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Antimicrobial Resistance Patterns and Protective Effects of Statins in Bacteremic Patients

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ANTIMICROBIAL RESISTANCE PATTERNS AND PROTECTIVE EFFECTS OF
STATINS IN BACTEREMIC PATIENTS

By
AJINKYA PAWAR

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
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DOCTOR OF PHILOSOPHY DISSERTATION
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ABSTRACT

The significant increase in antimicrobial resistance over the past few years is a serious global public health concern, particularly as the development of new antimicrobial agents had been slow for many years. Infections with resistant organisms are associated with poor clinical outcomes and higher cost burdens. Determining antimicrobial resistance patterns can help identify problem areas and modify treatment practices to improve clinical outcomes. Additionally, identifying adjunctive therapies can also help improve clinical outcomes among infected patients. The objectives, hypotheses, methods and results of this dissertation are threefold:

Manuscript 1: The objective was to analyze antimicrobial resistance trends in *E. faecalis* and *E. faecium* between 2003 and 2015 in five acute care facilities of the Veterans Affairs New England Healthcare System as antimicrobial resistance patterns among *Enterococcus* have changed over the past decade. Using a multi-center ecologic study design, we evaluated antimicrobial resistance patterns for blood and urine cultures of enterococci. In *E. faecium* urine cultures, a decline in gentamicin resistance, as well as a small decrease in vancomycin resistance were observed. *Enterococcus* resistance towards ampicillin, linezolid, and tetracycline was stable over the study period. Daptomycin resistance did not emerge over the study period.

Manuscript 2: The objective was to evaluate the impact of statin exposure on clinical outcomes, including inpatient mortality and length of inpatient stay, among bacteremic patients. The hypothesis was that statin use would be associated with positive clinical outcomes compared to non-statin use. We conducted a retrospective cohort study using the deidentified Optum Clinformatics™ (OptumInsight, Eden

Prairie, MN) with matched Premier Hospital data (October 2009-March 2013). Our retrospective cohort study observed lower mortality for incident users and prevalent users continuing statin use during admission. Though non-significant in incident users, the point estimate was similar to that observed in other studies.

Manuscript 3: The objective was to identify a statin therapy duration among pre-defined baseline statin users at which use of statins minimizes the risk of inpatient mortality among bacteremic patients. The hypothesis was that a certain minimum duration of statin use during the hospitalization would improve survival. A case-control design was used to test this hypothesis using the Optum Clinformatics™ with matched Premier Hospital data (October 2009-March 2013). Classification and regression tree analysis was conducted among cases and controls matched on disease risk scores. Among matched pairs of cases and controls with at least 90 days of pre-admission statin use, the continuation of statin use during admission for at least 2 days provided a better survival benefit among bacteremic patients.

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PREFACE

This dissertation is written in the manuscript format, and is comprised of three manuscripts, which evaluated (1) antimicrobial resistance patterns in *Enterococcus* pathogens, (2) the impact of statin exposure on clinical outcomes in bacteremic patients, and (3) optimal statin adjunctive therapy duration among bacteremic patients.

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Manuscript 1

Title: Antimicrobial resistance trends in *Enterococcus* pathogens

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1.1 Abstract

Enterococcus faecalis and *E. faecium* antibiotic resistance trends from 2003-2015 in clinical blood and urine cultures were evaluated among the New England Veteran Affairs hospitals using generalized linear mixed models. Over 10,000 unique isolates were included. In *E. faecium* urine cultures, a decrease in gentamicin resistance was noted (mean 2.9%/year). Vancomycin resistance slightly decreased in *E. faecium* urine cultures (mean 0.1%/year). Daptomycin resistance did not emerge, while ampicillin, linezolid, and tetracycline resistance remained stable over the study period.

1.2 Introduction

Antimicrobial resistance among *Enterococcus* has been increasing in the United States (U.S.) over the past several years.^{1,2} These bacteria have developed resistance to nearly every antibiotic used for treatment.^{2,3} Further, the occurrence of resistance in enterococci to comparatively new antibiotics, such as daptomycin⁴ and tigecycline,⁵ as well as developing resistance to adjunctive therapies, such as gentamicin, is a substantial public health concern.² Infections with resistant organisms are associated with poor clinical outcomes,⁶ and increased health and cost burdens.⁷ As antibiotic resistance changes, enterococcal infections are becoming more difficult to treat, potentially leading to the administration of inappropriate empiric therapies^{8,9} that could increase mortality risk.¹⁰ Vancomycin resistance in enterococci (VRE) has increased extensively in the past few decades, and is considered a "serious threat" as each year, 20,000 (or 30%) *Enterococcus* healthcare-associated infections are vancomycin-resistant causing an estimated 1,300 deaths in the U.S.¹¹ With the changing epidemiology of infections,^{12,13} frequent review of resistance, with respect to historical patterns, is crucial to identifying problems with resistance and response to such changes, such as modifications to treatment practices.¹⁴ This study aimed to describe antimicrobial resistance trends of *E. faecalis* and *E. faecium* in a large, regional healthcare system.

1.3 Methods

A multi-center ecologic study design was used to evaluate annual antibiotic susceptibility from 2003 to 2015 among blood and urine isolates from five New England Veteran Affairs (VA) Medical Centers (Boston MA, Providence RI, Togus ME, White River Junction VT, and West Haven CT), based on Clinical and Laboratory Standards Institute (CLSI) guidance^{15,16}. Changes in the percent resistance over the

study period were assessed with generalized linear mixed models (GLMM). GLMM accounts for the clustered nature of the study design by incorporating correlations among responses through the inclusions of random effects in the linear predictor and/or by modeling the correlations among the data directly.¹⁶ Generalized models are commonly used when response variables have error distribution models other than a normal distribution.¹⁶ The general form of the model is: $y = X\beta + Z\gamma + \varepsilon$. The events/trial syntax (number resistant/number of isolates tested for a given antibiotic) served as the response variable and the 'year' functioned as the independent categorical variable. The binomial distribution and logit link were used for all GLMM models due to the event/trial syntax of a dependent variable. To account for the interdependence of samples within the five facilities (clusters), 'facility' was included as a random effect in the GLMM models. Significance was defined as an α (alpha) of 0.05 and all models were run in SAS 9.4 (SAS Institute, Cary, NC, USA).

1.4 Results

Over the thirteen-year study period, 10,257 unique enterococci isolates were extracted from blood and urine culture sites, of which 86.7% (n=8,894) were *E. faecalis* [blood=585 (6.6%), urine=8,309 (93.4%)] and 13.3% (n=1,363) were *E. faecium* [blood=246 (18.0%), urine=1,117 (82.0%)].

E. faecalis resistance remained steady between 2003 and 2015, except for resistance to tetracycline. We observed a significant increase in the annualized modeled change in tetracycline resistance for *E. faecalis* urine cultures (0.4%/year, mean isolates tested per year [mean n]=370, % resistance in 2003 and 2015 [resistance y03]=66.1%, [y15]=70.7%, $p < 0.01$, Figure 1). Vancomycin resistance in *E. faecalis* remained low, and decreased non-significantly by an average 0.43%/year in

blood (mean n=45, resistance y03=5.1%, y15=0.0%, p=0.67) and 0.16%/year in urine cultures (mean n=639, resistance y03=5.1%, y15=3.2%, p=0.26). Resistance to ampicillin, a commonly used therapy for *E. faecalis* infections,^{17,18} remained low and stable in both blood (resistance all years, <3.1%) and urine (resistance all years, <1.4%). Linezolid resistance was also low and stable in *E. faecalis* urine cultures (mean n=112, resistance y03=1.9%, y15=2.3%, p=1.00).

In *E. faecium* urine isolates, a small annual decrease of 0.10%/year in vancomycin resistance was observed (mean n=86, resistance y03=68.7%, y15=67.3%, p=0.01, Figure 2). While the trend was statistically significant, the clinical relevance of a 1.20% decrease in resistance over the study period may be negligible. Conversely, vancomycin resistance in *E. faecium* blood isolates increased non-significantly by 1.59%/year (mean n=19, resistance y03=63.3%, y15=82.4%, p=0.70). In *E. faecium* urine cultures, a statistically significant decrease in gentamicin resistance was observed (2.93%/year, mean n=13, resistance y03=35.1%, y15=0.0%, p<0.0001). Tetracycline resistance increased significantly in blood (5.56%/year, mean n=11, resistance y03=50.0%, y15=100.0%, p<0.01) and urine isolates (0.21%/year, mean n=54, resistance y03=73.1%, y15=75.6%, p=0.01).

Resistance towards ampicillin remained high, but stable in *E. faecium* blood (mean 1.40%/year decrease, mean n=19, resistance y03=98.8%, y15=80.0%, p=0.81) and urine (mean 0.68%/year decrease, mean n=80, resistance y03=95.1%, y15=86.9%, p=0.07) cultures. Linezolid resistance in *E. faecium* was observed, but remained low and non-significantly decreased by 0.53%/year in urine (mean n=55, resistance y03=7.9%, y15=1.5%, p=0.69). We did not observe any daptomycin-

resistant isolates in either *E. faecalis* (0/552) or *E. faecium* (0/195) from 2007 when daptomycin susceptibility testing began.

