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Statins and Outcomes in Patients with Bloodstream Infection: A Propensity-Matched Analysis

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Abstract

Background—The pleiotropic effects of statins, 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitor, have been shown to modify inflammatory cell signaling on the immune response to infection. It was postulated that statins may be a good candidate as novel therapeutic agents for the treatment of sepsis.

Objective—We investigated whether ongoing statin therapy is associated with mortality in patients with bloodstream infection.

Design—A retrospective cohort study

Setting—Two tertiary hospitals in Bronx, New York

Patients—Adult patients in the hospital with bloodstream infection and categorized according to statin therapy as an outpatient or inpatient prior to bacteremia.

Intervention—None.

Measurement and Main Results—Of 2139 bacteremic hospitalized patients, 592 (28%) received statins prior to blood cultures and 677 (32%) died within 90-days. On multivariate adjustment, the association between statin therapy and 90-day all-cause mortality was statistically significant (HR 0.78; 95% C.I. 0.65 – 0.94) but statin users and non-users differed significantly on many baseline clinical factors. Using the propensity score matched analysis to balance the differences between groups, the association was no longer significant (HR 0.99, 95% CI 0.77 – 1.25). Multivariate analysis after stratifying by decile in propensity score for statin use demonstrated similar results (HR 0.86; 95% CI 0.70 – 1.06). Statin use was not associated with reduced ICU admission (OR 0.86; 95% CI 0.59 – 1.26), hospital LOS (β = –0.8 days, 95% CI –2.2 – 1.7 days), ICU LOS (β = –0.1 days, 95% CI –3.7 – 3.8 days), or need for mechanical or non-invasive ventilation (OR 1.03; 95% CI 0.70 – 1.51).

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Conclusion—After adjusting for the propensity to receive statin therapy, no statistically significant association between statin therapy prior to bloodstream infection and survival was identified.

Keywords

statins; bacteremia; sepsis; propensity score analysis; mortality; cohort study

INTRODUCTION

The hallmark of sepsis syndrome is an intense inflammatory response. The pathogenesis of the conditions is now becoming better understood. Increasing evidence implicates the production of proinflammatory cytokines, adhesion molecules, vasoactive mediators and reactive oxygen species in the immuno-inflammatory process common to both systemic inflammatory response syndrome and sepsis (1).

Statins inhibit 3-hydroxy-3 methylglutaryl coenzyme A (HMG CoA) reductase and recently have been postulated to have beneficial effects on anti-inflammatory and immunomodulatory. Moreover, statins may have a direct antimicrobial effect (1). Early data suggest statins to be beneficial before and after septic insults. When mice were challenged with endotoxin lipopolysaccharide, pretreatment of statins restored responsiveness to the vasopressor phenylephrine by reducing nitric oxide production (2). In healthy volunteers treated with *E. coli* endotoxin, simvastatin was able to restore radial artery responsiveness to norepinephrine and acetylcholine (3). In Buerke et al., pretreatment with simvastatin protected against *S. aureus* alpha-toxin-induced sepsis associated with reduced p53, TNF-alpha, apoptosis, and necrosis with improvement in systemic hemodynamics, coronary perfusion pressure and myocardial function in a mouse model (4). In Merx et al., mice treated with statins hours after a septic insult demonstrated significantly increased survival times due to the restoration of cardiac function and hemodynamic status (5).

Statins may be a good candidate as novel therapeutic agents for the treatment and prevention of sepsis. To date, there was no large randomized controlled trial investigating the role of statins in sepsis. Three observational studies published for patients particularly with bacteremia over the past 10 years in which two of them showed potential benefits (6, 7, 8). However, each study had its imperative limitations. In general, they all demonstrated that the baseline characteristics and comorbidities were clearly different between groups, thus, susceptible to confounding by indications for statin therapy. In addition, the definition of statin use was dissimilar in all three studies. In Thomsen et al., the data of statin use was retrieved from an outpatient prescription database with a lack of data on inpatient use when the patients were hospitalized with bacteremia (6). Liappis et al. only included patients taking statins throughout the course of hospitalization which may indicated these patients were clinically more stable to allow a continuation of statin therapy that may result in selection bias (7). Despite a potential benefit, the types of statins were not examined.

The objective of this study was to further define the association between statin therapy and mortality among hospitalized patients with bacteremia after accounting for baseline differences between statin users and non-users. We hypothesize that patients on statin therapy prior to bacteremic episode would have improved hospital survival compared to bacteremic hospitalized patients not on statins.

METHODS

Study Subjects and Design

We performed a retrospective cohort study of patients with culture positive bacteremia at Weiler Hospital and the Moses Division of the Montefiore Medical Center (both in Bronx, New York) from January 1, 2008 to December 31, 2009. Patients were eligible for inclusion if they were 18 years or older and had at least one documented positive blood culture during hospitalization. Bacteremia was defined as one or more blood cultures positive for potential pathogenic organism isolated from a patient during hospitalization. For common skin contaminant (Table supp.), two or more positive blood cultures drawn on separate occasions were required for bacteremia (9). Patients were excluded in whom all organisms identified from the blood culture are considered to be common skin contaminants. For patients with multiple episodes of bacteremia within the same admission, only the first episode of bacteremia was analyzed. This study was approved by the Montefiore Medical Center institutional review board and the need for patient consent was waived.

