

2017

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

Aisling R. Caffrey  
*University of Rhode Island, aisling\_caffrey@uri.edu*

T. Timbrook  
*University of Rhode Island*

Eunsun Noh  
*University of Rhode Island*

George Sakoulas

Steven M. Opal

Follow this and additional works at: [https://digitalcommons.uri.edu/php\\_facpubs](https://digitalcommons.uri.edu/php_facpubs)

The University of Rhode Island Faculty have made this article openly available.  
Please let us know how Open Access to this research benefits you.

### Terms of Use

This article is made available under the terms and conditions applicable towards Open Access Policy Articles, as set forth in our [Terms of Use](#).

---

### Citation/Publisher Attribution

Caffrey AR, Timbrook TT, Noh E, Sakoulas G, Opal SM, Nizet V, LaPlante KL. 2017. Evidence to support continuation of statin therapy in patients with Staphylococcus aureus bacteremia. *Antimicrob Agents Chemother* 61:e02228-16. doi: 10.1128/AAC.02228-16  
Available at: <http://dx.doi.org/10.1128/AAC.02228-16>

This Article is brought to you for free and open access by the Pharmacy Practice at DigitalCommons@URI. It has been accepted for inclusion in Pharmacy Practice Faculty Publications by an authorized administrator of DigitalCommons@URI. For more information, please contact [digitalcommons-group@uri.edu](mailto:digitalcommons-group@uri.edu).

---

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

### Authors

Aisling R. Caffrey, T. Timbrook, Eunsun Noh, George Sakoulas, Steven M. Opal, Victor Nizet, and Kerry L. LaPlante

**The University of Rhode Island Faculty have made this article openly available.  
Please let us know how Open Access to this research benefits you.**

This is a pre-publication author manuscript of the final, published article.

### Terms of Use

This article is made available under the terms and conditions applicable towards Open Access Policy Articles, as set forth in our [Terms of Use](#).

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

3  
4

5 Aisling R. Caffrey, Ph.D.<sup>a,b,c,#</sup>, Tristan T. Timbrook, Pharm.D.<sup>a,b</sup>, Eunsun Noh, Ph.D.<sup>b</sup>,  
6 George Sakoulas, M.D.<sup>d</sup>, Steven M. Opal, M.D.<sup>e,f</sup>, Victor Nizet, M.D.<sup>d</sup>, and Kerry L.  
7 LaPlante, Pharm.D.<sup>a,b,f</sup>

8

9 <sup>a</sup>Veterans Affairs Medical Center, Infectious Diseases Research Program and Center of  
10 Innovation in Long Term Services and Supports, Providence, Rhode Island; <sup>b</sup>University  
11 of Rhode Island College of Pharmacy, Kingston, Rhode Island; <sup>c</sup>Brown University  
12 School of Public Health, Providence, Rhode Island; <sup>d</sup>University of California San Diego  
13 School of Medicine, La Jolla, California; <sup>e</sup>Infectious Disease Division, Memorial Hospital  
14 of Rhode Island, Providence, Rhode Island; <sup>f</sup>Warren Alpert Medical School of Brown  
15 University, Division of Infectious Diseases, Providence, Rhode Island

16

17 #Corresponding Author:

18 Aisling R. Caffrey, PhD, MS  
19 Assistant Professor, University of Rhode Island  
20 7 Greenhouse Road, Kingston, RI 02881  
21 Tel: 401-874-5320 ; e-mail: [Aisling\\_Caffrey@uri.edu](mailto:Aisling_Caffrey@uri.edu)

22

23 Alternate Corresponding Author:

24 Kerry L. LaPlante, Pharm.D.

25 Director of the Rhode Island Infectious Diseases (RIID) Research Program

26 Professor, University of Rhode Island, College of Pharmacy

27 7 Greenhouse Rd, Suite 295A, Kingston, RI 02881

28 Tel: 401.874.5560; Fax: 401.457.3305; E-mail: [KerryLaPlante@uri.edu](mailto:KerryLaPlante@uri.edu)

29

30 **Running Title:** Continuation of statins in *S. aureus* bacteremia

31

32 **Keywords:** anti-inflammatory and immunomodulatory effects, bacteremia, mortality,