1.5 Discussion

In this ecologic study conducted in New England VA Medical Centers between 2003 and 2015, antibiotic resistance in enterococci was mostly stable. Decreased vancomycin resistance in *E. faecium* blood isolates was reported in an Italian study, with resistance dropping from 24.1% in 2003 to 4.3% in 2009, and remaining between 4-6% until 2013.¹⁹ A report from the SENTRY Antimicrobial Surveillance Program (2011–2014) among 21 Latin American medical centers (11 nations) observed a vancomycin resistance rate of 50.3% in *E. faecium* and 2.3% in *E. faecalis*.²⁰ Vancomycin resistance in *E. faecium* was high in our study, however, we observed a small, but significant decrease in urine isolates which could be a result of successful infection control strategies and antimicrobial stewardship activities.²¹ In *E. faecalis*, vancomycin resistance was low and decreased non-significantly in both culture sites. This findings are positive considering the spread of VRE over the past two decades.²²

Other encouraging results besides decreasing vancomycin resistance in *E. faecalis*, were the stable resistance rates or small decreases in resistance rates to conventional therapies,¹⁷ such as ampicillin, in *E. faecium*. Daptomycin has been approved by the Food and Drug Administration (FDA) to treat VRE due to in-vitro bactericidal activity against VRE,²³ however, the emergence of daptomycin resistance for *E. faecium* has been observed recently.^{4,24} Another positive finding in our study was the non-emergence of daptomycin resistance in enterococci blood and urine cultures.

An increasing trend of *E. faecium* resistance to ampicillin, which is used for the treatment of VRE *faecalis* and susceptible *E. faecium*, was reported in 28 hospitals in Thailand, growing from 52.0% in 2000 to 84.1% in 2005.²⁶ Ampicillin resistance in *E. faecium* is high,²⁷⁻²⁹ especially in VRE *faecium*.³⁰ Similar to the current literature, ampicillin resistance rates in *E. faecium* remained high (>75%) in our study, despite non-significant decreases in both urine and blood cultures. Compared to the high ampicillin resistance in *E. faecium*, VRE *faecalis* strains usually remain susceptible to ampicillin.³⁰ We also observed low ampicillin resistance in *E. faecalis*, which remained stable over the study period.

Tetracycline resistance in *E. faecium* increased in urine and blood cultures. While tetracycline exhibits clinically significant anti-enterococcal activity, it is generally considered a second-line agent and is seldom used for enterococci treatment.¹⁸ As a result, susceptibility testing against this antibiotic declined, and therefore, the tetracycline resistance was only tested in few blood isolates after 2010 (n<3), resulting in larger differences in percent resistance year to year. Tetracycline resistance increases were not as large in years when more isolates were tested.

Linezolid resistance was observed in 4 of 5 facilities in our study, but the rates remained stable and low (<3%) over the study period. Linezolid is approved by FDA for the treatment of VRE *faecium* infections³¹ and it remains a crucial therapy for linezolid-susceptible isolates of both *E. faecalis* and *E. faecium*. Linezolid resistance is usually low in enterococci and was rarely reported in VRE until the past few years, however, recent VRE outbreaks have resulted in higher rates of linezolid resistance.³²⁻³⁵ A recent study³⁶ reported a linezolid resistance rate of 30.2% among *E. faecalis* urine isolates, but was only 0.8% in our study. Linezolid resistance in

enterococci has been linked with increasing linezolid use,³⁷ highlighting the role of antibiotic selective pressure and resulting changes in antibiotic resistance.

E. faecalis and *E. faecium* susceptibility to ampicillin, linezolid, tetracycline, and vancomycin, was relatively stable. Though some of these resistance trends were statistically significant, the small changes in resistance may not be clinically relevant. The spread of multi-resistant enterococci has been associated with the selective antibiotic pressure in tertiary care institutions³⁸ and patients with recurrent health-care exposures, so future research should quantify the impact of changing antibiotic pressure on antimicrobial resistance and clinical outcomes.

Our study findings may be useful for informing antimicrobial stewardship programs, which play a key role in directing empiric therapy and raising awareness of new problems with resistance, which in turn improves antimicrobial resistance³⁹ and healthcare costs⁴⁰. However, there are limitations to this study. First, this is an ecologic study of facility-level resistance. Individual patients could have contributed multiple isolates over the study period.⁴¹ Second, antimicrobial resistance in certain strains of enterococci may be attributed to prior use of antibiotics⁴² which could not be studied due to the lack of patient-level data. Third, the generalizability of the study will be limited to the New England VA population that consists mostly of older, white males. Forth, aggregated microbiology trend data offer less detailed information than active surveillance, although, they are adequate at estimating the prevalence of resistance.⁴³ Fifth, there may have been differences in enterococci resistance rates across the 5 facilities. Lastly, our results are limited by the number of cultures taken and the changes in the number of isolates tested against a specific antibiotic over the study period. Small changes in resistance patterns in a large number of isolates

(mostly urine), may not be clinically significant but were statistically significant. Conversely, larger changes in resistance in blood isolates were not statistically significant due to a small number of isolates, but the changes may be clinically important.

In conclusion, despite concerns surrounding VRE outbreaks multi-drug resistance that makes the *Enterococcus* difficult to treat,² we found stable vancomycin resistance in *Enterococcus* among VA Medical Centers in New England. Similarly, *Enterococcus* resistance was stable for other common treatments. Additionally, daptomycin resistance did not emerge over the study period and gentamicin resistance decreased.

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Appendix

Fig 1: Trends in *E. faecalis* resistance (2003-2015) for blood and urine cultures

Fig 2: Trends in *E. faecium* resistance (2003-2015) for blood and urine cultures

Manuscript 2

Title: Evaluation of Protective Effects of Statins in Bacteremic Patients

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2.1 Abstract

Background: Several meta-analyses and observational studies have reported improved clinical outcomes in patients with inflammatory conditions among users of statins.

Objectives: To evaluate the impact of statin exposure on clinical outcomes in bacteremic patients.

Methods: A retrospective cohort study was conducted using Optum Clinformatics™ with matched Premier Hospital data to assess inpatient mortality and length of stay (LOS) among statin-exposed vs. non-exposed bacteremic patients hospitalized between April 2010-March 2013. Patients who received at least two consecutive days of antibiotic therapy within the first three days of hospital admission were included. In the primary analysis, only incident statin users were included to avoid the "healthy user" bias. Non-users were defined as patients without any pharmacy records for statins. Cox proportional hazards regression models, adjusted by propensity scores, were developed to evaluate the effect of statins on clinical outcomes. Secondary analyses were conducted among existing statin users.

Results: Our study included 112 incident statin users and 1,597 non-users. Inpatient mortality in bacteremic patients was non-significantly lower among statin users compared to non-users (adjusted hazard ratio [HR] 0.45, 95% confidence interval [CI] 0.18-1.16). Reduction in inpatient mortality was significant among existing statin users with at least 90 days of continuous therapy prior to admission, who continued statin therapy during the admission (n=232, HR 0.37, 95% CI 0.14-0.96), and was non-significant among existing users not continuing statin therapy during the admission (n=401, HR 1.12, 95% CI 0.75-1.86). LOS was similar between all groups.

Conclusion: Our retrospective cohort study observed lower mortality for incident users and existing users continuing statin use during admission. Though non-

significant in incident users, the point estimate was similar to that observed in other studies.

2.2 Introduction

Bloodstream infections are the sixth most common principal reason for hospitalization, accounting for 836,000 hospital stays in 2009.¹ Moreover, it is the most expensive cause of hospitalization in the United States (U.S.), accruing almost \$15.4 billion in collective hospital costs in 2009.¹ Statins, inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, decreases cardiovascular events among patients with elevated cholesterol.² Protective effects with statins have been observed in inflammatory conditions, such as bacteremia³⁻⁶, sepsis⁷⁻⁹, pneumonia, and other infections in terms of 30-day, 90-day, in-hospital, and long-term (>1 year) mortality reductions, and these protective effects have been most pronounced in bacteremic patients.¹⁰

The specific mechanism by which mortality is reduced among patients with bacteremic infections remains undefined. A proposed mechanism has been the moderation of the overall inflammatory response.¹¹ Other previously observed anti-inflammatory effects with statins have included lowering of C-reactive protein (CRP), chemokine release (MCP-1, RANTES), cytokines (IL-1 β , TNF α , IL-6, IL-8), and adhesion molecules (P-selectin, VLA 4, CD11a, CD11b, CD18).^{12,13} Statins may also have a direct antimicrobial effect¹⁴, and possible antibacterial activity of statins against a variety of pathogens may be attributed to their ability to suppress cell growth, and to promote apoptosis.¹⁵⁻¹⁷ In murine models, statin treatment inhibits apoptosis in sepsis¹⁸, reduces nitric oxide overproduction¹⁹, regresses the endotoxic shock induced damaged vascular responsiveness¹⁹, and also improves survival as it maintains cardiac function and hemodynamic status after an onset of sepsis.²⁰ A randomized double-blind placebo-controlled trial among patients with acute bacterial

infections found a significant reduction in the levels of inflammatory cytokines among statin users.²¹

A number of meta-analyses^{10,22} and observational studies^{4-6,23} have reported survival benefits among bacteremic patients exposed to statins compared to those not exposed to statins. However, published research has not reached a consensus on this association as several studies failed to observe significant results^{24,25} and/or result estimates varied considerably.^{4,5,23,25} Optimal statin use duration required to provide mortality benefits is still unknown, but the continuation of statin use during hospital admission has been found to offer pronounced effects on survival.⁴

Differences between statin users and non-users in previous studies have varied by data source^{6,22}, study designs^{10,22-25} and sample size of the statin user group.^{4,5,23} Observational studies evaluating this association have evident differences in statin user and non-user group, potentially causing confounding of the exposure-outcome relationship.^{4,5,23} Many hospital based studies evaluating protective effects of statins did not have information about medical history or medication use prior to the admission.^{23,25,26} Therefore, this study aimed to determine whether the association between statins and better clinical outcomes was observed among a privately insured population with administrative data linked to hospital data. The primary objective of this study was to evaluate the impact of incident statin use, and secondarily existing statin exposures, on clinical outcomes, including inpatient mortality and length of hospital stay, in bacteremic patients exposed to statins versus those not exposed to statins in a large real-world clinical setting.