Data Collection and Measurement

The exposure of interest was ongoing statin therapy at the time of positive culture for bacteremia. Statin therapy was defined as administration of any statin medication at the time blood culture was sampling and/or documentation of statin use as an outpatient prior to hospitalization if the bacteremic blood culture was drawn within 24 hours of admission. We identified 592 patients who had received statin therapy, in which 551 (93.1%) received treatment as outpatient and 173 (29.2%) received treatment as inpatient prior to sampling of blood culture. One hundred and eighty patients discontinued statin therapy after sampling of blood culture and 412 patients continued their statin therapy during their hospitalization. For those who received statin therapy during hospitalization, the minimal number of days of statin administration was one day at the time of blood culture sampling. Chart review was used to extract information on outpatient medication and the site of infection. The electronic patient record was reviewed to isolate data on physiological parameters, laboratory parameters, inpatient medication record, use of mechanical ventilation and non-invasive positive pressure ventilation (NIPPV), intensive care unit (ICU) admission and transfer, ICU and hospital length of stay (LOS) and in-house mortality. The definition of sepsis was fulfilling two or more following criteria and a proven infection: temperature more than 100.4°F or less than 96.5°F; heart rate greater than 90 beats per minute; respiratory rate greater than 20 breaths per minute and white blood cell greater than 12,000 cells/mm³ or less than 4,000 cells/mm³ (10). A random sample of 5% of the charts was reassessed to verify data entry and to ensure accuracy.

Study Outcomes

The primary study outcome was 90-day all-cause mortality from date of sampling of blood culture which was based on a publicly available database - Social Security Death Master File. The Social Security Administration receives approximately 90% of its death notifications from funeral homes, friends, and relatives of the deceased, 5% from postal authorities and financial institutions, and 5% are derived from computer matches with federal and state agency data. The file is updated on a weekly basis. The date of death of the deceased was obtained by matching the social security number from the database. In our cohort of 2177 patients with eligible bacteremia, 2129 (97.8%) had social security number. Of the remaining 48 patients, ten expired during hospitalization. Since we could not determine the survival data on the other 38 (1.7%) patients who had missing social security number, they were excluded from the final cohort. Secondary outcome included ICU admission, ICU and hospital LOS and acute respiratory failure indicated by the need of mechanical ventilation and NIPPV.

Statistical Analysis

Baseline characteristics of the study groups were compared with the Fisher's exact test for categorical variables and *t* test for continuous variables. Non-normally distributed continuous variables were analyzed with Wilcoxon rank sum test.

Stepwise backward Cox proportional hazards regression was used to determine factors associated with 90-day all-cause mortality. The initial model consisted of all the independent variables that have a $p < 0.25$ in the bivariate analysis. Variables were removed one at a time if it did not contribute to the model assessed by the likelihood ratio test ($P < 0.05$) and they did not contribute to the model as a confounder defined by change in estimate of 15% of the beta coefficient for the variable. We then expanded the model to include interaction terms with statins and biological plausible independent variables (age, gender, race, body mass index and charlson's score). No interaction was found ($p > 0.192$). To evaluate whether there is any violation of the Cox proportional hazard assumptions, graphical approach using log-log plots and statistical approach using goodness-of-fit with Schoenfeld residuals were employed and no violations were found.

The major limitation of observational studies is unequal distributions of important covariates between comparison groups since random assignment is impossible. To minimize biases, propensity score analysis was employed. Variables were chosen for inclusion into the propensity score calculation according to the methods of Brookhart et al. and included variables associated with statin use (age, gender, race, body mass index, use of beta blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blockers (ARBs) and aspirin, history of myocardial infarction, cerebrovascular accident, congestive heart failure, peripheral vascular disease, diabetes mellitus with and without complications, pulmonary disease, mild liver disease, renal disease, malignancy, HIV/AIDS, and dementia) and variables associated with the outcome (nursing home residents, hospital acquired infection, recent admission within 2 months, pneumonia, unknown source of infection, sepsis, acute physiology age chronic health evaluation (APACHE) II, low systolic blood pressure, low diastolic blood pressure, bradycardia, tachycardia, tachypnea, hypothermia, hyperthermia, hypoalbuminemia, high INR and low platelets, elevated aspartate transaminase and alanine transaminase, and low bicarbonate (11)).

For the propensity score analysis, two approaches were employed. First, users and non-users were matched by propensity score using conventional greedy algorithms with nearest neighbor matching minimizing the absolute difference between PS, with no match exceeding the predetermined caliper of 0.25 of standard deviation of the sample estimated propensity scores. A 0.015 caliper of propensity was used. Secondly, multivariate analysis was used after stratification by deciles of propensity score. The Breslow-Day test for homogeneity of the hazard ratios was performed, and the Mantel-Haenszel estimate of the pooled hazard ratio was determined. This approach allowed full use of the data and also stratum-by-stratum estimates of the statins hazard ratio.