33 *Staphylococcus aureus*, statins, HMG-CoA Reductase Inhibitors

34

35 **Abstract Word Count:** 248

36 **Manuscript Word Count:** 3,353

37

38 **Abstract**

39 In addition to cholesterol lowering capabilities, statins possess antiinflammatory and  
40 immunomodulatory effects. We sought to quantify the real-world impact of different  
41 statin exposure patterns on clinical outcomes in *Staphylococcus aureus* bacteremia. We  
42 conducted a retrospective cohort study among hospitalized patients with positive *S.*  
43 *aureus* blood cultures receiving appropriate antibiotics within 48 hours of culture  
44 collection (Veterans Affairs hospitals, 2002-2013). Three statin exposure groups were  
45 compared to non-users: pretreated statin users initiating therapy in the 30 days prior to  
46 culture and either (1) continuing statin therapy after culture, or (2) not continuing after  
47 culture, and (3) *de novo* users initiating at culture. Non-users included patients without  
48 statins in the year prior to culture through discharge. Propensity score matched Cox  
49 proportional hazards regression models were developed. We were able to balance  
50 significantly different baseline characteristics using propensity score matching for  
51 pretreated without continuation (n=331), pretreated with continuation (n=141), and *de*  
52 *novo* (n=177) statin users as compared to non-users. We observed a significantly lower  
53 30-day mortality rate (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.25-0.84;  
54 number needed to treat [NNT] 10) among pretreated and continued statin users, while  
55 protective effects were not observed in *de novo* (HR 1.04, 95% CI 0.60-1.82; NNT  
56 undefined) or pretreated but not continued (HR 0.92, 95% CI 0.64-1.32; NNT 47) users.  
57 In our national cohort study among patients with *S. aureus* bacteremia, continuation of  
58 statin therapy among incident statin users was associated with significant beneficial  
59 effects on mortality, including a 54% lower 30-day mortality rate.

60

## 61 **Introduction**

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

75

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

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

91

## 92 **Methods**

### 93 *Data Source*

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

105

### 106 *Study Population*

107 We conducted a retrospective cohort study quantifying the effect of statin use on clinical  
108 outcomes among patients with *S. aureus* bacteremia. We identified adult patients (age  $\geq$   
109 18 years) admitted to VA hospitals whose blood cultures were positive for *S. aureus*  
110 between January 1, 2002 and December 1, 2013. We then assessed antibiotic therapy  
111 for each patient during the hospital admission. We included patients who received  
112 intravenous  $\beta$ -lactam therapy (ampicillin-sulbactam, nafcillin, oxacillin, piperacillin-  
113 tazobactam, cefazolin, cefotetan, cefoxitin, ceftazidime, ceftriaxone, ceftaroline,  
114 ertapenem, doripenem, imipenem-cilastatin, or meropenem) or vancomycin for  
115 methicillin-susceptible *S. aureus* [MSSA] and vancomycin or ceftaroline for methicillin-  
116 resistant *S. aureus* [MRSA] within 48 hours of culture collection. Due to the existing  
117 labeling guidance (drug interactions) on temporality suspending statins in patients  
118 receiving daptomycin, we did not include patients with initial daptomycin therapy. We  
119 excluded patients who died or were discharged on the day of culture or the day after  
120 culture. We only evaluated the first admission within the study period after accounting  
121 for all inclusion and exclusion criteria.

122

### 123 *Statin Use*

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



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

134

### 135 *Outcomes*

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

148

### 149 *Statistical Analysis*

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

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

159  
160 To quantify the effect of statin therapy on clinical outcomes, we used Cox proportional  
161 hazards regression models. Cox proportional hazards regression assumptions were  
162 assessed, including proportionality (19). These analyses were conducted separately for  
163 each statin exposure group, in which separate propensity score models were built for  
164 pretreated users with continuation, pretreated users without continuation, and *de novo*  
165 users. Subsequent outcomes, compared to non-users, were assessed separately for  
166 each of these statin exposure groups. A hazard ratio (HR) above 1 indicated an  
167 increased probability of the outcome occurring sooner in the statin exposure group  
168 compared to non-users. Number needed to treat was calculated from risk differences  
169 among matched pairs. In sensitivity analyses, Cox models were adjusted for propensity  
170 score quintiles, with quintile I serving as the reference, and weighted by the inverse  
171 probability of treatment (20). All analyses were performed using SAS (SAS Institute Inc.,  
172 Cary, NC, Version 9.2).