2.3 Methods

2.3.1 Research Design and Methodology

A retrospective cohort study design was used to assess two different outcomes, inpatient mortality and length of hospital stay, among statin-exposed vs. non-exposed patients. A retrospective cohort study design was used because it allows the comparison of individuals with differing exposures, which can be observed in order to determine the health effects of the exposure over a period of time.²⁷

2.3.2 Data Sources

This study was conducted using deidentified Optum Clinformatics™ (OptumInsight, Eden Prairie, MN) with matched Premier Hospital data (10/01/2009-03/31/2013), which is an administrative claims database from a large commercial health plan (Optum Clinformatics™) matched with hospital data (Premier).

2.3.3 Study Population

Included in the analysis were adult patients (>18 years) having a primary diagnosis for bacteremia or septicemia (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 003.1, 020.2, 022.3, 036.2, 038.0, 038.1, 038.10-038.12, 038.19, 038.2, 038.3, 038.40-038.44, 038.49, 038.8, 038.9, 054.5, 449, 771.81, 995.91, 995.92, 790.7) caused by any organism during the study period.²⁸ We only included patients with hospital admissions between 04/1/2010 and 03/31/2013, to allow for a continuous enrollment period of 6 months prior to admission (Figure 1). Antibiotic therapy for each patient during the hospital stay was assessed. Patients who received at least two consecutive days of at least one antibiotic therapy for bacteremia²⁹⁻³² within the first three days of the admission were included. For patients with multiple admissions for bacteremia, only the first

admission was included. Medication use was identified from both outpatient prescriptions and medications given during the hospital stay.

2.3.4 Definition of Statin Use

For the primary analysis, we identified incident statin users, which was defined as those initiating a statin (i.e., atorvastatin, cerivastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) within 90 days of hospital admission, or during the hospitalization, after having not used statins in the three months prior to the initial pharmacy record. A one-day gap in therapy was allowed, including separate one-day gaps on several different occasions. Non-users were patients without any pharmacy records for statins from the study start period through hospital discharge. The date of the hospital admission was defined as the index date.

Secondary analyses were conducted among existing statins users. These analyses were conducted separately among patients who, irrespective of their statin initiation time, had at least a continuous 90-day exposure for statins prior to hospitalization and did not continue during admission (existing, outpatient-only users), and among patients who had a continuous statin exposure for at least 90 days prior to hospitalization and continued statins for at least the first 5 days after hospitalization (existing-continuous users). These existing statin users were compared with non-users to assess differences in the outcomes.

2.3.5 Outcomes

The primary outcome of interest in this analysis was inpatient mortality. The secondary endpoint that we evaluated was hospital length of stay. Inpatient mortality was defined as death occurring during the hospital stay. The length of hospital stay

was calculated as the number of days between hospital admission and the hospital discharge date. For the length of stay, patients who died during the admission were excluded from the analysis.

2.3.6 Statistical Analysis

To identify baseline differences between the exposed and non-exposed groups, we analyzed demographic and clinical data including current and prior comorbidities.²⁸ For categorical variables, if the assumptions for the chi-squared test were not met (expected count of 75% of cells >5), the Fisher's exact test was utilized. For continuous variables, the t-test was used for normally distributed data, and the non-parametric Wilcoxon Rank Sum test was used if the normality assumption of t-test was violated as assessed graphically and the Shapiro-Wilk test for normality.

The propensity score is the probability of treatment assignment conditional on observed baseline characteristics, derived from the inclusion of various demographic, hospitalization-related, and clinical characteristics in a logistic regression model. The propensity score attempts to mimic a randomized controlled trial (RCT) by balancing the exposure groups on observed baseline characteristics.^{33,34} In this study, the propensity score was the predicted probability of statin use, as calculated from the baseline covariates included in an unconditional logistic regression model which was built with manual backward elimination.³⁴⁻³⁷ The model included type of statin, other inpatient and outpatient medication use, such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics. Further, we included type of antibiotic as differences in antibiotic therapy could have a large influence on bacteremic mortality. The propensity score model also controlled for various pathogens, where available, and comorbidities such as metabolic syndromes, HIV,

cancer, and liver cirrhosis³⁸. Initially, likelihood ratio tests were conducted on all independent variables individually and variables with a p-value <0.25 were considered as a candidate for inclusion in the multivariable model. Variables with a p-value ≥0.05 were removed one at a time using backward elimination to determine the final propensity score model. We assessed multicollinearity among independent variables by review of correlation matrices and confirmed that all variance inflation factor (VIF) values were <3.³⁹ Further, we assessed goodness of fit with the Hosmer-Lemeshow goodness-of-fit test,³⁹ and plotted propensity scores to review the overlap of propensity score between groups. Patients from the statin user and non-user groups were stratified by propensity score quintile to achieve homogeneity between exposure groups within quintiles of the predicted probability of statin use.³⁹ Covariate balance within propensity score quintiles was reviewed.^{35,36} The general propensity score equation is illustrated below, where T is a binary treatment, Y is an outcome, and X are background variables: $p(x) \equiv \Pr(T = 1 | X = x)$. The final propensity score model equations are included as footnotes in the results table.

Propensity score-adjusted Cox proportional hazards regression models were used to assess the impact of statin use on time to occurrence of inpatient mortality and the hazard ratios and 95% confidence intervals were calculated. We checked Cox proportional hazards models for non-informative censoring and proportionality using graphical displays, as well as the Supremum test.⁴⁰ A PS-adjusted Cox proportional hazards model offers an estimate of the impact of treatment on survival after adjustment for variables which predict exposure. A hazard ratio greater than 1 for inpatient mortality (dependent variable) means that the hazard is higher in the statin-exposed patients, and therefore the prognosis worse. On the other hand, a hazard ratio <1 implies a better prognosis for statin users. The general form of the

Cox proportional hazards model is: $h(t|X) = h(t) \exp(X_1\beta_1 + \dots + X_p\beta_p)$. To evaluate the association of statin use and in-hospital mortality, without accounting for the rate at which deaths occur (time to event), we also computed the odds of inpatient mortality in statin users versus non-users using conditional logistic regression model, adjusting for PS quintiles. To assess the differences in length of stay between statin users and non-users, we developed a PS-adjusted Poisson regression model with log link.

The secondary analyses performed among existing statin users assumed the proximity of statin-exposure to the admission, regardless of previous duration, could offer protective effects. Separate propensity models were developed and used to adjust Cox-proportional hazards models. These models were used to study the survival benefits of existing, outpatient-only, as well as existing, continuous statin use. For all analyses, statistical significance was considered a p-value of ≤ 0.05 . All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

2.4 Results

For the primary analysis, we identified 1,709 patients who met our inclusion and exclusion criteria (see Figure 2). This included 112 new initiators of statin use and 1,597 non-users. Among statin users, 53 (47%) initiated statin in the 90 days prior to admission and 59 (53%) anytime after admission. Of those initiating prior to admission, 33 (62%) continued statin therapy. The results of the descriptive analyses indicated that the cohorts differed with respect to baseline demographic and clinical characteristics. Among statin users vs. non-users (Table 1), significant ($p < .01$)

differences in age (median 61 vs. 53 years) and gender (39% vs. 53% females) were observed. The median Charlson comorbidity index (CCI) was significantly higher for statin users than non-users during the admission (2.7 vs. 2.1, $p<0.0001$; table 2) and also during the 6 months prior to admission (4.0 vs. 2.7, $p<0.0001$). Admission from the emergency room occurred for 91% statin users and 96% non-users ($p=0.01$). Marital status, race, region, and admitting physician specialty were similar between statin users and non-users. Simvastatin (54.5%) and atorvastatin (28.6%) were the most commonly used statins. Inpatient mortality among statin users was non-significantly lower (4.46% vs. 7.07%, $p=0.4375$) and LOS was higher (median 8.0, interquartile range [IQR] 3.5-10.0 vs. 7.3 days, IQR 3.0-9.0], $p=0.052$) compared to non-users. The crude absolute risk reduction (ARR) with statin use was 2.6%. Variables that differed significantly, no longer differed within PS quintiles. The final PS model c-statistic was 0.92, suggesting a strong model for predicting the probability of statin use.³⁷

The PS-adjusted Cox proportional hazards regression model evaluating time to inpatient mortality demonstrated non-significantly lower inpatient mortality among bacteremic statin users (hazard ratio [HR] 0.45, 95% CI 0.18-1.16; Table 3). In the unadjusted analysis, the statin users had lower mortality rates than non-users (HR 0.56, 95% CI 0.23-1.38), despite being older and having more comorbidities. After PS-adjustment, however, the inpatient mortality rates were slightly lower among statin users. Length of hospital stay in statin users and non-users (median 6.0, IQR 3.-10.0 vs. 5.0 days, IQR 3.0-9.0, $p=0.0821$) was similar in adjusted analyses. In secondary analyses, we identified 401 existing statin users with only outpatient statin use. After PS-adjustment, we observed similar inpatient mortality among existing, outpatient only statin users (HR 1.12, 95% CI 0.75-1.86) vs. non-users. However, survival was

significantly higher in existing-continuous users (n=232, HR 0.37, 95% CI 0.14-0.96) compared to non-users. Statin users had non-significantly lower odds of inpatient mortality than non-users (odds ratio [OR] 0.44, 95% CI 0.14-1.44).