To address the association of statins in bacteremic patients who fulfill criteria for sepsis, we performed a sensitivity analysis with an adjusted Cox regression restrictive to those patients (1735 out of 2139) who met the criteria of sepsis within 24 hours before or after the bacteremic episode. The logistics were the same as those for performing multivariate Cox regression described above. Furthermore, to account for the lack of independence between cohorts induced by matching, a sensitivity analysis using unadjusted Cox regression stratified on the matched pairs was performed.

For secondary outcomes of ICU and hospital LOS, multivariate linear regression model was employed. Stepwise backward multivariate linear regression was used to determine factors

associated with LOS. The model consisted of all the independent variables that have a $p < 0.25$ in the bivariate analysis. Variables were removed one at a time after determining that there was no significant change in the regression coefficient of statins ($<15\%$). Potential effect modifiers were explored, and interaction between all the variables and statins with biological plausibility was tested and no interaction was found ($p>0.428$). Histogram, pp-plot confirms normality of raw, standardized and studentized residuals. Residual-versus-fitted and residual-versus-predictors and cpr plot with LOWESS graphically confirmed that the assumptions of linearity and equal variance were not moderately violated.

For secondary outcomes of acute respiratory failure, a surrogate marker as the need of mechanical ventilation and/or NIPPV was analyzed using stepwise backward multivariate logistic regression methods. The logistics were the same as those for performing multivariate linear regression described above.

All statistical analyses were performed using Stata version 11.2 (StataCorp, College Station, Texas) software with 2-sided tests. $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

During the two-year period, 2,139 patients were hospitalized with the first episode of bloodstream infection; of whom 49% were men with a mean age of 64 ± 17 years. Statin therapy was administered to 592 (27.7%) patients with bacteremia (Fig. 1). Overall, there were a total of 451 patients on simvastatin, 98 on atorvastatin, 8 on pravastatin, 24 on lovastatin and 11 on rosuvastatin who were taking statins as an outpatient and/or inpatient prior to bacteremia.

The baseline demographics, preexisting medical conditions, and relevant clinical, physiologic, and laboratory parameters of the study groups are summarized in Table 1. Statin users were older with higher body mass index, and they were less likely to receiving antibiotics within six hours, had higher rates of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, pulmonary disease, diabetes, and renal disease while non-statin users acquired more infections during hospitalization and had more malignancy, HIV/AIDS and less mild liver disease (Table 1). Use of β blockers, ACE inhibitors, ARBS, and aspirin was higher in the statin group. Statin users had higher APACHE II score, but less sepsis syndrome than non statin users. Vascular access catheter infections and urinary tract infection were higher in the statin group while respiratory and unknown source of infection as well as *streptococcus pneumoniae* infections were higher in the non-statin group. Serum creatinine and white cell counts were higher in the statin group on the day of culture positive, while serum albumin, bicarbonate and platelet count were lower in the non-statin group.

In creating a propensity score for each subject, thirty-two were excluded because no propensity score was assigned due to missing data. Propensity score matches were found for 447 (75.5%) out of 592 patients receiving statin therapy. The matching process eliminated all significant differences that existed between both groups regarding patient demographics, epidemiologic factors, preexisting medical conditions, physiologic and laboratory parameters, source of infection, and acquired pathogens (Table 1). Only significant differences between groups found were the higher percentage of patients received antibiotics within 6 hours at the time of bacteremia in the non-statin group (Table 1).

Mortality

The main clinical outcomes are shown in Table 2. All cause in-house and 90-day mortality, ICU admission and use of mechanical ventilation were statistically-significant higher in the non statin group in the bivariate analysis. In the unmatched cohort, the adjusted Cox proportional hazards model showed a 22% decreased hazard in death in the statin users compared to the non-statin and it was statistically significant [hazard ratio (HR) 0.78; 95% C.I. 0.65 – 0.94].

We performed a propensity score matched analysis between statin users and non-users based on caliper matching as outlined above. The mean and standard deviation of the propensity score of the statin and non-statin groups were 0.39 ± 0.20 and 0.38 ± 0.20 respectively. In the adjusted Cox analysis, there was no statistically-significant association between statin therapy and 90-day all-cause mortality (HR 0.99, 95% CI 0.77 – 1.25). The details of the multivariate Cox analysis are shown in Table 3. In a subgroup analysis for different types of statins compared to non users, there was no association with 90-day mortality (Table supp). Furthermore, statins use and 90-day mortality did not differ between gram positive bacteremia caused by exotoxin (HR 0.91, 95% CI 0.72 – 1.15) and gram negative bacteremia caused by endotoxin (HR 1.10, 95% CI 0.87 – 1.39).

We further confirmed the results by performing an adjusted analysis stratified by deciles of propensity score was shown in Table 3. There were residual heterogeneity within strata as indicated by strata specific hazard ratio ranging from 0.68 (95% CI 0.37 – 1.25) to 1.18 (95% CI 0.62 – 2.24) and by the Breslow-Day test for homogeneity ($p=0.956$). The pooled hazard ratio from the Mantel-Haenszel test was found to be 0.88 (95% CI 0.72 – 1.07). Among the 2,105 patients included in the adjusted Cox model matched by deciles of propensity score, 663 (31.5%) died within ninety days from the onset of bacteremia. Mortality over ninety days was not significantly reduced with statin therapy (160 of 681 [27.5%] vs. 503 of 1524 [33.0%]; HR 0.88; 95% CI 0.72 – 1.07) (Table 3). The details of multivariate Cox analysis are presented in Table 4.

