1 statins, though a similar finding was not appreciated on the endpoint of ALI/ARDS (Table 3).

Because the diagnoses of severe sepsis and ALI/ARDS may be collinear (ie, one leads to the other and vice-versa), we explored the association of prehospital statin use on the combined endpoint of severe sepsis and ALI/ARDS. Of the 298 patients who met diagnostic criteria for severe sepsis during the first four ICU days, 126 (43.3%) met diagnostic criteria for ALI/ARDS as well. The combined endpoint of severe sepsis with ALI/ARDS occurred in 22/149 (14.8%) of statin users, and 104/426 (24.4%) of nonusers (OR .54, 95% CI 0.32 – 0.89, $p = .015$).

In a multivariable logistic regression model including age, gender, race, current tobacco use, prehospital aspirin use, and APACHE II score, prehospital statin use was significantly associated with a lower rate of diagnosis of severe sepsis (OR 0.62, 95% CI 0.40 – 0.96, $p = .03$) (Table 4, Figure 2) and ALI/ARDS (OR 0.60, 95% CI 0.36 – 0.99, $p = .05$) (Table 5, Figure 3). APACHE II score was significantly associated with higher risks in both models (severe sepsis: OR 2.35 for increment of 10, 95% CI, 1.87 to 2.95; ALI/ARDS: OR 2.00 for increment of 10, 95% CI, 1.57 to 2.53).

Among prehospital statin users, there was no statistically significant association with the discontinuation of statin therapy during the hospitalization and the subsequent diagnosis of severe sepsis or ALI/ARDS, though the sample size was very small. As noted in Table 2, three patients with prehospital statin use were diagnosed with severe sepsis on days two through four of the study period, with two of these diagnosed in patients in whom statin therapy was discontinued on enrollment. Four patients with prehospital statin use were diagnosed with ALI/ARDS on days two through four of the study period. All four of these patients had statin therapy discontinued on enrollment.

Association Between Prehospital Statin Use and Other Clinical Outcomes

Despite the lower prevalence of ALI/ARDS and severe sepsis in statin users, prehospital statin use had no statistically significant association with ventilator-free days, ICU length-of-stay, and hospital length-of-stay (Table 6). Prehospital statin users were less likely to have or develop hepatic failure (OR 0.23, 95% CI 0.12 – 0.45, $p < .001$) or coagulation failure (OR 0.39, 95% CI 0.24 – 0.62, $p < .001$). There was no statistically significant difference in the development of circulatory failure (OR 0.90, 95% CI 0.57 – 1.44, $p = 0.67$) or renal failure (OR 1.18, 95% CI 0.81 – 1.73, $p = 0.39$).

Mortality

Of the 575 patients in our cohort, 112 (19.5%) died prior to discharge from the hospital. A total of 152 patients met diagnostic criteria for ALI/ARDS, and 298 met diagnostic criteria for severe sepsis within the first four days of ICU admission. Both of these conditions were

associated with increased hospital mortality in univariable analysis; mortality was 32.9% in ALI/ARDS compared to 14.7% in those without ALI/ARDS ($p < .001$) and 27.9% in those with severe sepsis compared to 10.5% in those without severe sepsis ($p < .001$). There was no statistically significant difference in mortality between prehospital statin users and nonusers in a univariate analysis (18.1% vs 20.0%, $p = .72$). Stopping statin therapy in patients with prehospital statin use was not associated with increased mortality (OR 1.3, 95% CI 0.54 – 3.12, $p = 0.56$). In a multivariable analysis including prehospital statin use, age, gender, race, current tobacco use, prehospital aspirin use, and APACHE II score (Table 7, Figure 4), only APACHE II was an independent predictor of mortality. An increase of 10 in APACHE II score corresponds to doubling odds of death (OR 2.02, 95% CI, 1.56 to 2.63) when other variables are held unchanged. Prehospital statin use had no significant association with hospital mortality in this model (OR 1.06, 95% CI 0.62 – 1.83).

Aspirin Use

In a univariable analysis, prehospital use of aspirin (either 81 mg daily or 365 mg daily) had no statistically significant association with death, diagnosis of ALI/ARDS, or diagnosis of severe sepsis. There was a statistically significant association between prehospital statin use and prehospital aspirin use, as 50.3% (75/149) of patients taking prehospital statins were also taking daily aspirin, while only 14.3% (61/426) of those not taking prehospital statins were taking daily aspirin ($p < .001$). Though aspirin had no association with the primary endpoints in univariable analysis, rates of ALI/ARDS, severe sepsis and hospital mortality were lowest in those who received both aspirin and statins prior to hospitalization (Figure 5). In the multivariable analyses, prehospital aspirin use did not have an independent association with the diagnosis of ALI/ARDS or sepsis, or on hospital mortality (Figures 2–4, Tables 3, 4, 7).