2.5 Discussion

In the primary analysis of this retrospective cohort study among privately insured patients with bacteremia, the difference in inpatient mortality among incident statin users compared to non-users was not significant, although the point estimate (OR 0.44) was similar to a meta-analysis published in 2010.²² This meta-analysis reported a 51% lower risk of mortality (OR 0.49, 95% CI 0.37-0.61) among patients with bacteremia, pneumonia, or sepsis, and 67% lower bacteremia-related mortality (evaluated in 4 studies out of 20, pooled OR 0.33, 95% CI 0.09-0.75) in statin users compared to non-statin users.²² In our study, statin users were significantly older and had a higher comorbidity burden compared to non-users, as observed in a previous study⁴¹ evaluating protective effects of statins in inflammatory conditions.

In our secondary analyses, we observed higher survival among existing-continuous users. The magnitude of association for this analysis (63% lower mortality) was similar to a meta-analysis from 2012 that detected protective effects with statin use (62% lower mortality) against infection-related death in the 9 studies that focused on severe bacteremia (pooled OR 0.38, 95% CI 0.15–1.01), though these findings were also non-significant.¹⁰ This meta-analysis also observed a 29% decreased risk of all-cause mortality in patients with any type of infection (pooled OR 0.71, 95% CI 0.64-0.78).¹⁰ These results suggest better clinical outcomes among statin users with infections. However, several of the studies included in the meta-

analysis were subject to healthy user effects, by including existing statin users, and may not represent the true association between statin use and mortality.^{47-49,64}

Our findings for existing, outpatient-only statin use are consistent with the results of two other meta-analyses that observed similar mortality rates among bacteremic patients with statin use vs. non-use. The first meta-analysis of 4 randomized trials (1,818 patients) evaluating statin use in critically ill patients with severe sepsis did not observe a significant reduction compared to placebo in 28-day (risk ratio [RR] 0.95, 95% CI 0.72-1.27) and 60-day (RR 0.93, 95% CI 0.72-1.20) mortality rates.²⁴ In the other meta-analysis of 7 randomized trials comprising 1,720 patients, there was no difference in 28-day mortality (statin vs. placebo RR 0.93, 95% CI 0.46-1.89).⁴² The risk of mortality was similar between the statin and placebo groups in the aforementioned meta-analyses, which may be attributed to the inclusion of critically-ill patients with severe sepsis²⁴, short statin therapy durations (14-28 days),^{24,42} or stoppage of statin therapy during the crucial period of inflammation and hospital admission.⁴²

The continuation of statin use during hospital admission was found to offer a greater benefit, in terms of inpatient mortality. Similar results have been observed in a retrospective cohort study.⁴ Additionally, a recent RCT reported a significantly lower 28-day mortality rate (5% vs. 28%; $P=0.01$) in the subgroup of existing-continuous statin users.⁴³ These results support continuing statins through the period of inflammation, as the inflammatory response has been found to be lower among patients on statins at the same time as they developed an infection.^{44,45}

Additional limitations of a number of the studies included in the aforementioned meta-analyses were (a) control for few confounders^{23,5,8,11,25}, (b) lack of information about pre-hospitalization medication use^{23,25,26}, (c) combined incident and existing statin use^{8,11,26}, and (d) combined pre-hospital and post-hospital use.^{26,46} These limitations may explain the conflicting findings between studies in regards to the impact of statin use on mortality among patients with infections.

Well-designed RCTs can overcome these limitations. Several RCTs have evaluated the anti-inflammatory or immunomodulatory effects of statins, including the ASEPSIS trial (EUCTR2005-004636-52), which investigated the difference in rates of sepsis converting to severe sepsis and of critical care admissions between statin-treatment and placebo groups, and found the acute administration of atorvastatin in patients with sepsis may prevent sepsis progression.⁴⁷ The “Statin Therapy in the Treatment of Sepsis” trial (NCT00676897), found significantly lower coenzyme Q10 levels, which may be associated with the inflammatory cascade in septic shock, in septic shock patients compared to healthy controls.⁴⁸ The “Statin for Immunomodulation in Sepsis” trial (NCT00452608) and “Effect of Atorvastatin on the Frequency of Ventilator-associated Pneumonia in Patients with Ischemic Stroke” trials (NCT01550419), evaluated if atorvastatin can improve inflammation in septic patients and if early use of statin (40mg oral atorvastatin during admission) prevents infections such as ventilator-associated pneumonia (VAP), respectively. The results of these trials are not yet available.

The effects of statin exposure on bacteremic mortality has been assessed more frequently than other clinical outcomes, including hospital and intensive care length of stay (LOS). According to the National Center for Healthcare Statistics

(NCHS), hospitalization rates for septicemia or sepsis more than doubled from 2000 through 2008 and the average LOS was 75% longer than those hospitalized for other conditions.⁴⁹ To our knowledge, only one study has explored the association of statin use with LOS, and found non-significant results for hospital ($\beta = -0.8$ days, 95% CI - 2.2-1.7 days) or intensive care unit LOS ($\beta = -0.1$ days, 95% CI -3.7 to 3.8 days) length of stay.²⁵

The present study has several strengths. Firstly, we used administrative data from a major private insurer linked to hospital data which allowed us to evaluate medical history, previous medication use, as well as conditions present during the admission and all medication exposures during the hospitalization. Secondly, we attempted to account for "healthy user bias" by including incident statin users in our primary analysis since patients taking preventive medications, such as statins, are more likely to engage in healthy behaviors leading to favorable health outcomes compared to non-statin users.^{50,51} Additionally, patients taking preventive medications have a higher probability of being up-to-date with immunizations and having quit smoking, and are less likely to have been admitted to a nursing home or need advanced medical care.⁵² Third, we balanced baseline characteristics between statin users and non-users that were significantly different using PS methods in an effort to control for confounding. Lastly, to account for possible biases in socioeconomic and health behaviors,⁵³ we included demographic and clinical characteristics in the PS models.

2.6 Limitations

The results of this study have potential limitations. We could not study the protective effects of each statin separately due to small numbers. The effect of statins

on inpatient mortality in patients with sepsis may be different for individual statins.⁵⁴ We also could not assess dose-dependent effects, changes in statin therapy (drug or dose) prior to admission, at admission, or during the admission, or the effects of adherence due low sample sizes. In our review of statin doses, dispensing quantity in incident users mostly reflected moderate to high doses. As we used an administrative claims database for our analysis, we assumed outpatient statin exposure to be equivalent to filling a prescription. In the primary analysis, our definition of incident statin use was broad due to small numbers and included patients initiating prior to admission or after admission, and also included those not continuing statins during the admission (38%). As such, we could not evaluate the association using more specific definitions of incident statin use.

Furthermore, there is a possibility of statins having a different impact on clinical outcomes based on the causative pathogen, since the mechanism of action is not exactly known and it may vary for different pathogens. Microbiology data was not available for potential causative pathogen, but we identified organisms using ICD-9 codes, where available. Bacteremic treatment varies by organism type and we were only able to use general inclusion criteria of having received an antibiotic which may be used for bacteremia.²⁹⁻³² Since we only evaluated a general bacteremic population, our results may not be generalized to pathogen-specific bacteremias. As such, patients without appropriate initial antibiotic treatment may have been included. Despite using propensity scores to control for confounding, we could not control for unmeasured confounding. We also could not differentiate bacteremic severity, although we included ventilation status and sepsis proxies using diagnosis-related groups (DRG).

2.7 Conclusions

In conclusion, our retrospective cohort study quantified the effect of both incident and existing statin use on clinical outcomes such as inpatient mortality and hospital length of stay among bacteremic patients in a real-world clinical population. Result estimates for incident and existing-continuous statin use, although non-significant for incident users, were similar to previous meta-analyses that observed reductions in inpatient mortality after statin use among bacteremic patients. Further unaddressed questions related to this research question include appropriate statin exposure time and duration needed for maximum clinical benefits, and differences in the magnitude of each statin's protective effects. Future studies should control for healthy-user bias and differences in baseline characteristics between statin-users and non-users.