Sensitivity Analyses

Since the hypothesis of statin use is to target the systemic inflammatory response to infection. To investigate this further, additional Cox regression model on performed on patients who met the sepsis criteria. There were 350 in the statin treatment group and 358 in the non treatment group. The mean and standard deviation of the propensity score of the statin and non statin groups were 0.38 ± 0.20 and 0.37 ± 0.21 respectively ($p=0.683$). In the adjusted Cox analysis, there was no statistically-significant association between statin therapy and 90-day all-cause mortality (HR 0.86, 95% CI 0.66 – 1.12).

A second approach to the sensitivity analyses was conducted that an unadjusted Cox regression stratified on the matched pairs to account for the lack of independence between cohorts induced by matching. The pooled hazard ratio from the Mantel-Haenszel test was found to be 1.00 (95% CI 0.77 – 1.30).

Secondary Outcomes

The main secondary clinical outcomes were shown in Table 2. The need for mechanical ventilation/NIPPV, ICU admission, ICU LOS and hospital LOS were not significantly different in the two groups.

DISCUSSION

In this present work, we aimed to better define the association between statin therapy and survival after bacteremia. While the crude analysis indicated a protective effect with statin therapy in patients with bacteremia, there were numerous significant differences in the baseline characteristics and clinical parameters between the groups, indicating that the propensity of receiving statins was intrinsically different. To address confounding by the indication for statin use, a propensity score analysis was used. In the propensity score matched analysis, the association disappeared. The adjusted analysis by deciles of propensity score further confirmed this finding. For the secondary outcomes, statin therapy was not associated with the reduction of ICU admission, ICU and hospital length of stay or acute respiratory failure.

Over the last decade, statins has been studied extensively in the animal model and the preclinical evidence has been promising. However, in the clinical setting, observational studies in humans have shown mixed results (6, 7, 8). A recent meta-analysis from Tleyjeh and colleagues was carefully carried out (12). The role of statins was analyzed separately between the treatment and prevention cohorts. In the nine treatment cohorts (3 on bacteremia, 3 on pneumonia, 2 on sepsis and 1 on bacterial infection), the pooled adjusted effect estimate was 0.55 (95% CI 0.35 to 0.83) in favor of statins. The author pointed out that there was evidence of heterogeneity and publication bias. Among the three studies that examined patients with bacteremia, the sample sizes of the statin groups were small (ranging from 35 to 176 patients) (6, 7, 8). The baseline characteristics and comorbidities were evidently different between the groups. The cohort from Liappis et al. was in a veterans' hospital with predominately male (99.5%) patients. The study was also restricted only to gram negative bacilli and *Staphylococcus aureus* pathogens. They found that statins decreased 87% risk of all-cause in-hospital mortality with a widened 95% confidence interval between 0.11 and 0.99 (7). However, no other prognostic predictor, including age or comorbidity was reportedly associated with mortality in their model. In Thomsen et al., the prevalence of statin use was extremely low (3.3%). They used the prescription of statins from a pharmacy database as a surrogate for statin therapy (6). This long-term adherence of statin users may be a marker for unmeasured factors associated with a better prognosis and attributed to healthy user effect. Nevertheless, the study did not show a mortality benefit at the 30-day mark (HR 0.93, 95% CI 0.66 – 1.30). Lastly, Kruger et al. studied 438 patients with bacteremia. Sixty-six patients were prescribed with statin prior to admission, and 56 of them continued statin therapy during their bacteremia episode. Mortality was lower in the statin group (OR 0.06; 95% CI 0.0008 – 0.43), but it raised a concern as to whether these patients are clinically more stable to allow a continuation of statin therapy (8).

The definitive way to answer our research question would be to conduct a large clinical trial in which patients are randomized to receive statin therapy with suspected bacteremia upon admission, and to determine whether statin therapy would improve survival after an eligible bloodstream infection. One randomized prospective trial involved 150 subjects investigated the benefit of continuation of statin in sepsis in patients already on statin (13). No survival benefit to continuing statin therapy was found after accounting for differences between groups. Currently, there are a few RCTs ongoing, including the HARP 2 trial (Hydroxymethylglutaryl-CoA reductase inhibition with simvastatin in Acute lung injury to Reduce Pulmonary dysfunction ISRCTN88244364) and the SAILS trials (Statins for Acutely Injured Lungs from Sepsis, clinicaltrials.gov identifier NCT00979121). They both aim to examine the effect of statins in acute lung injury.

Statins seems to influence a broad array of pathogenic microorganisms and appears to decrease the infectivity and replication rates of a number of microorganisms. However,

whether statins have the same effect on endotoxin and exotoxin has not been examined. In our study, we failed to show that statins has a different effect between these toxins.

Our study has a number of notable strengths. Unlike other several prior investigations, baseline differences between patients prescribed statins and those who were not were more rigorously accounted for and balanced between statin users and non-users with propensity score analysis. In addition, other cardiovascular medications, such as β blockers, aspirin, ACE inhibitors and ARBS, were adjusted in the model, since very often, patients who are on statin therapy are also treated with these medications. Also, the sample size of the statin group as well as the matched cohort was the largest compared to other bacteremia cohort. Lastly, distinct from all other observational studies, we included the types of statins used in our study.

