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

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31

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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

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 ≥

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 β-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

Conclusions

360

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.

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,

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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)	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	**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)		

0   1   2

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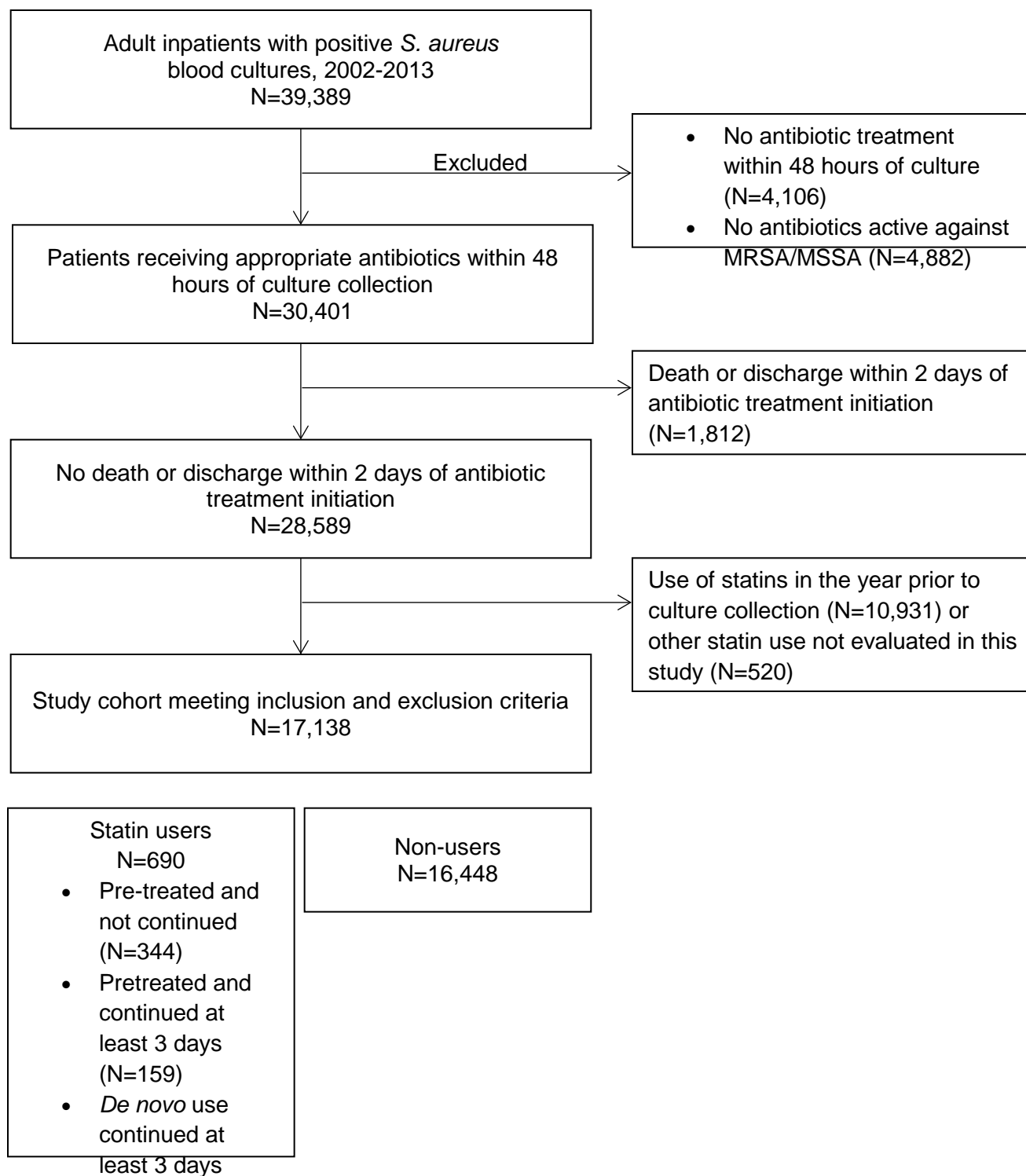
Figure 2a. 14-day survival probability curve among propensity-matched statin users with continuation and non-users.

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