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Evidence to support continuation of statin therapy in patients with *Staphylococcus aureus* bacteremia

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Abstract

In addition to cholesterol lowering capabilities, statins possess antiinflammatory and immunomodulatory effects. We sought to quantify the real-world impact of different statin exposure patterns on clinical outcomes in *Staphylococcus aureus* bacteremia. We conducted a retrospective cohort study among hospitalized patients with positive *S. aureus* blood cultures receiving appropriate antibiotics within 48 hours of culture collection (Veterans Affairs hospitals, 2002-2013). Three statin exposure groups were compared to non-users: pretreated statin users initiating therapy in the 30 days prior to culture and either (1) continuing statin therapy after culture, or (2) not continuing after culture, and (3) *de novo* users initiating at culture. Non-users included patients without statins in the year prior to culture through discharge. Propensity score matched Cox proportional hazards regression models were developed. We were able to balance significantly different baseline characteristics using propensity score matching for pretreated without continuation (n=331), pretreated with continuation (n=141), and *de novo* (n=177) statin users as compared to non-users. We observed a significantly lower 30-day mortality rate (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.25-0.84; number needed to treat [NNT] 10) among pretreated and continued statin users, while protective effects were not observed in *de novo* (HR 1.04, 95% CI 0.60-1.82; NNT undefined) or pretreated but not continued (HR 0.92, 95% CI 0.64-1.32; NNT 47) users. In our national cohort study among patients with *S. aureus* bacteremia, continuation of statin therapy among incident statin users was associated with significant beneficial effects on mortality, including a 54% lower 30-day mortality rate.

Introduction

Statins, selective and competitive inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase, are widely used for primary and secondary prevention of cardiovascular diseases (1). The anti-inflammatory, immunomodulatory, and endothelial barrier protection potential of statins have received considerable research attention (1). It has been postulated that the pleiotropic effect of statins may reflect reduced pathogen invasion of host cells (2), decreased levels of proinflammatory cytokines (e.g. tumor necrosis factor-α [TNF-α]), interleukin-6 [IL-6]), and acute phase proteins such as C-reactive protein) (3, 4), or diminished activation of inflammatory cells (e.g. macrophages, T-cells) (5, 6). In fact, a randomized double-blind placebo controlled clinical trial among patients with bacterial infections found significant reductions in TNF-α and IL-6 levels in the statin group compared to the placebo group (7) and another trial observed sinficantly lower IL-6 and improved survival among prior statin users continuing statin therapy (8).

Staphylococcus aureus is one of the most prevalent pathogens of bacteremia (9). *S. aureus* bacteremia is associated with a significant burden of disease and a high case fataility, ranging from 20-30% (10). Laboratory studies have found that statins inhibit *S. aureus* invasion of human endothelial cells (2, 11) and enhance clearance of *S. aureus* by phagocytes through the induction of DNA-based extracellular traps (12). Whether these impressive laboratory observations with statins consistenly result in significant real-world clinical benefits in complex patients with invasive *S. aureus* infections remains unclear. Even less clear is the relationship between statin therapy timing and

duration and subsequent effects on mortality, including the impact of statin initiation at admission/culture, as adjunctive therapy to antibiotics. Though two large meta-analyses have demonstrated protective effects with statins, exposure periods prior to hospitalization (pretreated) and during hospitalization (continuation, *de novo*) vary widely (13, 14). Therefore, the purpose of this study was to compare clinical outcomes in patients with *S. aureus* bacteremia with various statin exposure patterns to those not exposed to statins among a large, national cohort.

Methods

Data Source

The Veterans Health Administration is a nationwide healthcare system for Veterans in the United States (US) which has utilized an electronic medical record since 1999 (15). National VA databases provide comprehensive information on patient care, including International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic and procedure codes, laboratory and microbiology results, vital signs and vital status, and pharmacy data including barcode medication administration records for inpatients, inpatient and outpatient prescription and fill records, and medications prescribed by non-VA providers or purchased by patients at non-VA pharmacies. This study was approved by the Institutional Review Board and Research and Development Committee at the Providence Veterans Affairs Medical Center. The methods described hereafter were pre-specified in our research plan.

Study Population

We conducted a retrospective cohort study quantifying the effect of statin use on clinical outcomes among patients with *S. aureus* bacteremia. We identified adult patients (age ≥ 18 years) admitted to VA hospitals whose blood cultures were positive for *S. aureus* between January 1, 2002 and December 1, 2013. We then assessed antibiotic therapy for each patient during the hospital admission. We included patients who received intravenous β-lactam therapy (ampicillin-sulbactam, nafcillin, oxacillin, piperacillin-tazobactam, cefazolin, cefotetan, cefoxitin, ceftazidime, ceftriaxone, ceftaroline, ertapenem, doripenem, imipenem-cilastatin, or meropenem) or vancomycin for methicillin-susceptible *S. aureus* [MSSA] and vancomycin or ceftaroline for methicillin-resistant *S. aureus* [MRSA] within 48 hours of culture collection. Due to the existing labeling guidance (drug interactions) on temporality suspending statins in patients receiving daptomycin, we did not include patients with initial daptomycin therapy. We excluded patients who died or were discharged on the day of culture or the day after culture. We only evaluated the first admission within the study period after accounting for all inclusion and exclusion criteria.

Statin Use

All statin users were incident users not having used statins in the one year prior to culture. The study was designed with this restriction criterion to avoid healthy user bias. We defined incident pretreated statin users as those initiating a statin (i.e. atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) in the 30 days prior to culture collection. Among pretreated statin users, we included those continuing therapy for at least three days after culture (pretreated with continuation) and those not

continuing therapy after culture (pretreated without continuation). *De novo* users initiated statins on the day of culture or the day after culture. Non-users included patients without any pharmacy records for statins in the year prior to culture collection through discharge.

Outcomes

Our primary outcome was time to 30-day mortality, defined as mortality within 30 days of the index date, i.e. the culture collection date. The secondary outcomes of interest were time to 14-day mortality (mortality within 14 days of the index date), inpatient mortality (mortality during the hospitalization), hospital discharge, intensive care unit (ICU) discharge, 30-day readmission, and 30-day *S. aureus* re-infection. We calculated time for each endpoint from the index date to the event date. ICU discharge was examined among patients whose cultures were taken while in the ICU. For ICU and hospital discharge, if patients died during the hospital admission, we censored them on their date of death. For readmission and re-infection, we computed time from the hospital discharge date to the event date. Patients who died during the admission were not included in the evaluation of post-discharge outcomes. We censored patients on their date of death if they died within 30 days after discharge.