We acknowledge the retrospective observational design of the present study. Even as propensity score matching was employed; these results do not account for important unmeasured confounding, e.g. inappropriate empirical antimicrobial treatment and patients who were in septic shock. However, we included the APACHE II score at the time of blood culture sampling which serves as a surrogate of severity of illness. Secondly, while we only examined patients with bloodstream infections, we did not include all patients with sepsis. Thirdly, we did not have data on indications or duration of statin therapy prior to admission.

CONCLUSION

In this retrospective, large cohort propensity matched study, we were not able to find evidence of survival benefits with statin therapy. Statin therapy was not associated with reducing acute respiratory failure, ICU admission, ICU and hospital LOS. Given that the discrepant findings from observational studies and preclinical evidence, a large RCT administering statins as a therapeutic agent in patients with bacteremia is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Terblanche M, et al. Statins and sepsis: multiple modifications at multiple levels. *Lancet Infect Dis*. 2007 May; 7(5):358–368. [PubMed: 17448939]
2. Giusti-Paiva A, et al. Simvastatin decreases nitric oxide overproduction and reverts the impaired vascular responsiveness induced by endotoxic shock in rats. *Shock*. 2004; 21:271–275. [PubMed: 14770041]
3. Pleiner J, et al. Simvastatin prevents vascular hyporeactivity during inflammation. *Circulation*. 2004; 110:3349–3354. [PubMed: 15520323]
4. Buerke U, et al. Apoptosis contributes to septic cardiomyopathy and is improved by simvastatin therapy. *Shock*. 2008 Apr; 29(4):497–503. [PubMed: 18598004]
5. Merx MW, et al. Statin treatment after onset of sepsis in a murine model improves survival. *Circulation*. 2005; 112:117–124. [PubMed: 15998696]
6. Thomsen RW, et al. Statin use and mortality within 180 days after bacteremia: a population-based cohort study. *Crit Care Med*. 2006 Apr; 34(4):1080–1086. [PubMed: 16484926]

7. Liappis AP, et al. The effect of statins on mortality in patients with bacteremia. *Clin Infect Dis*. 2001 Oct 15; 33(8):1352–1357. [PubMed: 11565076]
8. Kruger P, et al. Statin therapy is associated with fewer deaths in patients with bacteraemia. *Intensive Care Med*. 2006 Jan; 32(1):75–79. [PubMed: 16283159]
9. http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABSCurrent.pdf
10. Levy MM, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003 Apr; 31(4):1250–1256. Review. [PubMed: 12682500]
11. Brookhart MA, et al. Variable selection for propensity score models. *Am. J. Epidemiol*. 2006 Jun; 163(12):1149–1156. [PubMed: 16624967]
12. Tleyjeh IM, et al. Propensity score analysis with a time-dependent intervention is an acceptable although not an optimal analytical approach when treatment selection bias and survivor bias coexist. *J Clin Epidemiol*. 2010 Feb; 63(2):139–140. [PubMed: 19913387]
13. Kruger PS, et al. Continuation of Statin Therapy in Patients with Presumed Infection: A Randomised Controlled Trial. *Am. J. Respir*. 2011 Mar 15; 183(6):774–781.
14. Knaus WA, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985 Oct; 13(10):818–829. [PubMed: 3928249]

† These were normal oral flora pathogens and common skin contaminant (See Supplementary for the list of pathogens)

Figure 1.
Flowchart of Selection of Study Patients

Table 1

Unmatched and Propensity Score-matched Baseline Characteristics

Characteristic	Unmatched Cohort			Propensity Matched Cohort		
	Statin Users n=592	Non Statin Users n=1547	P value	Statin Users n=447	Non Statin Users n=458	P value
Demographics						
Age, mean (SD), year	69.5 (13.4)	62.3 (17.9)	<0.001	69.2 (13.8)	70.3 (15.4)	0.25
Men, No. (%)	297 (50.2)	748 (48.4)	0.47	228 (51.0)	234 (51.1)	0.99
Ethnicity, Hispanic, No. (%) [n=778]	222 (37.5)	543 (35.1)	0.56	159 (35.6)	162 (35.4)	0.99
Race, No. (%)						
White	143	362		113	112	
Black	195	574	0.39	149	164	0.81
Others	101	261		77	83	
Unknown	153	350		108	99	
BMI, median [IQR]	27.3 (23.9, 32.8)	26.6 (22.6, 31.0)	<0.001	27.0 (23.6, 32.3)	27.6 (24.0, 32.3)	0.36
Source of Admission, No. (%)						
Home	453	1196		333	332	
Nursing home/Facility	127	311	0.64	103	114	0.81
Transfer from other institutions	12	40		11	12	
Recent admission 2 mths, No. (%)	200 (33.8)	498 (32.2)	0.50	151 (33.8)	157 (34.3)	0.89
Admit location, No. (%)						
General Medicine/Surgical Ward	553	1361		410	409	
Progressive Care Unit	1	7	<0.01	1	3	0.35
ICU	38	179		36	46	
Comorbid diseases, No. (%)						
Previous myocardial infarction	177 (29.9)	159 (10.3)	<0.001	111 (24.8)	101 (22.1)	0.35
Congestive heart failure	282 (47.6)	404 (26.1)	<0.001	192 (43.0)	194 (42.4)	0.89
Peripheral vascular disease	191 (32.3)	217 (14.0)	<0.001	118 (26.4)	121 (26.4)	0.99
Cerebrovascular accident	167 (28.2)	225 (14.5)	<0.001	98 (21.9)	107 (23.4)	0.63
Dementia	44 (7.4)	94 (6.1)	0.28	31 (6.9)	35 (7.6)	0.70
Pulmonary disease	238 (40.2)	507 (32.8)	<0.001	171 (38.3)	176 (38.4)	0.99