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Appendix-

Table 1. Demographic and hospitalization-related characteristics in incident statin users and non-users

Characteristics	Statin users (N=112)		Non-users (N=1,597)		P-value
Age (years, median and IQR)	61	53-69.5	53	41-62	<.0001
Gender					0.0036
Female	44	39.3	854	53.48	
Male	68	60.7	743	46.52	
Race					0.8371
Black	10	8.9	167	10.5	
Other	18	16.0	270	16.9	
White	84	75.0	1160	72.6	
Census region					0.4675
East North Central	19	17.0	256	16.0	
East South Central	5	4.5	38	2.4	
Middle Atlantic	8	7.1	80	5.0	
Mountain	8	7.1	166	10.4	
New England	<5	1.8	15	0.9	
Pacific	7	6.3	157	9.8	
South Atlantic	39	34.8	505	31.6	
West North Central	12	10.7	149	9.3	
West South Central	12	10.7	231	14.5	
Admission Type					0.0116
Emergency	102	91.1	1534	96.1	
Non-emergency	10	8.9	63	3.9	
Admitting Physician Facility					0.5655
ICU/Surgery	<5	3.6	68	4.3	
Medicine	42	37.5	671	42.0	
Other	66	58.9	858	53.7	
Diagnosis-related group (DRG) description					0.0867
Non-ventilation	101	90.2	1504	94.2	
Ventilation	11	9.8	93	5.8	
Hospital admission year					0.1765
2010	37	33.0	385	24.1	
2011	38	33.9	572	35.8	
2012	37	33.0	640	40.1	

Data are median and interquartile range (IQR) or number and percent of patients.

Table 2. Clinical characteristics and health service utilization in incident statin users and non-users

Characteristics	Statin-users (n=112)		Non-users (n=1,597)		P-value
Comorbidities (during admission)					
Charlson score (median and IQR)	2	1-4	1	0-3	<.0001
Elixhauser score (median and IQR)	2	1-4	1	0-3	<.0001
Amputation	14	12.5	114	7.1	0.0399
Cardiac arrhythmia	38	33.9	344	21.5	0.0023
Coronary heart disease	46	41.1	136	8.5	<.0001
Chronic ulcer	17	15.2	95	6.0	0.0001
Coma stupor and brain	6	5.4	33	2.1	0.0381*
Chronic pulmonary disease	35	31.23	348	21.78	0.0201
Chronic renal disease	26	23.2	209	13.1	0.0026
Chronic respiratory disease	35	31.3	348	21.8	0.0201
Depression	24	21.4	208	13.0	0.0120
Diabetes complicated	16	14.3	61	3.8	<.0001*
Diabetes uncomplicated	43	38.4	251	15.7	<.0001
Dyslipidemia including hyperlipidemia	57	50.9	167	10.5	<.0001
Cellulitis or abscess	24	21.4	210	13.2	0.0136
Coronary atherosclerosis & other heart diseases	44	39.3	118	7.4	<.0001
Congestive heart failure	27	24.1	149	9.3	<.0001
Esophageal disorder	24	21.4	214	13.4	0.0175
Chronic kidney disease	26	23.2	197	12.3	0.0009
Other liver disease	8	7.1	276	17.3	0.0054
Acute myocardial infarction	11	9.8	34	2.1	<.0001*
Methicillin-resistant staphylococcus aureus	11	9.8	69	4.3	0.0168*
Myocarditis	11	9.8	86	5.4	0.0496
Other circulatory disease	26	23.2	261	16.3	0.0327*
Peripheral and visceral atherosclerosis	13	11.6	55	3.4	0.0005*
Hyperplasia of prostate	10	8.9	53	3.3	0.0065*

Skin or subcutaneous tissue	32	28.6	291	18.2	0.0119*
Peripheral vascular disease	13	11.6	46	2.9	<.0001*
Renal failure	61	54.5	615	38.5	0.0008
Medication use (during admission)					
Anti-hypertensive medication	90	80.4	850	53.2	<.0001
Diabetic medication	91	81.2	993	62.2	0.0075
Comorbidities (6 months prior)					
Charlson score (median and IQR)	3	1-6	1	0-3	<.0001
Elixhauser score (median and IQR)	3	2-6	2	0-4	<.0001
History of cardiac arrhythmia	36	32.1	299	18.7	0.0006
History of coronary heart	45	40.2	122	7.6	<.0001
History of chronic ulcer	17	15.2	96	6.0	0.0002
History of chronic pulmonary	36	32.1	327	20.5	0.0035
History of chronic renal	27	24.1	169	10.6	<.0001
History of chronic respiratory	36	32.1	327	20.5	0.0035
History of dyslipidemia including hyperlipidemia	59	52.9	244	15.3	<.0001
History of deficiency and other anemia	39	34.8	392	24.6	0.0153
History of coronary atherosclerosis diseases	42	37.5	106	6.6	<.0001
History of acute cerebrovascular disease	15	13.4	46	2.9	<.0001*
History of congestive heart	31	27.7	145	9.1	<.0001
History of crushing or internal injury	<5	2.7	9	0.6	0.0390*
History of disorders diagnosed for non-adults	5	4.5	11	0.7	0.0027*
History of diabetes w/ complication	35	31.3	167	10.5	<.0001
History of diabetes w/o complication	58	51.8	347	21.7	<.0001
History of heart valve disorder	19	17.0	136	8.5	0.0026
History of hepatitis	.	.	69	4.3	0.0208*
History of hypertension w/ complication	22	19.6	131	8.2	<.0001
History of infective arthritis	7	6.3	32	2.0	0.0131*
History of chronic kidney	22	19.6	147	9.2	0.0003

History of later effects of cerebrovascular disease	7	6.3	39	2.4	0.0272*
History of other diseases of	11	9.8	84	5.3	0.0415
History of malaise and fatigue	34	30.4	315	19.7	0.0069
History of acute myocardial infarction	11	9.8	16	1.0	<.0001*
History of myocarditis	16	14.3	70	4.4	<.0001*
History of occlusion or stenosis	5	4.5	25	1.6	0.0421*
History of other endocrine	13	11.6	84	5.3	0.0050
History of other & ill-defined cerebrovascular diseases	9	8.0	22	1.4	<.0001*
History of other & ill-defined heart diseases	14	12.5	89	5.6	0.0029
History of peripheral and visceral atherosclerosis	18	16.1	85	5.3	<.0001
History of skin or subcutaneous tissue infections	30	26.8	296	18.5	0.0314
History of open wounds of extremities	11	9.8	51	3.2	0.0017*
History of mild liver disease	5	4.5	175	11.0	0.0258*
History of peripheral vascular disease	19	17.0	102	6.4	<.0001
History of renal failure	31	27.7	262	16.4	0.0022
History of valvular disease	18	16.1	124	7.8	0.0021
Medication use history (6 months prior)					
Diabetic medication	38	34.0	554	34.7	0.1903

Data are median and interquartile range (IQR) or number and percent of patients.

*Values calculated using Fisher's Exact test

Table 3. Clinical outcomes in statin users vs. non-users

No. of events/No. of patients		HR (95% CI)	
Incident statin users ²	Non-users	Unadjusted	Propensity Adjusted ¹⁾
5/112	113/1,597	0.56 (0.23 - 1.38)	0.45 (0.18- 1.16)
Existing outpatient statin users ³	Non-users		
44/401	113/1,597	1.57 (1.11-2.23)	1.12 (0.75-1.86)
Existing outpatient statin users continuing statin use ⁴	Non-users		
6/232	113/1,597	0.34 (0.15-0.76)	0.37 (0.14-0.96)

HR=hazard ratio; CI=confidence interval.

¹⁾ Adjusted by propensity score quintiles (reference quintile I).

²⁾ The final PS model equation for predicting incident statin exposure.

$$\begin{aligned}
 y = & \alpha + \beta_1 \text{ age} + \beta_2 \text{ Antibiotic use on 1st day of admission} + \\
 & \beta_3 \text{ dyslipidemia including hyperlipidemia} + \beta_4 \text{ gender} + \beta_5 \text{ MRSA} + \\
 & \beta_6 \text{ admitting physician facility} + \beta_7 \text{ Payor} + \beta_8 \text{ DRG ventilation} + \\
 & \beta_9 \text{ DRG sepsis} + \beta_{10} \text{ race} + \beta_{11} \text{ admission type} + \beta_{12} \text{ admission year} + \\
 & \beta_{13} \text{ census region} + \beta_{14} \text{ diabetes mellitus} + \beta_{15} \text{ Allergic reaction} + \\
 & \beta_{16} \text{ Coronary Heart Disease} + \beta_{17} \text{ History of anti -} \\
 & \text{hypertensive medication} + \beta_{18} \text{ History of Coronary Heart Disease} + \\
 & \beta_{19} \text{ History of Phlebitis} + \beta_{20} \text{ History of myocarditis} + \beta_{21} \text{ anti -} \\
 & \text{hypertensive medication} + \beta_{22} \text{ History of Residual codes unclassified} + \\
 & \beta_{23} \text{ History of dyslipidemia including hyperlipidemia} + \\
 & \beta_{24} \text{ History of Chronic obstructive pulmonary disease} + \\
 & \beta_{25} \text{ History of Chest pain} + \beta_{26} \text{ History of Malignant Neoplasm} + \\
 & \beta_{27} \text{ History of anemia} + \beta_{28} \text{ History of Other \& ill - defined heart diseases} + \\
 & \beta_{29} \text{ Cellulitis or abscess} + \\
 & \beta_{30} \text{ History of Other nutritional endocrine metabolic disorder} + \\
 & \beta_{31} \text{ ciprofloxacin} + \beta_{32} \text{ Tobacco use disorder} + \beta_{33} \text{ Infective arthritis} + \\
 & \beta_{34} \text{ Esophageal disorder} + \beta_{35} \text{ History of Blindness and vision defects} + \\
 & \beta_{36} \text{ Chest pain} + \beta_{37} \text{ History of Other endocrine disorder} + \\
 & \beta_{38} \text{ History of Acute myocardial infarction} + \varepsilon
 \end{aligned}$$