Discussion

There are several potential mechanisms for the apparent protective effect of statins in sepsis and ALI/ARDS. The efficacy of statin therapy in reducing cardiovascular risk is well established, even in patients without elevated cholesterol levels[41]. As the understanding of atherosclerosis as an inflammatory disease has progressed[42], researchers have uncovered many mechanisms by which statins modulate the inflammatory response by decreasing inflammation[16] and attenuating endothelial dysfunction[28, 43, 44]. Furthermore, statins have antithrombotic effects[45, 46], a mechanism supported by a large, randomized, controlled trial [23]. There are striking similarities in the pathogenesis of atherosclerosis[42], sepsis[5], and ALI/ARDS[6], including inflammation, endothelial dysfunction, and thrombosis; the effects on any or all of these pathways may contribute to the observed beneficial effect of statins.

In this study of 575 critically patients at high risk for severe sepsis and ALI/ARDS, prehospital use of statins was associated with a lower rate of having or developing severe sepsis or ALI/ARDS during the first four days in the ICU. Our study supports the hypothesis that statin therapy may prevent serious inflammatory conditions such as severe sepsis and ALI/ARDS; however, we did not find any association between prehospital statin use and in-hospital mortality in our cohort of critically ill patients.

Previous observational investigations have also found that patients receiving statin therapy have a reduced risk of developing severe sepsis [24, 40]. Although our findings are congruent with these studies, our study has important differences. Because our cohort consisted entirely of patients admitted to intensive care units, the severity of illness, as determined by APACHE II score, was substantially higher than previously published reports describing statins as protective against the development of sepsis[24]. Also, while other

studies have investigated the protective effect of statins in patients with cardiovascular disease[40], we excluded patients admitted to the cardiovascular ICU and those with a primary cardiac diagnosis because this group might be less likely to have sepsis or ALI/ARDS but be more likely to have prehospital statin use.

In addition to a lower prevalence of severe sepsis, we found that prehospital statin use is associated with a lower prevalence of ALI/ARDS in the first four days of critical illness—a finding which is unique to this investigation. This finding is especially noteworthy considering that prehospital or in hospital statin use in 178 patients with ALI/ARDS did not alter the clinical course in a prior study[29]. Taken together these findings suggest that statins might have a role in preventing the initial inflammatory response which leads to severe sepsis or ALI/ARDS rather than having a therapeutic effect once organ failure or lung injury is established. However, prospective studies are needed to better determine the effects of statins on prevention and treatment of both sepsis and ALI/ARDS since causality can not be inferred from this observational study.

Although prehospital statin use was associated with a decreased rate of diagnosis of ALI/ARDS and severe sepsis, we detected no difference in mortality between prehospital statin users and nonusers. There are several potential explanations for this finding. First, the study was likely underpowered to detect any effect statin use may have on patient mortality. Second, we did not assess such important predictors of mortality as appropriateness or timing of initial antibiotic therapy, tidal volume, or underlying chronic medical conditions. Third, statin therapy was discontinued in the majority of patients after ICU admission; this may have led to a decline in protective effects over the course of hospitalization. Finally, ALI/ARDS and severe sepsis are syndromes that represent the clinical manifestations of severe inflammatory and metabolic dysregulation and derangement. The prevention of these clinical syndromes may not equate with preventing the underlying mechanisms that lead to patient mortality. Though there is concern that the discontinuation of statin therapy upon admission to the ICU increases mortality[47], in our cohort, we did not make this observation.

Animal models suggest that statins may attenuate lung injury by a variety of mechanisms, including modulation of endothelial nitric oxide synthase activity [48, 49] and suppression of leukocyte adhesion and free radical generation[50]. Kor et al[29] were unable to demonstrate that statin therapy affects the course of ALI/ARDS or prevents further organ failures in the setting of established disease; however, the available animal data suggests that statins may prevent lung injury, not modify the course once it has occurred. Furthermore, structural differences have led to the categorization of statins as either Type 1 (simvastatin, lovastatin, pravastatin) or Type 2 (fluvastatin, rosuvastatin, atorvastatin). These structural differences lead to differential binding of the HMG-CoA Reductase complex and may affect potency and biologic activity[51, 52]. In our observations, it appears that the Type 2 statins may be more protective against severe sepsis than the Type 1 statins while both seem equally protective against the development of ALI/ARDS. Although it is not possible to prove causality in an observational study, other investigations also suggest that statins may provide protection from the development of sepsis in both animal models[53–55] and humans [24, 26, 40]; our study supports this finding in a cohort of critically ill patients admitted with noncardiac diagnoses.