173

## 174 **Results**

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

176 exclusion criteria (Figure 1). Of them, 16,448 were non-users of statins, 344 were  
177 pretreated without continuation at culture, 159 were pretreated with continuation, and  
178 187 were *de novo* users. Mean statin duration prior to culture was 7 days both among  
179 those who continued (standard deviation [sd] 6.9, median 5, interquartile range [IQR] 3-  
180 10) and those who did not continue (sd 7.7, median 3, IQR 1-11) statin therapy. Statin-  
181 exposed patients were significantly older (mean 69.7 to 71.7 years; Table 1) and more  
182 likely to have been in intensive care at the time of culture collection (22.7% to 29.6%)  
183 than non-users (67 years, 19.8% intensive care at culture,  $p < 0.05$ ). Half of non-users  
184 had MSSA and half had MRSA. A similar distribution was observed among the statin  
185 exposure groups, except *de novo* users were more likely to have MSSA (58.3% versus  
186 50.2%,  $p < 0.05$ ). Sepsis was significantly less common among the pretreated exposure  
187 groups compared to non-users (pretreated without continuation 78.2% versus 83.2%,  
188  $p < 0.05$ ; pretreated with continuation 72.3% versus 83.2%,  $p < 0.05$ ).

189  
190 Comorbidity scores during the hospital admission were similar between the exposed  
191 groups and non-users (Table 2), however there was a lower overall comorbidity burden  
192 in the year prior to the current admission among pretreated users with continuation  
193 (mean Charlson 2.5, sd 2.9) and *de novo* users (mean Charlson 2.7, sd 3.1) compared  
194 to non-users (mean Charlson 3.2, sd 3.1,  $p < 0.05$  for both comparisons). Despite similar  
195 overall comorbidity burden between statin users and non-users, the burden of  
196 cardiovascular diseases was significantly higher among the statin exposure groups,  
197 both during the current admission and in the previous year, as was utilization of  
198 medications for hypertension and diabetes. The overall 30-day mortality rate was 20.2%

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

204  
205 Baseline characteristics were balanced between statin users and non-users within  
206 propensity score matched pairs (pretreated without continuation,  $n=331$ ; pretreated with  
207 continuation,  $n=141$ ; *de novo*,  $n=177$ ). Characteristics included in the propensity score  
208 models, including initial antibiotic treatment, treating specialty, MSSA/MRSA, sepsis,  
209 statin indication, and other characteristics independently associated with the exposure  
210 groups or the outcomes, can be found in Supplemental Table 1. Each model  
211 demonstrated goodness of fit, with high C-statistics of 0.86-0.92, indicating excellent  
212 discrimination between the groups (21), and complete overlap in propensity score  
213 distributions between statin exposure groups and non-users (pretreated without  
214 continuation, mean 0.094, sd 0.101, median 0.054, IQR 0.022-0.132; pretreated with  
215 continuation, mean 0.098, sd 0.110, median 0.052, IQR 0.020-0.137; *de novo*, mean  
216 0.076, sd 0.095, median 0.037, IQR 0.016-0.099).

217  
218 Time to event analyses comparing statin users to non-users (reference group) are  
219 presented in Table 3. No significant differences were observed between non-users and  
220 two of the statin exposure groups (pretreated without continuation, *de novo*) for any of  
221 the outcomes assessed. The rate of 30-day mortality was significantly lower in

222 pretreated statin users with continuation compared to propensity matched non-users  
223 (HR 0.46, 95% CI 0.25-0.84) but not among pretreated users who did not continue  
224 statin therapy after culture (HR 0.92, 95% CI 0.64-1.32) or *de novo* users (HR 1.04,  
225 95% CI 0.60-1.82). Among pretreated statin users continuing statin therapy after  
226 culture, 14-day mortality was also significantly lower than that of non-users (HR 0.35,  
227 95% CI 0.15-0.83), however, significant differences were not observed for the other  
228 outcomes assessed, including inpatient mortality.

229  
230 Similar results were observed in sensitivity analyses utilizing propensity score quintile  
231 adjustment (Supplemental Tables 2-4). Sensitivity analyses with inverse probability of  
232 treatment weighting (IPTW) also demonstrated significantly lower mortality rates among  
233 pretreated statin users with continuation (14-day mortality HR 0.15, 95% CI 0.07-0.32);  
234 30-day mortality HR 0.17, 95% CI 0.10-0.30; inpatient mortality HR 1.39, 95% CI 1.19-  
235 1.62; Supplemental Tables 2-4). Alternatively, in IPTW analyses, statin users without  
236 continuation had significantly higher mortality compared with non-users, including 14-  
237 day mortality (HR 3.81, 95% CI 3.26-4.44), 30-day mortality (HR 2.84, 95% CI 2.46-  
238 3.28), and inpatient mortality (3.76, 95% CI 3.23-4.36). In *de novo* statin users, the 30-  
239 day readmission rate was significantly higher than non-users (HR 1.75, 95% CI 1.11-  
240 2.75), as was 30-day *S. aureus* reinfection (HR 12.33, 95% CI 1.21-125.59).