Statistical Analysis

We assessed baseline differences between statin exposure group and non-users using a chi-square or Fisher's exact test for categorical variables and a t-test or non-parametric Wilcoxon Rank Sum test for continuous variables. To generate propensity

scores (the predicted probability of statin use), we developed an unconditional logistic regression model using a manual backward elimination approach (16, 17). In the final propensity score models, we checked for multicollinearity and goodness of fit, and ran propensity score diagnostics (18). We performed nearest neighbor propensity score matching within 0.005 caliper (18) and reviewed subsequent covariate balance between the matched groups (16, 17).

To quantify the effect of statin therapy on clinical outcomes, we used Cox proportional hazards regression models. Cox proportional hazards regression assumptions were assessed, including proportionality (19). These analyses were conducted separately for each statin exposure group, in which separate propensity score models were built for pretreated users with continuation, pretreated users without continuation, and *de novo* users. Subsequent outcomes, compared to non-users, were assessed separately for each of these statin exposure groups. A hazard ratio (HR) above 1 indicated an increased probability of the outcome occurring sooner in the statin exposure group compared to non-users. Number needed to treat was calculated from risk differences among matched pairs. In sensitivity analyses, Cox models were adjusted for propensity score quintiles, with quintile I serving as the reference, and weighted by the inverse probability of treatment (20). All analyses were performed using SAS (SAS Institute Inc., Cary, NC, Version 9.2).

Results

We identified 17,138 patients with *S. aureus* bacteremia who met our inclusion and

exclusion criteria (Figure 1). Of them, 16,448 were non-users of statins, 344 were pretreated without continuation at culture, 159 were pretreated with continuation, and 187 were *de novo* users. Mean statin duration prior to culture was 7 days both among those who continued (standard deviation [sd] 6.9, median 5, interquartile range [IQR] 3-10) and those who did not continue (sd 7.7, median 3, IQR 1-11) statin therapy. Statin-exposed patients were significantly older (mean 69.7 to 71.7 years; Table 1) and more likely to have been in intensive care at the time of culture collection (22.7% to 29.6%) than non-users (67 years, 19.8% intensive care at culture, $p<0.05$). Half of non-users had MSSA and half had MRSA. A similar distribution was observed among the statin exposure groups, except *de novo* users were more likely to have MSSA (58.3% versus 50.2%, $p<0.05$). Sepsis was significantly less common among the pretreated exposure groups compared to non-users (pretreated without continuation 78.2% versus 83.2%, $p<0.05$; pretreated with continuation 72.3% versus 83.2%, $p<0.05$).

Comorbidity scores during the hospital admission were similar between the exposed groups and non-users (Table 2), however there was a lower overall comorbidity burden in the year prior to the current admission among pretreated users with continuation (mean Charlson 2.5, sd 2.9) and *de novo* users (mean Charlson 2.7, sd 3.1) compared to non-users (mean Charlson 3.2, sd 3.1, $p<0.05$ for both comparisons). Despite similar overall comorbidity burden between statin users and non-users, the burden of cardiovascular diseases was significantly higher among the statin exposure groups, both during the current admission and in the previous year, as was utilization of medications for hypertension and diabetes. The overall 30-day mortality rate was 20.2%

in our study population. The median time to 30-day mortality was similar between non-users (11 days, IQR 5-18, 20.3%) and pretreated statin users without continuation (12 days, IQR 6-18, 19.0%) and *de novo* users (12 days, IQR 9-17, 16.6%), yet it was significantly lower among pretreated statin users with continuation of therapy (18 days, IQR 9-23, 13.8%, $p<0.05$).

Baseline characteristics were balanced between statin users and non-users within propensity score matched pairs (pretreated without continuation, n=331; pretreated with continuation, n=141; *de novo*, n=177). Characteristics included in the propensity score models, including initial antibiotic treatment, treating specialty, MSSA/MRSA, sepsis, statin indication, and other characteristics independently associated with the exposure groups or the outcomes, can be found in Supplemental Table 1. Each model demonstrated goodness of fit, with high C-statistics of 0.86-0.92, indicating excellent discrimination between the groups (21), and complete overlap in propensity score distributions between statin exposure groups and non-users (pretreated without continuation, mean 0.094, sd 0.101, median 0.054, IQR 0.022-0.132; pretreated with continuation, mean 0.098, sd 0.110, median 0.052, IQR 0.020-0.137; *de novo*, mean 0.076, sd 0.095, median 0.037, IQR 0.016-0.099).

Time to event analyses comparing statin users to non-users (reference group) are presented in Table 3. No significant differences were observed between non-users and two of the statin exposure groups (pretreated without continuation, *de novo*) for any of the outcomes assessed. The rate of 30-day mortality was significantly lower in

pretreated statin users with continuation compared to propensity matched non-users (HR 0.46, 95% CI 0.25-0.84) but not among pretreated users who did not continue statin therapy after culture (HR 0.92, 95% CI 0.64-1.32) or *de novo* users (HR 1.04, 95% CI 0.60-1.82). Among pretreated statin users continuing statin therapy after culture, 14-day mortality was also significantly lower than that of non-users (HR 0.35, 95% CI 0.15-0.83), however, significant differences were not observed for the other outcomes assessed, including inpatient mortality.

Similar results were observed in sensitivity analyses utilizing propensity score quintile adjustment (Supplemental Tables 2-4). Sensitivity analyses with inverse probability of treatment weighting (IPTW) also demonstrated significantly lower mortality rates among pretreated statin users with continuation (14-day mortality HR 0.15, 95% CI 0.07-0.32); 30-day mortality HR 0.17, 95% CI 0.10-0.30; inpatient mortality HR 1.39, 95% CI 1.19-1.62; Supplemental Tables 2-4). Alternatively, in IPTW analyses, statin users without continuation had significantly higher mortality compared with non-users, including 14-day mortality (HR 3.81, 95% CI 3.26-4.44), 30-day mortality (HR 2.84, 95% CI 2.46-3.28), and inpatient mortality (3.76, 95% CI 3.23-4.36). In *de novo* statin users, the 30-day readmission rate was significantly higher than non-users (HR 1.75, 95% CI 1.11-2.75), as was 30-day S. aureus reinfection (HR 12.33, 95% CI 1.21-125.59).

The 30-day mortality risk difference in pretreated statin users with continuation versus non-users, was 99 per 1,000 patients (95% CI 10-189 per 1,000) and the number needed to treat (NNT) was 10. For 14-day mortality, the risk difference was 78 per

1,000 patients (95% CI 8-148 per 1,000) and the NNT was 13. The 14-day and 30-day survival probability curves for pretreated statin users with continuation versus non-users can be found in Figure 2.