In addition to the statins, aspirin, through its antiplatelet effects, has been postulated to attenuate lung injury in animal models [33, 34]. Prior to the current investigation, there have been no studies which have evaluated the effect of aspirin on the clinical syndromes of sepsis and ALI/ARDS, despite the fact that aspirin is commonly used in conjunction with statins for the primary or secondary prevention of coronary artery disease. Although aspirin

alone did not have a significant association with development of severe sepsis or ALI/ARDS, the lowest rates of both severe sepsis and ALI/ARDS were in patients who were taking both statins and aspirin prior to hospitalization (Figure 5). Furthermore, mortality was significantly lower in patients taking both aspirin and statin therapy than in patients taking statins alone or neither medication (Figure 5). These findings suggest that aspirin use might potentiate the protective effects of statins in severe sepsis and ALI/ARDS. However, larger prospective studies will be needed to test this hypothesis.

Because of the observational design of our study, it has several limitations. Importantly, we were unable to control the administration of statin therapy, as patients were prescribed therapy at the discretion of their outpatient physicians. Furthermore, we could neither control the specific agent administered nor the dosage prescribed, and the combinations were too varied to allow for further analysis of individual types or doses of statin drug or aspirin. Because statins are indicated for a number of medical conditions, this study is subject to confounding by these indications as well as the patient's underlying medical condition, as many of these conditions portend a higher mortality. Furthermore, access to healthcare and other socioeconomic factors such as race, language, and level of education may have led to differences in both statin use and outcome. Because we did not measure plasma levels of these medications, we could not verify compliance with the stated medical regimen or assess absorption of the prescribed agent. Finally, our study is subject to the "healthy-user bias," as those who are prescribed medications for the management of chronic medical conditions and primary prophylaxis of cardiovascular disease may be healthier than those who are not prescribed medications for these reasons.

Conclusions

Sepsis and acute lung injury are common syndromes with a high mortality. Statins are proven to be effective in the primary and secondary prevention of atherosclerotic cardiovascular disease, a condition which shares many pathophysiologic pathways with sepsis and ALI/ARDS. We found that prehospital statin use was associated with fewer diagnoses of sepsis and ALI/ARDS in patients admitted to the ICU with critical illness. Given the importance of these conditions, as well as the accepted safety profile and desirable effects of statin therapy, large, randomized, controlled trials should be undertaken to confirm these findings, similar to the studies of statin therapy in the prevention of venous thromboembolism[23]. In addition, aspirin may provide additional benefit, and further investigations should evaluate the possible additive effect of aspirin with statins on the prevention of these syndromes.

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Figure 1.
Study Flow Diagram

Figure 2.
Logistic Regression Analysis for the Diagnosis of Severe Sepsis.

Figure 3.
Logistic Regression Analysis for the Diagnosis of ALI/ARDS.

Figure 4.
Logistic Regression Analysis for In-Hospital Mortality

Figure 5. Percentages of Patients with Severe Sepsis (A), ALI/ARDS (B), or In-Hospital Mortality (C) in Statin Nonusers, Statin Users without Aspirin, and Statin and Aspirin Users. P-values Indicate Chi-Square Test for Trend.

Table 1

Baseline Characteristics

	Statin Users (N=149)	Statin Nonusers (N=426)	P-value
Age	65 (59 – 71)	57 (50 – 64)	<0.001 ¹
Male	56.4 % (84)	56.1 % (239)	1.0 ²
White	80.5 % (120)	88.0 % (375)	0.03 ²
Creatinine, mg/dL (N=144/415)	1.6 (0.9 – 2.4)	1.2 (0.8 – 2.2)	0.005 ¹
APACHE II	24 (20 – 32)	25 (20 – 32)	0.65 ¹
Current Tobacco Use	30.2 % (45)	30.3 % (129)	1.0 ²
Diabetes Mellitus	45.6 % (68)	28.1 % (120)	<0.001 ²
Weight (kg)	80 (70 – 95)	76 (62 – 92)	.011 ¹
Hematocrit	31 (27 – 36.5)	30 (25 – 34)	.001 ¹
Glasgow Coma Score	10 (5 – 14)	9 (4 – 14)	.923 ¹
History of Malignancy	9.4 % (14)	7.3 % (31)	.478 ²
Primary Solid Tumor	8	11	
Metastatic	5	14	
Acute Leukemia	0	1	
Chronic Leukemia	1	3	
Hodgkin's Lymphoma	0	1	
Non-Hodgkins Lymphoma	0	1	
Illicit Drug Use	6.7% (10)	8.9% (38)	.492 ²
Marijuana	8	21	
Cocaine	4	20	
Heroin	1	5	
Methamphetamine	0	2	
Prehospital Aspirin Use	14.3% (61)	50.3% (75)	<.001 ²
Statin used (prehospital)			
Type I Statins			
Pravastatin, % of users (n)	3.4 (5)		
Simvastatin	51.0 (76)		
Lovastatin	10.7(16)		
Type II Statins			
Atorvastatin	22.8 (34)		