241  
242 The 30-day mortality risk difference in pretreated statin users with continuation versus  
243 non-users, was 99 per 1,000 patients (95% CI 10-189 per 1,000) and the number  
244 needed to treat (NNT) was 10. For 14-day mortality, the risk difference was 78 per

245 1,000 patients (95% CI 8-148 per 1,000) and the NNT was 13. The 14-day and 30-day  
246 survival probability curves for pretreated statin users with continuation versus non-users  
247 can be found in Figure 2.

248

## 249 **Discussion**

250 Recent statin initiation with continuation of statin therapy for at least 3 days after culture  
251 was associated with a substantial protective effect on mortality among our large,  
252 national, real-world cohort with *S. aureus* bacteremia. These findings were robust in our  
253 primary analyses using propensity score matching, and in our sensitivity analyses using  
254 propensity score quintile adjustment and inverse probability of treatment weighting. *In*  
255 *vitro* research suggests statins may confer protective effects in *S. aureus* bacteremia  
256 since they i) inhibit *S. aureus* invasion of human endothelial cells (2, 11); ii) interfere  
257 with *S. aureus* biofilm formation (22); and iii) enhance clearance of *S. aureus* by  
258 phagocytes through the induction of DNA-based extracellular traps (12). Consistent  
259 with our findings, several meta-analyses have identified protective effects with statins on  
260 all-cause mortality among patients with various types of infections. Pleiotropic effects  
261 with statins were evaluated among patients with sepsis, pneumonia, or bacteremia by  
262 pooling 20 published studies (13). The authors reported a 50% reduced mortality in  
263 statin users (pooled OR 0.49, 95% CI 0.37-0.61). The bacteremia-related mortality  
264 (evaluated in 4 studies out of 20) was also significantly lower in statin users (pooled OR  
265 0.33, 95% CI 0.09-0.75). Another meta-analysis found that outpatient use of statins was  
266 associated with a 29% decreased risk of all-cause mortality in patients with any infection  
267 (pooled OR across 41 studies 0.71, 95% CI 0.64-0.78) (14).

268

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

281

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

291 less than 2 weeks of statin use prior to admission were excluded. Pretreated statin users  
292 assigned to statin therapy had a lower 28-day mortality (5% vs 11%;  $p = 0.01$ ) compared  
293 to placebo, although like our study, inpatient mortality was not significantly lower. Further,  
294 28-day mortality in *de novo* users was similar to the placebo group (16.3% vs 14.9%;  
295  $p=0.78$ ). It should be noted that duration of previous statin use was not assessed in the  
296 clinical trial and as such, variations in outcomes may have existed by duration. Although  
297 the study size was likely too small to detect any such differences (pretreated assigned to  
298 statins  $n=37$ , pretreated assigned to placebo  $n=40$ ).

299  
300 We only know of one other study specifically examining the effects of statins on patient  
301 mortality in *S. aureus* bacteremia (25). A prospective cohort study, which included 160  
302 *S. aureus* bacteremia episodes from one hospital in Spain, found that the 33 statin  
303 users were less likely to die within 14 days than non-users (adjusted odds ratio [OR]  
304 0.08, 95% CI 0.01-0.66) but a significant difference between groups was not observed  
305 for 30-day (adjusted OR 0.35, 95% CI 0.10-1.23;  $p=0.10$ ). Statin exposure was defined  
306 as prevalent statin use at bacteremia onset, and all users had at least one month of  
307 previous statin therapy. Another limitation of this Spanish study, besides prevalent statin  
308 use, was that 23/33 (70%) of the statin users had a vascular catheter as the source of  
309 bacteremia, compared to only 46/127 (36%) in non-users. Given that vascular catheters  
310 are a readily removable source of bacteremia with lower mortality rates than other  
311 sources, such a difference is difficult to ignore (26). In our study, catheter source was  
312 similar between statin exposure groups and non-users (Table 1).