Discussion

Recent statin initiation with continuation of statin therapy for at least 3 days after culture was associated with a substantial protective effect on mortality among our large, national, real-world cohort with *S. aureus* bacteremia. These findings were robust in our primary analyses using propensity score matching, and in our sensitivity analyses using propensity score quintile adjustment and inverse probability of treatment weighting. *In vitro* research suggests statins may confer protective effects in *S. aureus* bacteremia since they i) inhibit *S. aureus* invasion of human endothelial cells (2, 11); ii) interfere with *S. aureus* biofilm formation (22); and iii) enhance clearance of *S. aureus* by phagocytes through the induction of DNA-based extracellular traps (12). Consistent with our findings, several meta-analyses have identified protective effects with statins on all-cause mortality among patients with various types of infections. Pleiotropic effects with statins were evaluated among patients with sepsis, pneumonia, or bacteremia by pooling 20 published studies (13). The authors reported a 50% reduced mortality in statin users (pooled OR 0.49, 95% CI 0.37-0.61). The bacteremia-related mortality (evaluated in 4 studies out of 20) was also significantly lower in statin users (pooled OR 0.33, 95% CI 0.09-0.75). Another meta-analysis found that outpatient use of statins was associated with a 29% decreased risk of all-cause mortality in patients with any infection (pooled OR across 41 studies 0.71, 95% CI 0.64-0.78) (14).

Among the included studies in both meta-analyses, exposure periods prior to hospitalization (pretreated) and after hospitalization (continuation, *de novo*) varied widely, and sensitivity analyses by statin exposure timing and duration were not conducted (13, 14). Indeed, some studies have included patients with such varied statin exposures, application of the study findings to clinical practice would not be possible. One observational study defined statin use as presence of a statin on the day of culture, regardless of previous or continued use (23). This statin exposure definition combined both prevalent (of unknown timing and duration) and incident statin users, as well as patients continuing and not continuing statin therapy. Not surprisingly, statin use in this study was not associated with reductions in 90-day mortality, ICU admission, or hospital/ICU discharge when adjusting for confounders, including indications for statin therapy, using propensity score methods (23).

In our study, pretreated patients who continued on statin therapy experienced decreased rates of mortality while these protective effects were not observed in pretreated patients who did not continue statin therapy or in patients with *de novo* use. These results support statin continuation through the period of inflammation, as effects on the inflammatory response are no longer observed once the statin is discontinued (24). Similar results were observed in a multicenter randomized placebo-controlled trial of 250 patients with severe sepsis assigned to statin therapy (n=123) or placebo (n=127) (8). Randomization accounted for prior statin use, defined as at least 2 weeks of statin use prior to hospitalization (prevalent users) or no use in the 2 weeks before admission; those with

less than 2 weeks of statin use prior to admission were excluded. Pretreated statin users assigned to statin therapy had a lower 28-day mortality (5% vs 11%; p = 0.01) compared to placebo, although like our study, inpatient mortality was not significantly lower. Further, 28-day mortality in *de novo* users was similar to the placebo group (16.3% vs 14.9%; p=0.78). It should be noted that duration of previous statin use was not assessed in the clinical trial and as such, variations in outcomes may have existed by duration. Although the study size was likely too small to detect any such differences (pretreated assigned to statins n=37, pretreated assigned to placebo n=40).

We only know of one other study specifically examining the effects of statins on patient mortality in *S. aureus* bacteremia (25). A prospective cohort study, which included 160 *S. aureus* bacteremia episodes from one hospital in Spain, found that the 33 statin users were less likely to die within 14 days than non-users (adjusted odds ratio [OR] 0.08, 95% CI 0.01-0.66) but a significant difference between groups was not observed for 30-day (adjusted OR 0.35, 95% CI 0.10-1.23; p=0.10). Statin exposure was defined as prevalent statin use at bacteremia onset, and all users had at least one month of previous statin therapy. Another limitation of this Spanish study, besides prevalent statin use, was that 23/33 (70%) of the statin users had a vascular catheter as the source of bacteremia, compared to only 46/127 (36%) in non-users. Given that vascular catheters are a readily removable source of bacteremia with lower mortality rates than other sources, such a difference is difficult to ignore (26). In our study, catheter source was similar between statin exposure groups and non-users (Table 1).

Although most observational studies have confirmed the protective effects of statins on clinical outcomes in bacterial infections (25, 27-29), there is a concern surrounding this association due to the possibility of healthy user bias (30, 31). Patients taking preventive medications, such as statins, are more likely to have healthier behaviors resulting in favorable outcomes, including lower mortality rates, compared with sicker patients (32, 33). A multicenter inception cohort study conducted by Yende et al. supported this trend among statin users, providing evidence that statin use was significantly associated with good health behaviors, including health insurance, good functional status, and immunizations (34). Our approach to minimizing healthy user bias in our study was three-fold (35). First, we designed our study to only include incident statin users and to assess patients continuing statin therapy as one exposure group and those not continuing as a separate exposure group, both of which were compared to a common reference group of non-users. Second, we included proxies for healthy behaviors in our propensity score model, including use of preventative services (e.g. vaccination and health screenings) and conditions that impact health behaviors. Third, we implemented propensity score matching to identify non-users with similar distributions of important patient characteristics related to health. By excluding prevalent statin users, we believe our study minimized the potential for healthy user bias as this bias is observed in chronic medication use (31).

There are limitations in our study. First, although we employed propensity score methods to address potential confounders of the association between use of statins and the clinical outcomes, we were unable to control for unmeasured confounding. These

methods allowed us to balance confounders of the exposure-outcome relationship that were included in the propensity score, however it could not control for unbalanced factors that were not measured in our study. Second, variations in point estimates were observed with propensity score matching, adjustment, and inverse probability of treatment weighting. Though propensity score matching produced the most conservative estimates, it also resulted in the greatest balance between groups. Third, we attempted to identify incident statin use in order to assess the effect of statins at the time of *S. aureus* infection. We defined incident use as initiation in the 30 days prior to culture, with no prior statin exposure in the previous year. As such, incident use did not necessarily mean throughout the patient's lifetime. Therefore, our estimates may not completely rule out the influence of historical statin use (beyond the window that we defined in this study) on the outcomes. Fourth, our study results should be applied carefully in the general population since our study was conducted among Veterans, and approximately 98% were male. Fifth, as a retrospective study of existing data, the accuracy of operational definitions depends on the data source. Though we utilized one of the most comprehensive and accurate data sources for health outcomes research available in the United States, misclassification may still occur. For example, culture source is a free text field in the microbiology data, and therefore, without mention of a catheter in that field, we could not determine whether it was a catheter source. Lastly, we did not assess outcomes for specific statins or doses, which is an important area of inquiry as some data suggests added benefit of high potency or high dose statins (36, 37).