Characteristic	Unmatched Cohort			Propensity Matched Cohort		
	Statin Users n=592	Non Statin Users n=1547	P value	Statin Users n=447	Non Statin Users n=458	P value
Rheumatological disease	32 (5.4)	81 (5.2)	0.91	22 (4.9)	29 (6.3)	0.39
Mild liver disease	39 (6.6)	204 (13.2)	<0.001	35 (7.8)	33 (7.2)	0.80
Diabetes	366 (61.8)	533 (34.5)	<0.001	246 (55.0)	252 (55.0)	0.99
Diabetes with complications	261 (44.1)	258 (16.7)	<0.001	152 (34.0)	156 (34.1)	0.99
Hemiplegia or Quadriplegia	34 (5.7)	73 (4.7)	0.32	28 (6.3)	26 (5.7)	0.78
Renal disease	282 (47.6)	387 (25.0)	<0.001	186 (41.6)	188 (41.1)	0.89
Malignancy	122 (20.6)	402 (26.0)	0.01	93 (20.8)	103 (22.5)	0.57
Moderate to Severe liver disease	124 (21.0)	375 (24.2)	0.11	91 (20.4)	96 (21.0)	0.87
Metastatic cancer	36 (6.1)	133 (8.6)	0.06	29 (6.5)	30 (6.6)	0.99
HIV/AIDS	8 (1.4)	117 (7.6)	<0.001	7 (1.6)	6 (1.3)	0.79
Charlson score, median [IQR]	5 (3, 8)	4 (2, 7)	<0.001	4 (2, 7)	5 (2, 8)	0.77
Medications, No. (%)						
Beta blocker	352 (59.5)	440 (28.4)	<0.001	233 (52.1)	231 (50.4)	0.64
ACE inhibitor	204 (34.5)	242 (15.6)	<0.001	143 (32.0)	136 (29.7)	0.47
ARBs	75 (12.7)	69 (4.5)	<0.001	41 (9.2)	38 (8.3)	0.72
Aspirin	280 (47.3)	275 (17.8)	<0.001	184 (41.2)	174 (38.0)	0.34
Physiologic Parameters						
Sepsis, No. (%)	448 (77.1)	1239 (81.3)	0.03	349 (78.1)	357 (78.0)	0.99
APACHE II, median [IQR]	16 (12, 21)	15 (11, 20)	<0.01	16 (12, 21)	16 (12, 20)	0.70
Laboratory Parameters						
Albumin, mean (SD), g/dL	3.0 (0.6)	2.8 (0.7)	<0.001	3.0 (0.7)	2.9 (0.7)	0.08
Bicarbonate, high, mean (SD), meq/L	24.3 (4.3)	23.7 (4.7)	<0.01	24.4 (4.4)	24.3 (4.5)	0.77
Bicarbonate, low, mean (SD), meq/L	20.7 (4.8)	20.1 (5.1)	0.02	20.7 (4.8)	20.9 (4.7)	0.51
ALT, median (IQR), U/L	27 (17, 41)	27 (18, 47)	0.10	27 (17, 39)	27 (18, 38)	0.95
AST, median (IQR), U/L	36 (24, 48)	36 (25, 68)	0.01	36 (23, 47)	36 (24, 55)	0.22
WBC, high, median (IQR), K/uL	15.1 (10.9, 20.2)	14.6 (9.5, 20.3)	0.05	14.9 (10.7, 20.0)	15.8 (11.3, 21.4)	0.14
WBC, low, median (IQR), K/uL	10.6 (7.5, 14.6)	9.9 (6.2, 14.6)	0.01	10.4 (7.4, 14.6)	11.2 (7.6, 15.7)	0.12
Creatinine, median (IQR), mg/dL	1.9 (1.2, 4.0)	1.4 (0.9, 2.7)	<0.001	1.8 (1.1, 3.7)	1.7 (1.1, 3.4)	0.36
INR, median (IQR)	1.2 (1.0, 1.4)	1.2 (1.1, 1.4)	0.14	1.2 (1.1, 1.4)	1.2 (1.1, 1.4)	0.17