313



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

333

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

337 methods allowed us to balance confounders of the exposure-outcome relationship that  
338 were included in the propensity score, however it could not control for unbalanced  
339 factors that were not measured in our study. Second, variations in point estimates were  
340 observed with propensity score matching, adjustment, and inverse probability of  
341 treatment weighting. Though propensity score matching produced the most  
342 conservative estimates, it also resulted in the greatest balance between groups. Third,  
343 we attempted to identify incident statin use in order to assess the effect of statins at the  
344 time of *S. aureus* infection. We defined incident use as initiation in the 30 days prior to  
345 culture, with no prior statin exposure in the previous year. As such, incident use did not  
346 necessarily mean throughout the patient's lifetime. Therefore, our estimates may not  
347 completely rule out the influence of historical statin use (beyond the window that we  
348 defined in this study) on the outcomes. Fourth, our study results should be applied  
349 carefully in the general population since our study was conducted among Veterans, and  
350 approximately 98% were male. Fifth, as a retrospective study of existing data, the  
351 accuracy of operational definitions depends on the data source. Though we utilized one  
352 of the most comprehensive and accurate data sources for health outcomes research  
353 available in the United States, misclassification may still occur. For example, culture  
354 source is a free text field in the microbiology data, and therefore, without mention of a  
355 catheter in that field, we could not determine whether it was a catheter source. Lastly,  
356 we did not assess outcomes for specific statins or doses, which is an important area of  
357 inquiry as some data suggests added benefit of high potency or high dose statins (36,  
358 37).

359

360 **Conclusions**

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

## **Acknowledgements**

The views expressed are those of the authors and do not necessarily reflect the position or policy of the United States Department of Veterans Affairs. This work was presented, in part, at the 31st International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August 25, 2015. This material is based upon work supported, in part, by the Office of Research and Development, Department of Veterans Affairs.

George Sakoulas and Victor Nizet have research support under a National Institutes of Health grant (1U54HD090259). Aisling Caffrey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We appreciate the assistance of Vrishali Lopes with data preparation and analyses.

## **Funding**

This work was unfunded.

## **Conflicts of Interest**

Aisling Caffrey has received research funding from Pfizer, Merck (Cubist), and The Medicines Company. Tristan Timbrook and Eunsun Noh have no conflicts to disclose. George Sakoulas has received speaking honoraria from Merck, Allergan, Sunovion, and The Medicines Company, and consulting fees from Allergan and the Medicines Company. Steven Opal is a consultant for AtoxBio BioAegis, Arsanis, Aridia, Battelle, and has received institutional grants from Glaxo-Smith-Kline, Asahi-Kasei, Cardeas and Ferring. Victor Nizet has received research funding, or acted as an advisor for InhibRx,

Altermune Technologies, Trius Therapeutics, Cidara Therapeutics and Roche Pharmaceuticals. Kerry LaPlante has received research funding or acted as a scientific advisor for Allergan, Bard, Merck (Cubist), Pfizer, and The Medicines Company.

## 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*  $\alpha$ -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](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, Rooijackers 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**

<b>Characteristics</b>	<b>Unexposed (n=16448)</b>	<b>Pretreated without continuation (n=344)</b>	<b>Pretreated with continuation (n=159)</b>	<b><i>De novo</i> (n=187)</b>
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 <sup>1)</sup>				
Catheter	349 (2.1)	10 (2.9)	3 (1.9)	2 (1.1)
Endocarditis <sup>2)</sup>	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)
<i>S. aureus</i> 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  $\pm$  standard deviation or number (%) of patients.

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

*Staphylococcus aureus*

1) Culture-confirmed source of infection  $\pm$ 24 hours from culture collection unless indicated otherwise.

2) Source of infection identified from ICD-9-CM diagnosis codes  $\pm$ 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**

<b>Characteristics</b>	<b>Unexposed (n=16448)</b>	<b>Pretreated without continuation (n=344)</b>	<b>Pretreated with continuation (n=159)</b>	<b><i>De novo</i> (n=187)</b>
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 <sup>1)</sup>				
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 <sup>2)</sup>				
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 <sup>1)</sup>	4956 (30.1)	115 (33.4)	32 (20.1)*	43 (23.0)*
Previous hospitalization <sup>1)</sup>	9294 (56.5)	220 (64.0)*	78 (49.1)	75 (40.1)*
Previous nursing home stay <sup>1)</sup>	1596 (9.7)	24 (7.0)	9 (5.7)	12 (6.4)

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

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

<sup>1)</sup> Present in the 1 year prior to the *Staphylococcus aureus* bacteremia hospitalization.

<sup>2)</sup> Present in the 90 days prior to the *Staphylococcus aureus* bacteremia hospitalization.

<sup>3)</sup>Source of infection identified from ICD-9-CM diagnosis codes.