Conclusions

Our large, national, real-world cohort study showed that continuation of statins in recent initiators significantly lowered the risk of 30-day mortality in *S. aureus* bacteremia. By continuing statins in 10 patients, 1 death would be prevented in the 30 days after culture. New initiation of statins as adjunctive therapy to antibiotics still requires further investigation as a potential measure to optimize positive clinical outcomes, and should include clinical observational research and pragmatic trials to assure greater real-world application of the findings.

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Conflicts of Interest

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References

1. **Hennessy E, Adams C, Reen FJ, O'Gara F.** 2016. Is There Potential for Repurposing Statins as Novel Antimicrobials? Antimicrob Agents Chemother **60:**5111-5121.
2. **Horn MP, Knecht SM, Rushing FL, Birdsong J, Siddall CP, Johnson CM, Abraham TN, Brown A, Volk CB, Gammon K, Bishop DL, McKillip JL, McDowell SA.** 2008. Simvastatin inhibits *Staphylococcus aureus* host cell invasion through modulation of isoprenoid intermediates. J Pharmacol Exp Ther **326:**135-143.
3. **Rosenson RS, Tangney CC, Casey LC.** 1999. Inhibition of proinflammatory cytokine production by pravastatin. Lancet **353:**983-984.
4. **Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S.** 2001. Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation **103:**1933-1935.
5. **Fehr T, Kahlert C, Fierz W, Joller-Jemelka HI, Riesen WF, Rickli H, Wüthrich RP, Ammann P.** 2004. Statin-induced immunomodulatory effects on human T cells in vivo. Atherosclerosis **175:**83-90.
6. **Kwak B, Mulhaupt F, Myit S, Mach F.** 2000. Statins as a newly recognized type of immunomodulator. Nat Med **6:**1399.
7. **Novack V, Eisinger M, Frenkel A, Terblanche M, Adhikari NJ, Douvdevani A, Amichay D, Almog Y.** 2009. The effects of statin therapy on inflammatory cytokines in patients with bacterial infections: a randomized double-blind placebo controlled clinical trial. Intensive Care Med **35:**1255-1260.

8. **Kruger P, Bailey M, Bellomo R, Cooper DJ, Harward M, Higgins A, Howe B, Jones D, Joyce C, Kostner K, McNeil J, Nichol A, Roberts MS, Syres G, Venkatesh B, Group AN-SI-ACT.** 2013. A multicenter randomized trial of atorvastatin therapy in intensive care patients with severe sepsis. Am J Respir Crit Care Med **187:**743-750.

9. **Goto M, Al-Hasan MN.** 2013. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect **19:**501-509.

10. **Kern WV.** 2010. Management of *Staphylococcus aureus* bacteremia and endocarditis: progresses and challenges. Curr Opin Infect Dis **23:**346-358.

11. **Pruefer D, Makowski J, Schnell M, Buerke U, Dahm M, Oelert H, Sibelius U, Grandel U, Grimminger F, Seeger W, Meyer J, Darius H, Buerke M.** 2002. Simvastatin inhibits inflammatory properties of *Staphylococcus aureus* α-toxin. Circulation **106:**2104-2110.

12. **Chow OA, von Köckritz-Blickwede M, Bright AT, Hensler ME, Zinkernagel AS, Cogen AL, Gallo RL, Monestier M, Wang Y, Glass CK, Nizet V.** 2010. Statins enhance formation of phagocyte extracellular traps. Cell Host Microbe **8:**445-454.

13. **Janda S, Young A, FitzGerald JM, Etminan M, Swiston J.** 2010. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. J Crit Care **25:**656.e657-656.e622.

14. **Ma Y, Wen X, Peng J, Lu Y, Guo Z, Lu J.** 2012. Systematic review and meta-analysis on the association between outpatient statins use and infectious disease-related mortality. PLoS ONE **7:**e51548.

15. **Hynes DM.** 2013. Overview of VA data, information systems, national databases and research uses, *on* VA Information Resource Center. http://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/video_archive.cfm?SessionID=751. Accessed Jun 25.

16. **D'Agostino RB, Jr.** 1998. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med **17:**2265-2281.

17. **Rubin DB.** 1997. Estimating causal effects from large data sets using propensity scores. Ann Intern Med **127:**757-763.

18. **Austin PC.** 2011. An Introduction to propensity score methods for rReducing the effects of confounding in observational studies. Multivariate Behav Res **46:**399-424.

19. **Hosmer DW, Lemeshow S.** 1999. Applied Survival Analysis: Regression Modeling of Time to Event Data. John Wiley & Sons, Inc, New York, NY.

20. **Hernán MA, Robins JM.** 2016. Causal Inference. Chapman & Hall/CRC, forthcoming, Boca Raton, FL.

21. **Hosmer DW, Lemeshow S.** 2000. Applied Logistic Regression, 2nd ed. Hohn Wiley & Sons, Inc., New York, NY.

22. **Graziano TS, Cuzzullin MC, Franco GC, Schwartz-Filho HO, de Andrade ED, Groppo FC, Cogo-Muller K.** 2015. Statins and antimicrobial effects: simvastatin

as a potential drug against *Staphylococcus aureus* biofilm. PLoS One **10:**e0128098.

23. **Leung S, Pokharel R, Gong MN.** 2012. Statins and outcomes in patients with bloodstream infection: a propensity-matched analysis. Crit Care Med **40:**1064-1071.

24. **Almog Y, Novack V, Eisinger M, Porath A, Novack L, Gilutz H.** 2007. The effect of statin therapy on infection-related mortality in patients with atherosclerotic diseases. Crit Care Med **35:**372-378.

25. **López-Cortés LE, Gálvez-Acebal J, del Toro MD, Velasco C, de Cueto M, Caballero FJ, Muniain MA, Pascual Á, Rodríguez-Baño J.** 2013. Effect of statin therapy in the outcome of bloodstream infections due to *Staphylococcus aureus*: a prospective cohort study. PLoS ONE **8:**e82958.

26. **Rose WE, Eickhoff JC, Shukla SK, Pantrangi M, Rooijakkers S, Cosgrove SE, Nizet V, Sakoulas G.** 2012. Elevated serum interleukin-10 at time of hospital admission is predictive of mortality in patients with *Staphylococcus aureus* bacteremia. J Infect Dis **206:**1604-1611.

27. **Liappis AP, Kan VL, Rochester CG, Simon GL.** 2001. The effect of statins on mortality in patients with bacteremia. Clin Infect Dis **33:**1352-1357.

28. **Kruger P, Fitzsimmons K, Cook D, Jones M, Nimmo G.** 2006. Statin therapy is associated with fewer deaths in patients with bacteraemia. Intensive Care Med **32:**75-79.

29. **Hsu J, Andes DR, Knasinski V, Pirsch J, Safdar N.** 2009. Statins are associated with improved outcomes of bloodstream infection in solid-organ transplant recipients. Eur J Clin Microbiol Infect Dis **28:**1343-1351.