3) The final PS model equation for predicting existing, outpatient-only statin exposure.

$$y = \alpha + \beta_1 \text{ age} + \beta_2 \text{ Antibiotic use on 1st day of admission} \\ + \beta_3 \text{ dyslipidemia including hyperlipidemia} + \beta_4 \text{ gender} \\ + \beta_5 \text{ MRSA} + \beta_6 \text{ admitting physician facility} + \beta_7 \text{ Payor} \\ + \beta_8 \text{ DRG ventilation} + \beta_9 \text{ DRG sepsis} + \beta_{10} \text{ race} \\ + \beta_{11} \text{ admission type} + \beta_{12} \text{ admission year} + \beta_{13} \text{ census region} \\ + \beta_{14} \text{ Coronary heart disease} + \beta_{15} \text{ Allergic reaction} \\ + \beta_{16} \text{ Cellulitis of abscess} + \beta_{17} \text{ History of anti} \\ - \text{hypertensive medication} \\ + \beta_{18} \text{ History of Coronary Heart Disease} + \beta_{19} \text{ Anemia} \\ + \beta_{20} \text{ Fever} + \beta_{21} \text{ anti} - \text{hypertensive medication} + \beta_{22} \text{ Gout} \\ + \beta_{23} \text{ Liver disorders} + \beta_{24} \text{ Pancreatic disorders} \\ + \beta_{25} \text{ Ceftriaxone} + \beta_{26} \text{ History of amoxicillin} \\ + \beta_{27} \text{ History of ceftriaxone use} + \beta_{28} \text{ History of depression} \\ + \beta_{29} \text{ History of dyslipidemia} \\ + \beta_{30} \text{ History of Enterococcus infection} \\ + \beta_{31} \text{ History of chronic steroids} + \beta_{32} \text{ History of obesity} \\ + \beta_{33} \text{ Immunization} + \beta_{34} \text{ Immunization} + \beta_{35} \text{ Phlebitis} \\ + \beta_{36} \text{ Chest pain} + \beta_{37} \text{ History of anxiety} \\ + \beta_{38} \text{ History of acute myocardial infarction} + \beta_{39} \text{ Doripenem} \\ + \beta_{41} \text{ History of diabetic medication} + \beta_{42} \text{ Respiratory failure} \\ + \beta_{43} \text{ Chest pain} + \varepsilon$$

4) The final PS model equation for predicting existing- continuous statin exposure.

$$y = \alpha + \beta_1 \text{ age} + \beta_2 \text{ Antibiotic use on 1st day of admission} \\ + \beta_3 \text{ dyslipidemia including hyperlipidemia} + \beta_4 \text{ gender} \\ + \beta_5 \text{ MRSA} + \beta_6 \text{ admitting physician facility} + \beta_7 \text{ Payor} \\ + \beta_8 \text{ DRG ventilation} + \beta_9 \text{ DRG sepsis} + \beta_{10} \text{ race} \\ + \beta_{11} \text{ admission type} + \beta_{12} \text{ admission year} + \beta_{13} \text{ census region} \\ + \beta_{14} \text{ Infective arthritis} + \beta_{15} \text{ History of rehabilitation} \\ + \beta_{16} \text{ History of infective arthritis} + \beta_{17} \text{ Pleurisy} \\ + \beta_{18} \text{ History of gastritis} + \beta_{19} \text{ History of coagulopathy} \\ + \beta_{20} \text{ Allergic reaction} + \beta_{21} \text{ anti} - \text{hypertensive medication} \\ + \beta_{22} \text{ History of dyslipidemia} + \beta_{23} \text{ Ceftriaxone} \\ + \beta_{24} \text{ History of nervous disorders} \\ + \beta_{25} \text{ History of lower respiratory disorders} \\ + \beta_{26} \text{ History of meropenem} \\ + \beta_{27} \text{ History of antibiotic use on 3rd day of admission} \\ + \beta_{28} \text{ Charlson's comorbidity score} \\ + \beta_{29} \text{ Poisoning by medication} + \beta_{30} \text{ Gastritis} \\ + \beta_{31} \text{ Mood disorder} + \beta_{32} \text{ Ampicillin} + \beta_{33} \text{ Glaucoma} \\ + \beta_{34} \text{ History of otitis} + \beta_{35} \text{ History of dizziness} \\ + \beta_{36} \text{ History of acute myocardial infarction} + \varepsilon$$

In the above equations, y is the probability of receiving a statin, α is the intercept, β 's are the coefficients on the independent variables and ε is standard error.

Figure 1. Study timeline for patient selection

Figure 2: Study cohort identification

Figure 3: Adjusted proportional hazards among incident statin users vs. non-users

Note- On the x-axis, 'tmdc' represents "time to death".

Manuscript 3

Title: Optimal Statin Therapy Duration in Bacteremic Patients

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3.1 Abstract

Background: There is no consensus as to whether statin therapy should be continued among patients presenting to the hospital with bacteremia, and if so, what duration would be associated with better survival.

Objectives: To identify a statin therapy duration that would decrease mortality in bacteremic statin users.

Methods: Using Optum Clinformatics™ with matched Premier hospital data (08/2009-03/2013), we conducted a case-control study among bacteremic statin users. Cases who died during the hospitalization were matched 1:1 to survivors on disease risk scores. Duration of statin therapy during the admission was evaluated in patients with at 3 months of pre-admission statin use. Classification and regression tree (CART) analysis was conducted to identify the optimal continued statin use duration which provided the lowest inpatient mortality, and logistic regression was used to calculate the odds of mortality associated with the duration identified in the CART analysis.

Results: We included 58 disease risk score matched pairs of cases and controls. Forty-one percent (n=47) of patients continued statin therapy during the hospital admission, of whom 15 (32%) were cases and 32 (68%) were controls. The CART analysis partitioned the continuation of statin therapy at 1.5 days, which predicted a lower inpatient mortality rate among bacteremic patients with statin exposure higher than this duration compared to those with lower duration, which included those not continuing statin therapy during the admission (29% vs. 62%). The odds of inpatient mortality for bacteremic patients with at least 2 days of continued statin use was

significantly lower than those with less than 2 days of continued use (OR 0.24, 95% CI 0.11-0.55).

Conclusion: Among matched pairs of cases and controls with statin use for at least 90 days prior to the admission, the continuation of statins during the admission for at least 2 days demonstrated a survival benefit among bacteremic patients.

3.2 Introduction

Bloodstream infections are the third most frequent hospital-wide infections in the United States (U.S.), along with pneumonia (both 11%), following urinary tract infection (36%) and surgical site infection (20%).¹ Between 2000 and 2009, inpatient mortality among patients with principal diagnoses of bloodstream infections remained high (16.7% and 16.3%, respectively).² Evidence suggests that statins may improve survival in patients with bacteremia³⁻⁶ and sepsis,⁷⁻⁹ including 14-day⁶, 15-day³, 31-180 day,¹⁰ and all-cause hospital mortality^{4,8}, as well as persistent bacteremia (PB).⁶ While numerous studies have found reduced mortality with statins in bacteremic patients, statin duration and measurement of outcomes differ across these studies.³⁻⁵ As a result, rates of survival vary, particularly as statin exposure varies.^{4,10} Several studies not only observed a decline in inpatient mortality after continuing statin use during admission,^{4,10} but also an increase in mortality after cessation of statin therapy.^{4,11} Since the length of statin treatment time varies between studies, there is no consensus on the duration of statin continuation that would provide the maximum advantage in terms of clinical outcomes.

While several meta-analyses^{12,13} and observational^{4-6,10} studies observed protective effects with statins in bacteremia, one meta-analysis¹⁴ did not observe improvements in clinical outcomes after statin use. However, this meta-analysis was conducted among critically-ill patients with severe sepsis, and some of the included studies only had short durations of statin use.^{4,5,10} Other studies with shorter statin durations also did not demonstrate a statistically significant association between statin use and mortality.^{10,14,15} A recent RCT evaluating benefits of continued statin therapy on inflammatory parameters and sepsis among patients with pre-existing

statin use¹⁶ did not find clinical benefits of continuation. As such, there is a lack of evidence regarding the appropriate exposure duration needed for statins to provide the utmost protective effects in bacteremic patients. The main objective of this study was to identify a time breakpoint of statin continuation which minimized inpatient mortality among bacteremic patients.

3.3 Methods

3.3.1 *Research Design and Methodology*

A case-control study design was used to estimate a time breakpoint in statin continuation at which the highest clinical benefit would be seen in terms of survival (i.e., lowest inpatient mortality). A case-control study is an analytical study that compares individuals who have a specific outcome (cases) with a group of individuals that do not have the outcome (controls). A case-control design was utilized because it is the most effective study design for evaluating multiple exposures when an outcome is rare.¹⁷

3.3.2 *Data Sources*

This study was conducted using deidentified Optum Clinformatics™ (OptumInsight, Eden Prairie, MN) with matched Premier hospital data (10/01/2009-03/31/2013) among adult (≥ 18 years) patients with a primary diagnosis of bacteremia during a hospital admission. This dataset is an administrative claims database from a large commercial health plan (Optum Clinformatics) matched with hospital data (Premier).