	Statin Users (N=149)	Statin Nonusers (N=426)	P-value
Fluvastatin	0.7 (1)		
Rosuvastatin	11.4(17)		

Data given as median (25th percentile, 75th percentile) or percent (number) of patients.

¹Wilcoxon rank sum test

²Fisher's exact test

Table 2

Patients meeting diagnostic criteria for ALI/ARDS and Severe Sepsis by study day

	ALI/ARDS		Severe Sepsis	
	All Cases	Statin *	All Cases	Statin *
Enrollment	119	25	278	61
Day 2	16	4	11	1
Day 3	10	0	6	1
Day 4	7	0	3	1
Total	152	29	298	64

* Denotes cases diagnosed in those with prehospital statin use

Table 3

Univariable Analysis*

	All Statin Users (N=149) Type 1 Users (N = 96) Type 2 Users (N = 53)	P-value[†]	Statin Nonusers (N=426)	P-value
Severe Sepsis	43.0% (64) Type 1: 49.0% (47) Type 2: 32.1% (17)	0.06	54.9% (234)	0.01
ALI/ARDS	19.5% (29) Type 1: 20.8% (20) Type 2: 17% (9)	0.67	28.9% (123)	0.03
Died	18.1% (27) Type 1: 17.7% (17) Type 2: 18.9% (10)	1.00	20.0% (85)	0.72

Data given as percent (number) of patients.

Type 1 Statins: Lovastatin, Pravastatin, Simvastatin

Type 2 Statins: Atorvastatin, Fluvastatin

* Comparisons of Statin Users and Nonusers by Fisher's exact test

[†] Comparisons of Type 1 and Type 2 by Fisher's exact test

Table 4

Logistic Regression Severe Sepsis

	Odds ratio	95% CI	P-value
Prehospital statin use	0.62	0.40 – 0.96	0.03
Age	0.94	0.79 – 1.12	0.47
Gender = Male	0.84	0.59 – 1.19	0.32
Current Tobacco Use	1.14	0.77 – 1.68	0.52
Race = White	1.23	0.73 – 2.06	0.44
Prehospital aspirin use	1.02	0.64 – 1.60	0.95
APAHCE-II score	2.35	1.87 – 2.95	< 0.001

Odds ratio for age is for increment of 10 years

Odds ratio for APACHE-II score is for increment of 10

Table 5

Logistic Regression ALI/ARDS

	Odds ratio	95% CI	P-value
Prehospital statin use	0.60	0.36 – 0.99	0.048
Age	1.05	0.87 – 1.28	0.61
Gender = Male	0.82	0.56 – 1.22	0.33
Current Tobacco Use	1.28	0.83 – 1.96	0.26
Race = White	0.83	0.48 – 1.44	0.51
Prehospital aspirin use	0.86	0.51 – 1.44	0.56
APACHE II score	2.00	1.57 – 2.53	< 0.001

Odds ratio for age is for increment of 10 years

Odds ratio for APACHE II score is for increment of 10

Table 6

Effect of prehospital statin use on Ventilator days, ICU Length-of-Stay, and Hospital Length-of-Stay

	Statin Users (N=149)	Statin Nonusers (N=426)	P-value
Ventilator days	2 (0, 7)	3 (0, 6)	0.72
ICU Length-of-stay	5 (3, 11)	6 (4, 10)	0.25
Hospital Length-of-stay	10 (6, 22)	12 (7, 22)	0.24

Data given as median (25th percentile, 75th percentile)

Table 7

Logistic Regression Mortality

	Odds ratio	95% CI	P-value
Prehospital statin use	1.06	0.62 – 1.83	0.82
Age	1.05	0.84 – 1.30	0.67
Gender = Male	0.97	0.63 – 1.50	0.89
Current Tobacco Use	0.87	0.53 – 1.42	0.57
Race = White	1.82	0.90 – 3.67	0.09
Prehospital aspirin use	0.65	0.36 – 1.17	0.15
APACHE II score	2.02	1.56 – 2.63	< 0.001

Odds ratio for age is for increment of 10 years

Odds ratio for APACHE II score is for increment of 10