30. **Majumdar SR, McAlister FA, Eurich DT, Padwal RS, Marrie TJ.** 2006. Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study. BMJ **333:**999.

31. **Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, Solomon DH.** 2007. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol **166:**348-354.

32. **Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA.** 2006. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ **333:**15.

33. **White HD.** Adherence and outcomes: it's more than taking the pills. Lancet **366:**1989-1991.

34. **Yende S, Milbrandt EB, Kellum JA, Kong L, Delude RL, Weissfeld LA, Angus DC.** 2011. Understanding the potential role of statins in pneumonia and sepsis. Crit Care Med **39:**1871-1878.

35. **Shrank WH, Patrick AR, Brookhart MA.** 2011. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med **26:**546-550.

36. **Ouellette DR, Moscoso EE, Corrales JP, Peters M.** 2015. Sepsis outcomes in patients receiving statins prior to hospitalization for sepsis: comparison of in-

hospital mortality rates between patients who received atorvastatin and those who received simvastatin. Ann Intensive Care **5:**9.

37. **Ou SY, Chu H, Chao PW, Ou SM, Lee YJ, Kuo SC, Li SY, Shih CJ, Chen YT.** 2014. Effect of the use of low and high potency statins and sepsis outcomes. Intensive Care Med **40:**1509-1517.

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

Characteristics	**Unexposed (n=16448)**	**Pretreated without continuation (n=344)**	**Pretreated with continutation (n=159)**	***De novo* (n=187)**
Age (years)	67.0 ± 12.5	69.7 ± 10.9*	71.7 ± 10.5*	71.6 ± 11.3*
Body mass index	26.6 ± 7.1	28.3 ± 7.1*	27.3 ± 6.8	27.3 ± 6.5
Male gender	16068 (97.7)	341 (99.1)	157 (98.7)	183 (97.9)
White race	10202 (62.0)	250 (72.7)*	105 (66.0)	112 (59.9)
Hispanic ethnicity	1013 (6.2)	18 (5.2)	7 (4.4)	9 (4.8)
Year				
2002-2005	6605 (40.2)	121 (35.2)	54 (34.0)	48 (25.7)*
2006-2009	5621 (34.2)	133 (38.7)	59 (37.1)	72 (38.5)*
2010-2013	4222 (25.7)	90 (26.2)	46 (28.9)	67 (35.8)*
Admission source				
Home	14632 (89.0)	303 (88.1)*	145 (91.2)*	161 (86.1)
Hospital	669 (4.1)	24 (7.0)*	10 (6.3)*	14 (7.5)

Nursing home	1147 (7.0)	17 (4.9)*	4 (2.5)*	12 (6.4)
Intensive care at culture	3262 (19.8)	78 (22.7)	47 (29.6)*	49 (26.2)*
Treating specialty				
General medicine	9807 (59.6)	185 (53.8)	82 (51.6)*	106 (56.7)*
Intensive care	3468 (21.1)	85 (24.7)	50 (31.5)*	56 (29.9)*
Surgery	1749 (10.6)	47 (13.7)	22 (13.8)*	17 (9.1)*
Other	1424 (8.7)	27 (7.8)	5 (3.1)*	8 (4.3)*
Region of facility				
Midwest	3096 (18.8)	58 (16.9)	30 (18.9)*	39 (20.9)*
Northeast	2295 (13.9)	50 (14.5)	14 (8.8)*	32 (17.1)*
South	7372 (44.8)	151 (43.9)	99 (62.3)*	94 (50.3)*
West	3685 (22.4)	85 (24.7)	16 (10.1)*	22 (11.8)*
Source of infection[1)]				
Catheter	349 (2.1)	10 (2.9)	3 (1.9)	2 (1.1)
Endocarditis[2)]	579 (3.5)	8 (2.3)	2 (1.3)	13 (6.9)
Respiratory culture site	1216 (7.4)	27 (7.8)	9 (5.7)	7 (3.7)
Skin and soft tissue culture site	2130 (12.9)	55 (16.0)	14 (8.8)	25 (13.4)
Urine	2083 (12.7)	31 (9.0)*	7 (4.4)*	31 (16.6)
S. aureus pathogen				
MRSA infection	8184 (49.8)	172 (50)	73 (45.9)	78 (41.7)*
MSSA infection	8264 (50.2)	172 (50.0)	86 (54.1)	109 (58.3)*

Sepsis	13676 (83.2)	269 (78.2)*	115 (72.3)*	156 (83.4)

Data are mean ± standard deviation or number (%) of patients.

MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible S*taphylococcus aureus*

[1)] Culture-confirmed source of infection ±24 hours from culture collection unless indicated otherwise.

[2)] Source of infection identified from ICD-9-CM diagnosis codes ±24 hours from culture collection.

* $p<0.05$ for pairwise comparison between statin exposure group and non-user group.

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

Characteristics	**Unexposed (n=16448)**	**Pretreated without continuation (n=344)**	**Pretreated with continuation (n=159)**	***De novo* (n=187)**
Time to antibiotic treatment initiation from culture collection (days)	0 (1-0)	0 (1-0)	0 (1-0)	0 (1-0)
Length of antibiotic therapy (days)	9 (15-5)	9 (14.5-6)	10 (14-6)	10 (15-6)
Time to culture collection from admission (days)	0 (5-0)	2 (9-0)*	4 (10-1)*	0 (0-0)*
Surgery during current admission	5808 (35.3)	123 (35.8)	65 (40.9)	62 (33.2)
Comorbidity during current admission				
Charlson score	3.2 ± 2.7	3.4 ± 2.6	3.4 ± 2.6	3.3 ± 2.5
Alcohol abuse	820 (5.0)	12 (3.5)	12 (7.6)	10 (5.4)
Cancer	1798 (10.9)	34 (9.9)	13 (8.2)	7 (3.7)*
Cardiac arrhythmia	2348 (14.3)	71 (20.6)*	32 (20.1)*	35 (18.7)
Cerebrovascular disease	1465 (8.9)	49 (14.2)*	25 (15.7)*	38 (20.3)*