Characteristic	Unmatched Cohort			Propensity Matched Cohort		
	Statin Users n=592	Non Statin Users n=1547	P value	Statin Users n=447	Non Statin Users n=458	P value
Platelet, median (IQR), K/uL	172 (122, 229)	162 (95, 237)	0.02	170 (119, 228)	174 (116, 254)	0.49
Source of Infection, No. (%)						
Respiratory infection	96 (16.2)	332 (21.5)	<0.01	81 (18.1)	78 (17.0)	0.73
Abdomen	54 (9.1)	126 (8.1)	0.49	40 (9.0)	39 (8.5)	0.91
Pancreatitis	2 (0.3)	12 (0.8)	0.37	2 (0.5)	2 (0.4)	0.99
Urinary tract infection	181 (30.6)	384 (24.8)	<0.01	132 (29.5)	149 (32.5)	0.35
Vascular access catheter	40 (6.8)	66 (4.3)	0.03	26 (5.8)	27 (5.9)	0.99
Skin and soft tissue	40 (6.8)	101 (6.5)	0.85	26 (5.8)	34 (7.4)	0.35
Wound infection	32 (5.4)	55 (3.6)	0.07	22 (4.9)	23 (5.0)	0.99
Others	47 (7.9)	124 (8.0)	0.99	40 (9.0)	37 (8.1)	0.72
Unknown source	120 (20.3)	390 (25.2)	0.02	93 (20.8)	89 (19.4)	0.62
Pathogens						
Gram positive organisms, No. (%)						
<i>Beta streptococcus</i>	285 (48.1)	727 (47.0)	0.66	215 (48.1)	208 (45.4)	0.43
<i>Enterococcus spp.</i>	31 (5.2)	78 (5.0)	0.83	20 (4.5)	20 (4.4)	0.99
<i>Streptococcus pneumoniae</i>	44 (7.4)	100 (6.5)	0.44	35 (7.8)	27 (5.9)	0.29
Methicillin-resistant <i>S. aureus</i>	22 (3.7)	96 (6.2)	0.03	21 (4.7)	11 (2.4)	0.07
Methicillin-sensitive <i>S. aureus</i>	69 (11.7)	172 (11.1)	0.76	50 (11.2)	56 (12.2)	0.68
Gram negative organisms, No. (%)						
<i>Acinetobacter spp.</i>	83 (14.0)	200 (12.9)	0.52	62 (13.9)	64 (14.0)	0.99
<i>Bacteroides</i>	307 (51.9)	820 (53.0)	0.66	232 (51.9)	250 (54.6)	0.43
<i>Escherichia</i>	18 (3.0)	43 (2.8)	0.77	17 (3.8)	17 (3.7)	0.99
<i>Klebsiella</i>	10 (1.7)	40 (2.6)	0.26	6 (1.3)	11 (2.4)	0.33
<i>Pseudomonas aeruginosa</i>	139 (23.5)	349 (22.6)	0.65	97 (21.7)	107 (23.4)	0.58
<i>Enterobacter spp.</i>	58 (9.8)	147 (9.5)	0.87	44 (9.8)	41 (9.0)	0.65
Culture positive, median (IQR), days	14 (2.4)	45 (2.9)	0.56	12 (2.7)	12 (2.6)	0.99
Bacteremia >48 hours from admission, No. (%)	19 (3.2)	48 (3.1)	0.23	17 (3.8)	12 (2.6)	0.30
Antibiotics administered 6 hrs	0.1 (0, 1.9)	0.1 (0, 3.6)	0.04	0.1 (0, 3.0)	0.1 (0, 2.7)	0.71
	146 (24.7)	460 (29.7)	0.02	120 (26.9)	125 (27.3)	0.69
	428 (73.7)	1206 (78.7)	0.02	322 (73.0)	369 (81.6)	<0.01

SD, standard deviation; IQR, interquartile range; No., number; ACE, angiotensin converting enzyme; ARBS, angiotensin receptor blocker; APACHE, acute physiology age chronic health evaluation; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; Temp, temperature; ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cell; INR = international normalized ratio.

^a APACHE II, a severity of disease classification system (14)

^b From hospital admission to sampling of blood culture

Table 2

Unadjusted Outcomes (Bivariate Analysis)

Unadjusted Outcomes	Unmatched Cohort			Propensity Matched Cohort		
	Statin Users n=592	Non Statin Users n=1547	P value	Statin Users n=447	Non Statin Users n=458	P value
All cause mortality, No (%)	89 (15.0)	337 (21.8)	<0.001	76 (17.0)	100 (22.1)	0.35
All cause mortality within 90 days, No (%)	161 (27.2)	516 (33.4)	0.01	133 (29.8)	144 (31.4)	0.61
ICU admission during hospitalization, No (%)	111 (18.8)	400 (25.9)	<0.01	96 (21.5)	109 (23.8)	0.43
Mechanical Ventilation use, No (%)	80 (13.5)	267 (17.3)	0.04	66 (14.8)	75 (16.4)	0.52
BiPAP use, No (%)	33 (5.6)	70 (4.5)	0.31	26 (5.8)	22 (4.8)	0.55
ICU LOS, median (IQR), days	7 (3, 16)	8 (3, 16)	0.67	7 (3, 16)	7 (3, 16)	0.73
Hospital LOS, median (IQR), days	11 (6, 19)	11 (6, 23)	0.65	12 (7, 20)	12 (6, 22)	0.87

ICU, Intensive Care Unit; NIPPV, Non Invasive Positive Pressure Ventilation.