3.3.3 *Study Population*

Adult patients with continuous enrollment for at least six months in the commercial health plan prior to hospital admission were included. Patients were included if they were hospitalized between 04/01/2010 and 03/31/2013 with a primary diagnosis of bacteremia or septicemia (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes 003.1, 020.2, 022.3, 036.2, 038.0, 038.1, 038.10-038.12, 038.19, 038.2, 038.3, 038.40-038.44, 038.49, 038.8, 038.9, 054.5, 449, 771.81, 995.91, 995.92, 790.7)¹⁸ by any causative organism. We excluded patients who, on the first three days after hospital admission, did not receive a minimum of two successive days of at least one bacteremic antibiotic therapy.¹⁹⁻²² The index date was defined as the date of the first hospital admission during the study period, and subsequent multiple hospital admissions were not considered for the analysis. From this cohort, only patients with a minimum of 3 months of continuous statin use in the 3 months prior to admission were selected for inclusion (Figure 1).

3.3.4 *Cases and controls*

Cases included those who died during the admission. In a case-control study, controls should be drawn from the same population from which cases are derived, in order to reduce the chance that group differences account for the difference in the exposure being evaluated.²³ Thus, controls were selected from the same cohort of adult patients who had a primary diagnosis of bacteremia on hospital admission and received an antibiotic therapy, but experienced a different outcome (i.e., no inpatient mortality). Controls were matched to cases on disease risk score (DRS).²⁴ DRS is a confounder summary method, commonly used in case-control studies to control for confounding by calculating the predicated probability of an outcome in the absence of

exposure.^{25,26} A recent simulation study²⁷ suggested the DRS model could cause higher bias due to misspecification at higher outcome incidences, however, when the outcome is rare, DRS matching would increase the statistical efficiency of case-control studies. The DRS is considered a useful method in case-control studies,²⁵ especially when the association between covariates and exposure is modest (squared multiple correlation coefficient amid exposure and confounders <90%).²⁸ The stratified DRS is a retrospective balancing score and therefore it works in a similar manner in case-control studies as the propensity score works in cohort studies.²⁶

3.3.5 *Statin duration*

Among the patients with at least 90 days of statin therapy in the 90 days before admission, the primary exposure of interest was the period of continued statin use during admission. The statins included were atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin. Statin use duration was counted as the number of days of statin use between initiation and the last pharmacy record without more than one day gap in therapy. The period of continued statin use during admission was considered to be an exposure among the patients having a similar, minimum pre-admission statin use of at least 3 months. A one day gap in therapy was allowed, but the gap was not counted in the calculation of the statin use period.

3.3.6 *Statistical Analysis*

Disease risk scores (DRS) were calculated to control for confounding. A DRS is the probability of a patient having a particular outcome in the absence of the exposure.^{24,25} Therefore, we calculated DRS as the probability of inpatient mortality among unexposed patients, that is, statin users not continuing use post-admission.

Using likelihood ratio tests, we compared each independent variable to the null model. Variables with a p-value <0.25 in likelihood ratio tests were included in an initial multivariate model and removed using a backward elimination approach, if the p-value of the parameter estimate was less than 0.05 to arrive at the final DRS model. The model was checked for multicollinearity using variance inflation factor (VIF) and correlation matrices, and goodness of fit was checked using the Hosmer-Lemeshow goodness-of-fit test.^{29,30} The final DRS model c-statistics was 0.91. The full DRS model equation can be found in the footnote of the main results. Using nearest neighbor matching within a caliper of 0.25 distance, a single control was selected for each case.³¹ We checked DRS balance between cases and controls using graphical displays (see figure 2).

To partition statin continuation days associated with the lowest risk of death (i.e., highest survival), we conducted a classification and regression tree analysis (CART).^{32,33} The CART analysis, which includes an optimal tree selection based on pruning and cross-validation, identified subsets of patients at lowest risk of death and determined the influence of statin exposure in these subsets of patients. The CART method employs a recursive partitioning for building hierarchical binary classification trees. The CART model fits a simple prediction model within each partition. Each partition is binary, occurring on one explanatory variable at a time and at the point of maximum heterogeneity of the two groups with regards to the dependent variable. CART models are useful because of their non-parametric, non-linear structure.³³ As a result, they do not make any distribution assumptions, they treat the data generation process as unknown, and they do not require a functional form for the predictors. Indeed, tree methods are probably one of the most easily interpreted statistical techniques; they are conceptually simple yet analytically powerful.^{33,34} In the CART

analysis, the primary dependent variable was inpatient mortality (case/control) and the independent variable was days of continued statin exposure during admission. The trees were automatically developed to forecast inpatient mortality by considering every possible cut-point on statin continuation duration at every node in the classification tree. We checked the fitness of the tree by plotting cross-validated error rate vs. size of a tree, and identified an appropriate complexity parameter (CP).^{33,34} Based on the split provided by the CART analysis, conditional logistic regression was conducted to calculate the odds of mortality. All statistical analyses were conducted using either SAS version 9.4 (SAS Institute, Cary, NC) or R software version 3.2.0 (The R Foundation for Statistical Computing) with a recursive partitioning technique “rpart” package that was developed for Splus (Insightful Corporation, Seattle, WA) by Therneau and Atkinson.³⁵ This study was reviewed and approved as exempt by the University of Rhode Island’s Institutional Review Board.

3.4 Results

During the three-year study period, 61 (6.9%) patients died and 821 (93.1%) did not die during their hospital stay amongst the 882 patients with at least 3 months of statin use in the 3 months before admission. Using DRS matching, 58 controls were matched to 58 cases using nearest neighbor matching at a caliper distance of 0.25. Due to matching, baseline characteristics were very similar between cases and controls in terms of age (median 68 vs. 67 years, $p=0.8520$; Table 1), gender (39.7% vs. 43.1% females, $p=0.7992$), race (20.7% vs. 15.5% non-whites, $p=0.7637$), as well as the Charlson comorbidity score during the admission (median=4 vs. 4, $p=0.8239$) and in the six months prior to admission (median=4 vs. 4, $p=0.4959$; Table 2). The length of hospital stay was significantly longer among controls compared to cases (median=9 vs. 5 days, $p=0.0005$). Of the 47 (41%) patients who continued statin use

during the hospital admission, 32% (n=15) were cases and 68% (n=32) were controls. The average statin therapy duration continued during admission among cases and controls was 1.5 ± 3.7 vs. 4.5 ± 7.5 days, respectively.

The CART analysis partitioned the dependent variable of statin therapy duration, suggesting differences in inpatient mortality at different statin continuation durations. See Fig. 3. The study included an equal number (n=58) of cases and controls, producing a 50% survival rate at the root node. The split at 1.5 days predicted patients with <2 days of continued-during-admission statin use (n=74, 64%) have 62.2% probability of inpatient mortality (n=46 of 74), while the patients with ≥ 2 days of continued-during-admission statin use (n=42, 36%), have only 28.6% (n=12 of 42) chances of inpatient mortality. In other words, among bacteremic patients with existing statin use, inpatient survival was higher among those continuing statins for at least 2 days after the admission compared to those not continuing or with 1 day of use (71.4% vs. 37.8%) and the odds of inpatient mortality was 76% lower (OR 0.24, 95% CI 0.11-0.55).

3.5 Discussion

In this DRS matched case-control study, we identified a specific continued statin use duration threshold required to provide the maximum survival benefit among bacteremic patients, which was the continuation of statin therapy for at least 2 days. The 76% lower odds of inpatient mortality among statin users continuing use for at least 2 days agreed with existing literature evaluating this association.^{4,5,10} A retrospective cohort study among bacteremic patients found a reduced adjusted hospital mortality rate (OR 0.39, 95% CI 0.17-0.91, p=0.029) in those taking statins prior to admission, which decreased even further with the continuation of statin during the admission (OR 0.06, 95% CI 0.01-0.44, p=0.0056).⁴ This study also observed

similar finding in terms of deaths attributable to bacteremia in patients with statin use only before admission (OR 0.29, 95% CI 0.10-0.86, $p=0.025$) versus continued during admission (OR 0.09, 95% CI 0.01-0.64, $p=0.016$).

Another study⁵ conducted among bacteremic patients taking a statin at the time of admission and continuing throughout the hospitalization at a Veterans Affairs Medical Center in Washington, identified a therapeutic benefit with statin continuation (adjusted OR 0.13, 95% CI 0.02–0.99). The aforementioned study included mostly males (99.5%), while females made up 41% of our study population.

Our findings imply that the statin use is necessary during a crucial phase of inflammation development, similar to previous studies^{36,37} observing a decline in inflammatory response among patients developing infections while on statin therapy. The extent of improvement in clinical outcomes after statin use among patients with inflammatory disorders is still a dilemma, and the mechanisms of action due to which statins provide clinical benefits remain unconfirmed. There are several possible reasons why existing statin use at the time of inflammation, is necessary to observe clinical benefits in bacteremic patients. Anti-inflammatory properties of statins have been credited to their ability to reduce C-reactive protein (CRP) and cytokines (IL-6, IL-8),^{38,39} and studies have demonstrated that the time required by statins to reduce CRP varies, based on statin dose, patient disease,⁴⁰ and type of statin^{41,42}. For example, pravastatin reduces CRP levels at 12 and 24 weeks,⁴¹ while simvastatin could reduce CRP within 14 days.⁴² Further, low levels (<20 mg/dL) of high-density lipoprotein (HDL) cholesterol on the first day of severe sepsis was found to be associated with an increase in mortality and adverse clinical outcomes.⁴³

Our results differed from the results of a meta-analysis¹² that evaluated an association between outpatient statin use and infectious disease-related mortality, with pooled ORs of 0.62 (95% CI 0.534-0.72), 0.68 (95% CI 0.53-0.89), and 0.86 (95% CI 0.70-1.07) for 30-day, 90-day, and long-term (>1 year) mortality, respectively. Our results may differ from this meta-analysis¹² as we only included bacteremia, while the meta-analysis included bacteremia, sepsis, pneumonia, and other infections in outpatient settings. Additionally, the meta-analysis only evaluated outpatient statin use prior to admission and continuation of statin use during admission was unknown. Conversely, we investigated both statin use before admission and continued during admission.