Chronic renal disease	1783 (10.8)	47 (13.7)	23 (14.5)	27 (14.4)
Chronic respiratory disease	815 (5.0)	15 (4.4)	12 (7.6)	6 (3.2)
Congestive heart failure	2924 (17.8)	99 (28.8)*	57 (35.9)*	57 (30.5)*
Coronary heart disease	1703 (10.4)	88 (25.6)*	55 (34.6)*	53 (28.3)*
Diabetes	5607 (34.1)	170 (49.4)*	58 (36.5)	83 (44.4)*
Hypertension	8175 (49.7)	210 (61.1)*	99 (62.3)*	111 (59.4)*
Mild liver disease	1792 (10.9)	10 (2.9)*	8 (5.0)*	8 (4.3)*
Myocardial infarction	860 (5.2)	52 (15.1)*	42 (26.4)*	45 (24.1)*
Peripheral vascular disease	414 (2.5)	19 (5.5)*	5 (3.1)	4 (2.1)
Medication use during current admission				
Anti-hypertensive medication	11590 (70.5)	306 (88.9)*	148 (93.1)*	163 (87.2)*
Diuretic	7896 (48.0)	209 (60.8)*	87 (54.7)	95 (50.8)
Diabetic medication (oral)	1971 (12.0)	68 (19.8)*	17 (10.7)	32 (17.1)*
Insulin	8174 (49.7)	229 (66.6)*	81 (50.9)	100 (53.5)
Corticosteroid	4283 (26.0)	99 (28.8)	27 (17.0)*	37 (19.8)
H2RA/PPI	12656 (76.9)	283 (82.3)*	129 (81.1)	133 (71.1)
NSAID	2820 (17.1)	46 (13.4)	18 (11.3)	29 (15.5)

Medical conditions in year prior to current admission[1)]				
Low-density lipoprotein testing	8358 (50.8)	220 (64.0)*	106 (66.7)*	88 (47.1)
Low-density lipoprotein (mg/dL)	83 (62-107)	82 (60-116)	89 (68-121)*	87 (65-120)
Previous alcohol abuse	632 (3.8)	9 (2.6)	5 (3.1)	2 (1.1)*
Previous cancer	897 (5.4)	18 (5.2)	2 (1.3)*	7 (3.7)
Previous cardiac arrhythmia	1220 (7.4)	36 (10.5)*	13 (8.2)	12 (6.4)
Previous chronic renal disease	968 (5.9)	23 (6.7)	9 (5.7)	10 (5.4)
Previous chronic respiratory disease	471 (2.9)	9 (2.6)	1 (0.6)	3 (1.6)
Previous coronary heart disease	1219 (7.4)	64 (18.6)*	25 (15.7)*	19 (10.2)
Previous hypertension	9313 (56.6)	236 (68.6)*	96 (60.4)	99 (52.9)
Previous mild liver disease	1030 (6.3)	11 (3.2)*	6 (3.8)	8 (4.3)
Previous myocardial infarction	654 (4.0)	47 (13.7)*	15 (9.4)*	15 (8.0)*

Previous skin or subcutaneous tissue infection	892 (5.4)	24 (7.0)	6 (3.8)	17 (9.1)*
History of medication use[2)]				
Anti-hypertensive medication	10253 (62.3)	314 (91.3)*	143 (89.9)*	93 (49.7)*
Diuretic	6836 (41.6)	210 (61.1)*	92 (57.9)*	49 (26.2)*
Diabetic medication (oral)	2336 (14.2)	98 (28.5)*	21 (13.2)	28 (15.0)
Insulin	5330 (32.4)	196 (57.0)*	77 (48.4)*	40 (21.4)*
Corticosteroid	3880 (23.6)	92 (26.7)	31 (19.5)	24 (12.8)*
H2RA/PPI	9455 (57.5)	262 (76.2)*	110 (69.2)*	59 (31.6)*
NSAID	3312 (20.1)	78 (22.7)	23 (14.5)	19 (10.2)*
Influenza vaccination	2010 (12.2)	44 (12.8)	15 (9.4)	26 (13.9)
Previous surgery[1)]	4956 (30.1)	115 (33.4)	32 (20.1)*	43 (23.0)*
Previous hospitalization[1)]	9294 (56.5)	220 (64.0)*	78 (49.1)	75 (40.1)*
Previous nursing home stay[1)]	1596 (9.7)	24 (7.0)	9 (5.7)	12 (6.4)

Data are mean ± standard deviation, median (interquatile range q1-q3) or number (%) of patients.

H2RA=histamine-2 receptor antagonist; PPI=proton pump inhibitor; NSAID= non-steroidal anti-inflammatory drug.

[1)] Present in the 1 year prior to the *Staphylococcus aureus* bacteremia hospitalization.

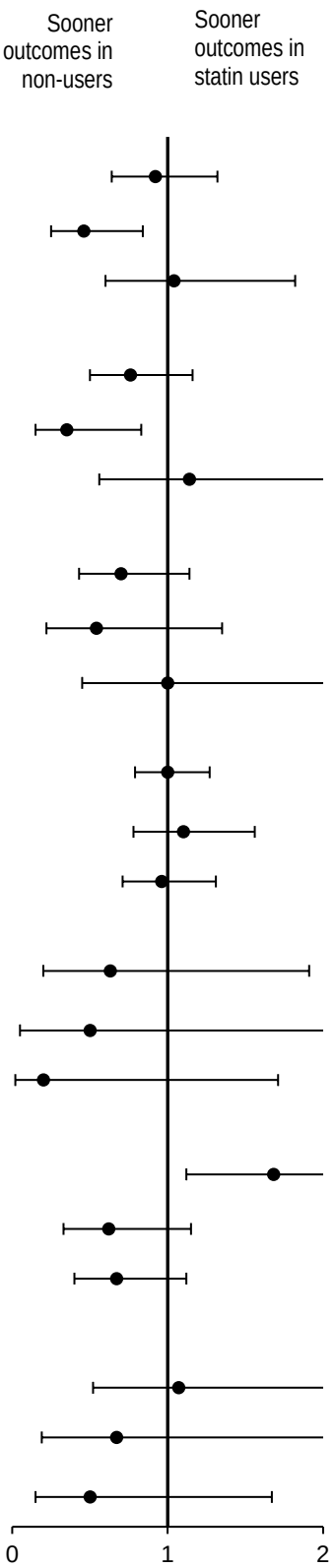
[2)] Present in the 90 days prior to the *Staphylococcus aureus* bacteremia hospitalization.

[3)]Source of infection identified from ICD-9-CM diagnosis codes.

* p<0.05 for pairwise comparison between statin exposure group and non-user group.