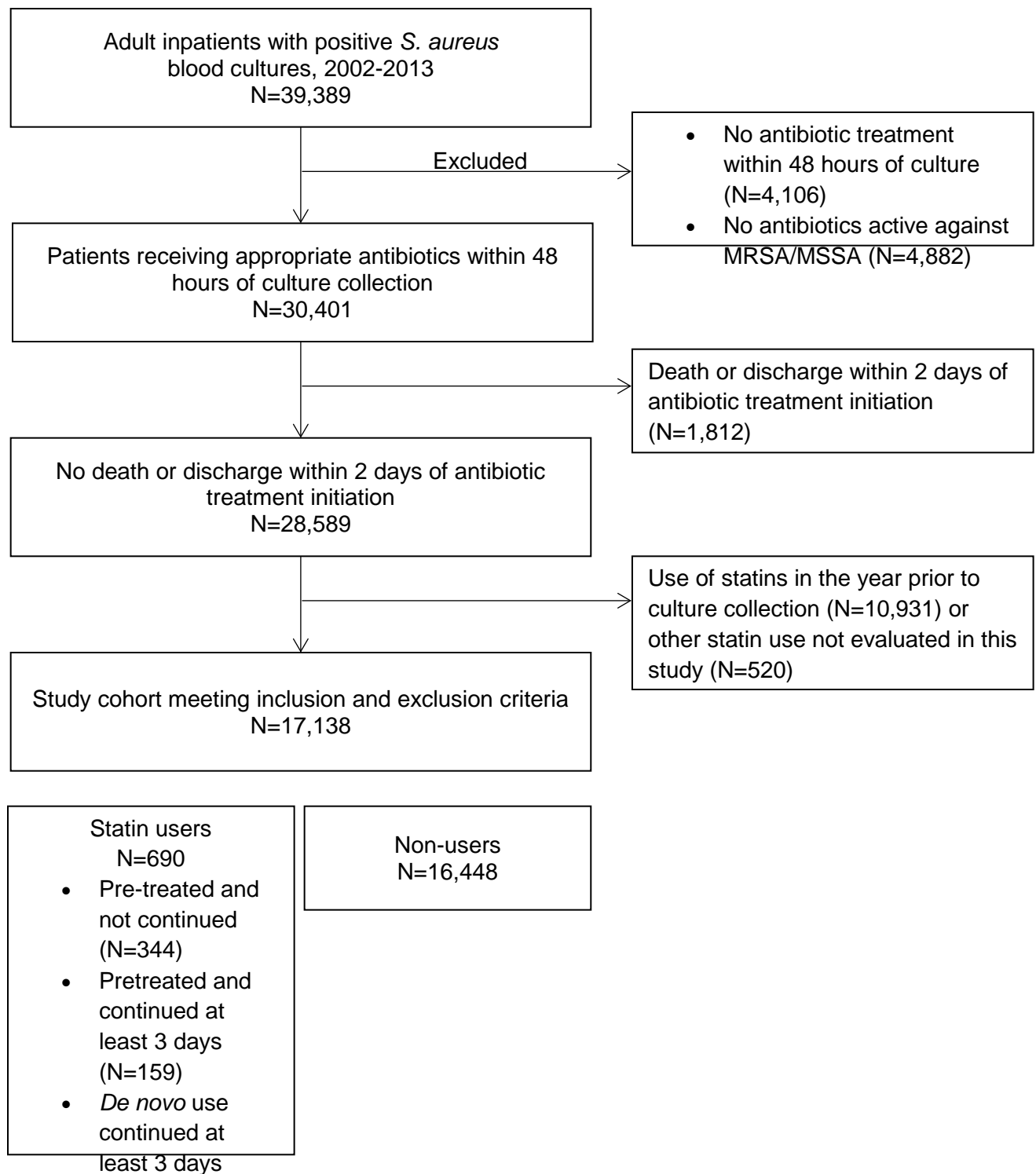
\*  $p < 0.05$  for pairwise comparison between statin exposure group and non-user group.

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

Outcomes	No. of events/No. of patients		HR (95% CI)	Sooner outcomes in non-users	Sooner outcomes in statin users
	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	<b>0.46 (0.25 - 0.84)</b>		
<i>De novo</i>	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	<b>0.35 (0.15-0.83)</b>		
<i>De novo</i>	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)		
<i>De novo</i>	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)		
<i>De novo</i>	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)		
<i>De novo</i>	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)		
<i>De novo</i>	33/156	42/158	0.67 (0.40 - 1.12)		
30-day <i>S. aureus</i> 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)		
<i>De novo</i>	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.**