A recent propensity-score matched cohort study¹⁵ found non-significant beneficial effects with statin use. However, the authors note that pre-admission indications and statin therapy duration were not available. A recent RCT also did not observe benefits of continued statin therapy on inflammatory parameters and sepsis among existing statin users.¹⁶ However, this study has several methodological issues as pointed out in a correspondence by Bostock et. al.,⁴⁴ including a vague primary endpoint, lack of information regarding previous statin therapy duration, and use of the Mann-Whitney test to evaluate the matched groups.

Our study is a step forward in the direction of identifying an optimal statin duration for inflammatory conditions. To the best of our knowledge, this is the first study in a large, privately insured population in the U.S. evaluating an optimal continued statin therapy duration among patients with inflammatory conditions. We utilized a machine-learning analysis method, CART, that allowed us to identify an exact statin therapy duration at which inpatient mortality was lowest among patients

with bacteremia. Other factors may affect the impact of statin therapy on mortality, including baseline differences in patient characteristics, differences in bacteremic severity, regional differences in infections, statin prescription patterns, pre-admission and post-admission comorbid conditions as well as medication use. However, we used DRS to match controls to cases in order to account for confounding. The strength of an observational study generally depends on the quality of the data source. However, we utilized administrative data from a large, national insurer, which is not affected by recall or surveillance bias. Further, used administrative and hospital linked data from a real-world clinical population with health-coverage from a major private payer.

Our study offers evidence regarding continuation of statin therapy in existing statin users presenting to the hospital with bacteremia. Although our findings indicate benefits with continuation of statins during admission, greater information is needed regarding the risks of continuation, in terms of adverse events, to enable a clear benefit-risk assessment. There is an ongoing controversy about the benefit-risk assessment of statins in general ("statin wars")⁴⁵ between editors of two English medical journals, the British Medical Journal (BMJ) and Lancet. In 2014, the BMJ published two papers claiming the side effects from statins are much higher than reported in clinical trials, while statin trial leaders published a review identifying the benefits of statins in the Lancet in 2016. Statins are life saving medications for many patients with evaluated cholesterol and cardiovascular risks, however, for the potential for adverse effects also exist, as with all medications. Despite the well-established benefits of statins in patients with cardiovascular diseases, statin side effects, such as liver damage, diabetes mellitus, and muscle pain, may outweigh the widely accepted benefits. Consequently, any future RCT evaluation of the association

between statin use and clinical outcomes in bacteremic patients should include a benefit-risk assessment.

3.6 Limitations

Our study has a few limitations. First, we were unable to assess adherence or dose-dependent effects of statins that might affect bacteremic mortality. Depending on the severity of the infection, different statin doses and different statins may be used. While statin therapy may be continued more frequently in lower-risk patients, as clinicians hear about the potential protective effects of statins, there may be channeling bias in the opposite direction, where more severe patients are kept on their statin therapy.⁴⁶ Second, our study relied on a claims database, which raises the concern of misclassification due to coding errors throughout medical claims processing. Further, use of this database assumed actual exposure from prescription claims and hospital charges for medications. Third, we could not study differences in mortality with statin continuation duration in bacteremia caused by specific pathogens. A previous study²⁶ observed greater protection with statins in *S. aureus* bacteremia compared to bacteremia caused by Gram-negative bacilli, while also suggesting greater survival in nosocomial versus community-associated bacteremia.²⁶ Our study could not evaluate these differences. Moreover, the sample size of our study was small. Lastly, the limitations of CART analysis include an inability to fully describe the observed data due to uncertainty that remains in the prediction of the model and potential existence of multiple threshold values despite a single “optimal” split.⁴⁷

3.7 Conclusions

In conclusion, this disease risk score matched case-control study conducted in a real-world clinical population identified a time breakpoint of statin continuation which maximized survival among bacteremic patients. Our results corroborate findings from previous studies which indicate continuation of statins during the hospital admission reduces mortality. The findings of our study are unique and add to the literature on regarding the minimal duration of continued statin use.

3.8 References

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Appendix-

Table 1. Demographic and hospitalization-related characteristics in cases and controls

Characteristics	Cases (n=58)		Controls (n=58)		P-value
Age (years)	68	61-77	67	60-82	0.8520
Gender					0.7061
Female	23	39.7	25	43.1	
Male	35	60.3	33	56.9	
Race					0.7637
Non White	12	20.7	9	15.5	
White	46	79.3	49	84.5	
Admitting Physician Facility					0.9190
ICU/Surgery	<5	3.4	<5	3.4	
Medicine	18	31.0	16	27.6	
Other	38	65.5	40	69.0	
Diagnosis-related group (DRG) description					0.8095
Non-Ventilation	47	81.0	48	82.8	
Ventilation	11	19.0	10	17.2	
Hospital admission year					0.9494
2010	10	15.5	9	15.5	
2011	18	37.6	21	36.2	
2012	30	51.7	28	48.3	
Comorbidities (during admission)					0.8239
Charlson score (during admission, median and IQR)	4	2-6	4	2-7	
Elixhauser score (during admission, median and IQR)	6	4-8	6	5-8	0.2870
Comorbidities (6 months prior)					0.4959
Charlson score-History (6 months prior, median and IQR)	4	2-8	4	1-7	
Elixhauser score-History (6 months prior, median and IQR)	5	2-8	5	2-8	0.8413

Data are median and interquartile range (IQR) or number and percent of patients.

Figure 2: Case-control study design

Figure 2: Disease risk scores distribution among cases and controls

Note: On the y-axis, 0 represent controls, while 1 represent cases.
On the x-axis, estimated probability is the disease risk score.

Figure 3: CART model predicting inpatient mortality risk based on continued during admission statin duration among patients with baseline pre-admission statin use of 90 days.

Note: "in.days" represents "continued-during-admission statin therapy duration".

The study included an equal number (n=58) of cases and controls, producing a 50% survival rate at the root node. The split at 1.5 days predicted patients with <2 days of continued-during-admission statin use (n=74, 64%) have 62.2% probability of inpatient mortality (n=46 of 74), while the patients with ≥2 days of continued-during-admission statin use (n=42, 36%), have only 28.6% (n=12 of 42) chances of inpatient mortality. In other words, among bacteremic patients with existing statin use, inpatient survival was higher among those continuing statins for at least 2 days after the admission compared to those not continuing or with 1 day of use (71.4% vs. 37.8%) and the odds of inpatient mortality was 76% lower (OR 0.24, 95% CI 0.11-0.55).

The final DRS model equation for predicting inpatient mortality developed in patients not continuing statins during the admission.

$$\begin{aligned}
y = & \alpha + \beta_1 \text{ age} + \beta_2 \text{ antibiotic use on 1st day of admission} \\
y = & \alpha + \beta_1 \text{ age} + \beta_2 \text{ antibiotic use on 1st day of admission} \\
y = & \alpha + \beta_1 \text{ age} + \beta_2 \text{ Antibiotic use on 1st day of admission} \\
& \beta_3 \text{ dyslipidemia including hyperlipidemia} + \beta_4 \text{ gender} + \beta_5 \text{ MRSA} \\
& + \beta_6 \text{ admitting physician facility} + \beta_7 \text{ Payor} \\
& + \beta_8 \text{ DRG ventilation} + \beta_9 \text{ DRG sepsis} + \beta_{10} \text{ race} \\
& + \beta_{11} \text{ admission type} + \beta_{12} \text{ admission year} + \beta_{13} \text{ census region} \\
& + \beta_{14} \text{ Charlson' comorbidity score during admission} \\
& + \beta_{15} \text{ Shock} + \beta_{16} \text{ History of Peripheral vascular disease} \\
& + \beta_{17} \text{ Chronic obstructive pulmonary disease} + \beta_{18} \text{ Anemia} \\
& + \beta_{19} \text{ History of anemia} + \beta_{20} \text{ Neurological Disorders} \\
& + \beta_{21} \text{ History of gastrointestinal disorders} \\
& + \beta_{22} \text{ nutritional endocrine metabolic disorder} \\
& + \beta_{23} \text{ Fluid and Electrolyte Disorders} \\
& + \beta_{24} \text{ Azithromycin use during admission} \\
& + \beta_{25} \text{ Esophageal disorder} \\
& + \beta_{26} \text{ Ceftriaxone use during admission} + \varepsilon
\end{aligned}$$

Here y is the probability of inpatient mortality, α is the intercept, β 's are the coefficients on the independent variables and ε is standard error.

Figure 4: Cross-validated error rate vs. size of tree for analysis on statin users