Table 3. Clinical outcomes in propensity matched statin users and non-users

Outcomes	No. of events/No. of patients		HR (95% CI)
	Statin users	Non-users	
30-day mortality			
Pretreated without continuation	63/331	70/331	0.92 (0.64 - 1.32)
Pretreated with continuation	19/141	33/141	**0.46 (0.25 – 0.84)**
De novo	27/177	27/177	1.04 (0.60 – 1.82)
14-day mortality			
Pretreated without continuation	40/331	54/331	0.76 (0.50-1.16)
Pretreated with continuation	9/141	20/141	**0.35 (0.15-0.83)**
De novo	16/177	16/177	1.14 (0.56-2.34)
Inpatient mortality			
Pretreated without continuation	53/331	60/331	0.70 (0.43 - 1.14)
Pretreated with continuation	21/141	27/141	0.54 (0.22 – 1.35)
De novo	21/177	19/177	1.00 (0.45 – 2.23)
Discharge			
Pretreated without continuation	278/331	271/331	1.00 (0.79-1.27)
Pretreated with continuation	120/141	114/141	1.10 (0.78-1.56)
De novo	156/177	158/177	0.96 (0.71-1.31)
ICU discharge			
Pretreated without continuation	61/72	52/68	0.63 (0.20-1.91)
Pretreated with continuation	33/39	17/28	0.50 (0.05-5.51)
De novo	33/42	32/39	0.20 (0.02-1.71)
30-day readmission			
Pretreated without continuation	83/278	58/271	1.68 (1.12 - 2.52)
Pretreated with continuation	27/120	34/114	0.62 (0.33 – 1.15)
De novo	33/156	42/158	0.67 (0.40 – 1.12)
30-day S. aureus re-infection			
Pretreated without continuation	20/278	16/271	1.07 (0.52-2.22)
Pretreated with continuation	5/120	7/114	0.67 (0.19-2.36)
De novo	4/156	9/158	0.50 (0.15-1.66)



HR=hazard ratio; CI=confidence interval; ICU=intensive care unit; DC=discontinued. Propensity score matched within a 0.005 caliper range. The propensity score was derived from an unconditional logistic regression model and controlled for the variables listed in Supplemental Tables 2-4.

Figure 1. Study cohort identification. MRSA= methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*