Table 3

Adjusted Analyses Evaluating the Association Between Statin Use Prior to Bacteremia and 90-day Mortality after Stratifying by Decile of Statin Propensity

Strata	Propensity Score Range	Proportion died within 90 days on Statin	Proportion Died with 90 days without Statin	Hazard Ratio	95% CI	P value
1 (n = 211)	0.001 to 0.034	0/1 (0%)	69/210 (32.9%)	--	--	--
2 (n = 210)	0.034 to 0.065	1/4 (25.0%)	62/206 (30.1%)	0.73	0.10 – 5.29	0.758
3 (n = 211)	0.065 to 0.100	7/22 (31.8%)	59/189 (31.2%)	0.98	0.45 – 2.15	0.961
4 (n = 210)	0.100 to 0.146	11/26 (42.3%)	71/184 (38.6%)	1.18	0.62 – 2.24	0.602
5 (n = 211)	0.146 to 0.203	12/36 (33.3%)	54/175 (30.9%)	1.08	0.58 – 2.02	0.801
6 (n = 210)	0.204 to 0.282	19/57 (33.3%)	52/153 (34.0%)	1.01	0.60 – 1.71	0.975
7 (n = 211)	0.282 to 0.368	20/75 (26.7%)	44/136 (32.4%)	0.81	0.48 – 1.38	0.437
8 (n = 210)	0.368 to 0.477	29/87 (33.3%)	45/123 (36.6%)	0.89	0.56 – 1.43	0.637
9 (n = 211)	0.477 to 0.633	29/116 (25.0%)	32/95 (33.7%)	0.70	0.42 – 1.15	0.158
10 (n = 210)	0.634 to 0.999	32/157 (20.4%)	15/53 (28.3%)	0.68	0.37 – 1.25	0.212
Overall (n = 2105)	0.001 to 0.999	160/581 (27.5%)	503/1524 (33.0%)	[†] 0.88	0.72 – 1.07	0.197

CI = confidence interval

^aOverall Mantel-Haenszel estimate, controlling for time and strata

Table 4

Adjusted Cox Proportional Hazards Models for Mortality within 90 Days

Variable	Propensity Matched			Stratified by Propensity Deciles		
	HR	95% CI	P value	HR	95% CI	P value
Statins	0.99	0.77 – 1.25	0.904	0.86	0.70 – 1.06	0.157
Age, year	1.02	1.01 – 1.03	0.001	1.02	1.01 – 1.02	<0.001
Nursing home/Facility/Transfer	1.57	1.21 – 2.05	0.001	1.55	1.30 – 1.85	<0.001
BMI > 25		<i>a.</i>		0.80	0.68 – 0.95	0.009
APACHE II	1.05	1.03 – 1.07	<0.001	1.06	1.04 – 1.07	<0.001
Hospital acquired >48 hours	1.40	1.04 – 1.90	0.029	1.27	1.05 – 1.53	0.013
Mechanical Ventilation	1.90	1.44 – 2.52	<0.001	1.79	1.49 – 2.14	<0.001
Temp <96.5 °F	2.21	1.46 – 3.33	<0.001	1.60	1.21 – 2.12	0.001
Temp >100.4 °F		--		0.65	0.55 – 0.78	<0.001
Heart rate > 100 bpm		--		1.35	1.13 – 1.62	0.001
Bicarbonate <24.0 meq/L	1.53	1.13 – 2.06	0.006	1.38	1.12 – 1.70	0.002
AST >40.0 U/L	1.42	1.09 – 1.85	0.009	1.31	1.11 – 1.56	0.002
INR >1.5	1.46	1.12 – 1.92	0.006	1.77	1.50 – 2.10	<0.001
Albumin <3.0 g/dL	1.88	1.39 – 2.56	<0.001	1.81	1.48 – 2.23	<0.001
Unknown source	1.48	1.12 – 1.96	0.006	1.94	1.60 – 2.35	<0.001
Respiratory infection				1.56	1.27 – 1.91	<0.001
<i>Acinetobacter</i> spp.	1.91	1.18 – 3.08	0.017	1.77	1.25 – 2.52	0.001
<i>Bacteroides</i>	2.68	1.34 – 5.36	0.005	2.13	1.40 – 3.26	<0.001
Methicillin-resistant <i>S. aureus</i>	1.89	1.34 – 2.65	<0.001	1.44	1.14 – 1.82	0.003
<i>Enterococcus</i> spp.	1.77	1.14 – 2.76	0.011	1.45	1.10 – 1.92	0.009
<i>Pseudomonas aeruginosa</i>		--		1.62	1.08 – 2.43	0.019
Congestive heart failure	1.40	1.08 – 1.81	0.010	1.29	1.07 – 1.54	0.006
Dementia	1.65	1.12 – 2.43	0.010	1.54	1.16 – 2.03	0.002
Metastatic cancer		--		1.55	1.22 – 1.98	<0.001
Antibiotics administered 6 hrs	1.11	0.81 – 1.51	0.517		--	

HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; SBP, systolic blood pressure; Temp, temperature; AST, aspartate aminotransferase; INR, international normalized ratio; BMI, body mass index; APACHE, acute physiology age chronic health evaluation; WBC, white blood cell.

^aIndependent variable did not include in the final model because hazard ratio was not statistically significant, and it was not a confounder or effect modifier