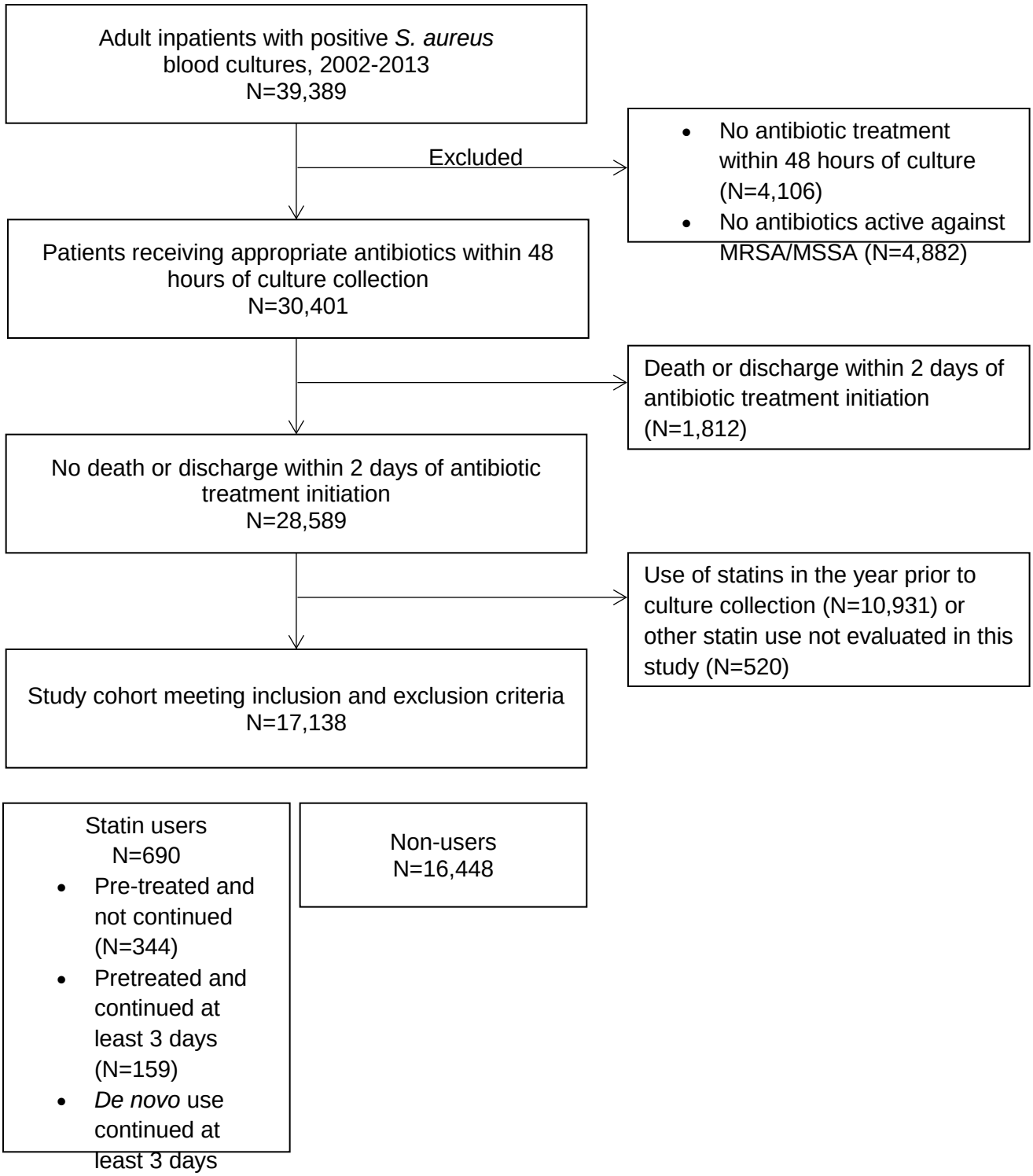
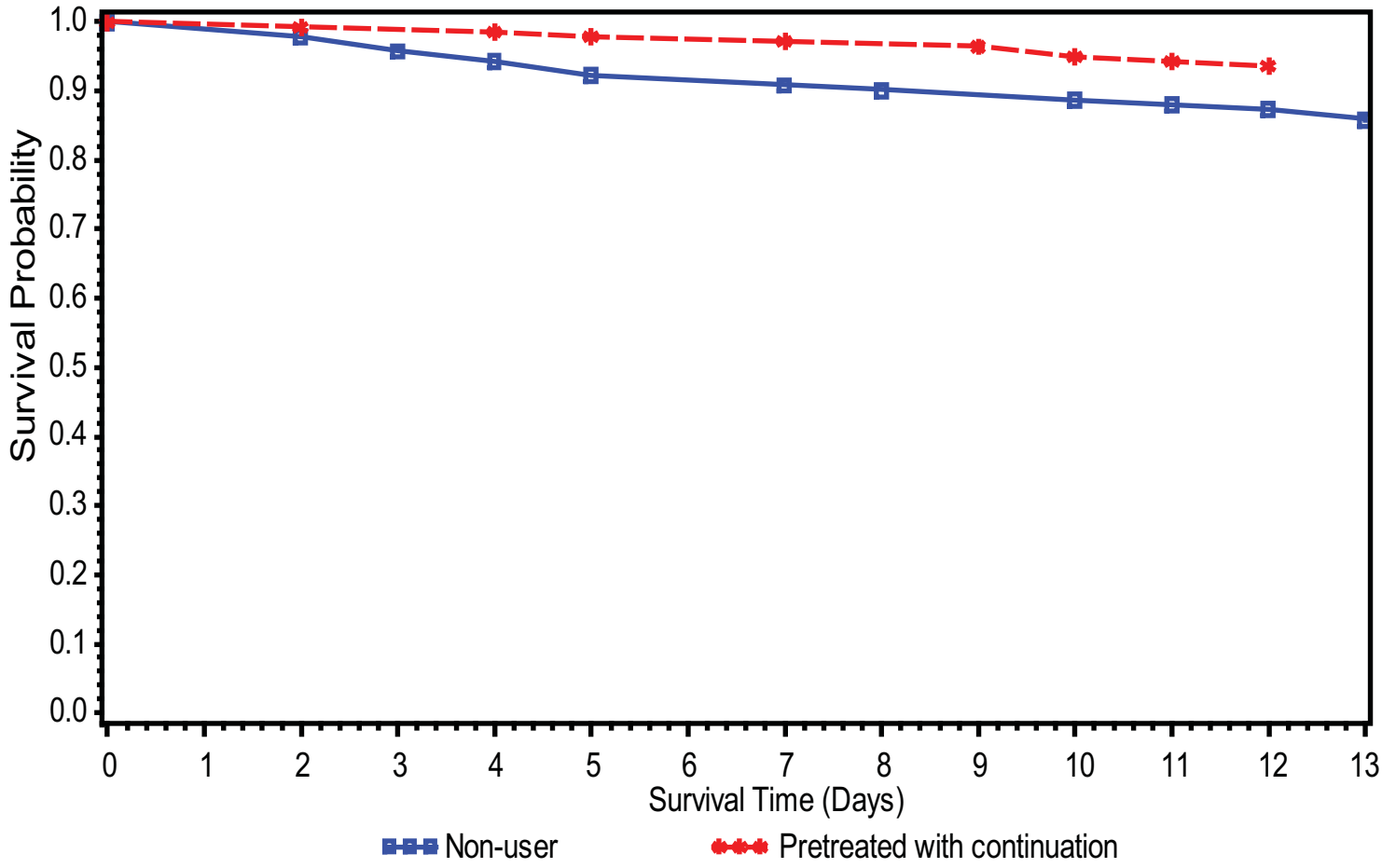
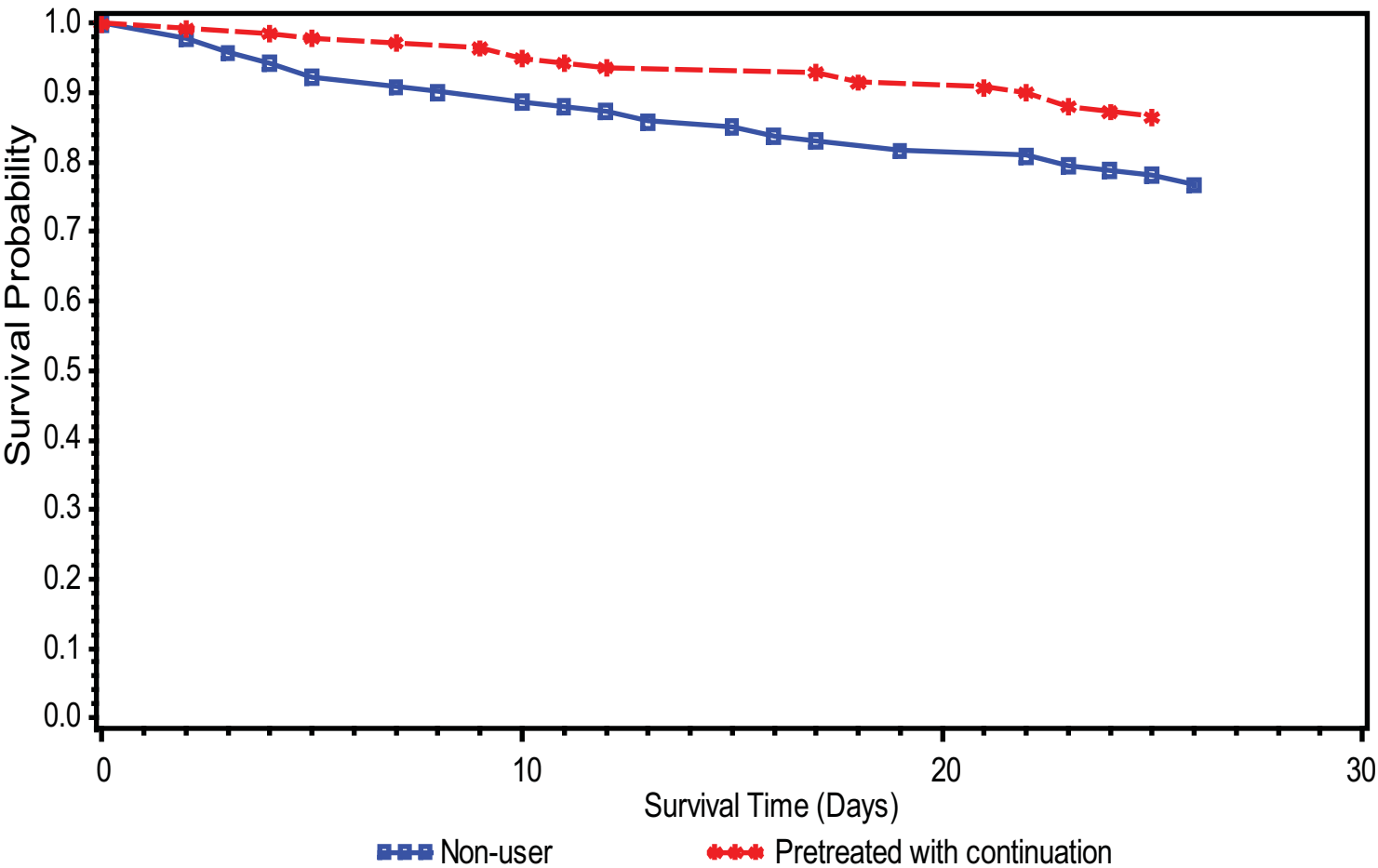


Figure 2a. 14-day survival probability curve among propensity-matched statin users with continuation and non-users.

Figure 2b. 30-day survival probability curve among propensity-matched statin users with continuation and non-users.


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Survival Time (Days)
Non-user
Pretreated with continuation


Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
10
20
30
Survival Time (Days)
Non-user
Pretreated with continuation