Improved survival with continuation of statins in bacteremic patients

Ajinkta M. Pawar  
*University of Rhode Island*

Kerry L. LaPlante  
*University of Rhode Island*, kerrylaplante@uri.edu

Tristan T. Timbrook

Aisling R. Caffrey  
*University of Rhode Island*, aisling_caffrey@uri.edu

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Improved survival with continuation of statins in bacteremic patients

Ajinkya M Pawar1, Kerry L LaPlante1,2, Tristan T Timbrook2 and Aisling R Caffrey1,2,3

Abstract

Objectives: Varying statin exposures in bacteremic patients have different impacts on mortality. Among patients with adherent statin use, we sought to evaluate the impact of statin continuation on inpatient mortality in bacteremic patients.

Methods: A retrospective cohort study was conducted using Optum ClinformaticsTM with matched Premier Hospital data (October 2009–March 2013). Patients with a primary diagnosis of bacteremia and 6 months of continuous enrollment prior to the admission, receiving antibiotics at least 2 days of antibiotics during the first 3 days of admission, were selected for inclusion. Furthermore, patients demonstrating adherent statin use based on 90 days of continuous therapy prior to admission were included. We then compared those continuing statin therapy for at least the first 5 days after admission and those not continuing during the admission.

Results: Simvastatin (53.2%) and atorvastatin (33.8%) were the most commonly used statins among the 633 patients who met our inclusion and exclusion criteria. Propensity score adjusted Cox proportional hazards regression models demonstrated significantly lower inpatient mortality among those continuing statin therapy compared with those not continuing (n = 232 vs 401, adjusted hazard ratio 0.25, 95% confidence interval 0.08–0.79).

Conclusion: Among patients adherent to their statin therapy prior to a bacteremia hospitalization, continued statin use after admission increased survival by 75% compared with those not continuing.

Keywords

Bacteremia, mortality, statins, exposure patterns, protective effects

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Introduction

Statins have been associated with improved survival among patients with infections,1–7 in meta-analyses,8,9 randomized trials, and observational studies.4,5,7,10 The proposed pleiotropic effects with statins, including a reduced inflammatory response,11,12 suggest that the critical period of exposure would be from time of onset of infection through the initial period of antibiotic therapy.5,10,13 Importantly, that period of onset is likely to occur outside of the healthcare setting, and therefore there will be a delay between onset and presentation to receive care. In previous research, definitions of statin exposure vary widely between studies, tend to be overly broad, and rarely take into account statin therapy adherence.3–5 This study sought to evaluate the impact of statin continuation during hospital admission compared with non-continuation, in a cohort of adherent statin users.

Methods

A retrospective cohort study design was used to assess inpatient mortality among adherent statin users. This study was conducted using de-identified Optum ClininformaticsTM (OptumInsight, Eden Prairie, MN) with matched Premier Hospital data (October 2009–March 2013). Patients with a primary diagnosis of bacteremia and 6 months of continuous enrollment prior to the admission, receiving antibiotics at least 2 days of antibiotics during the first 3 days of admission, were selected for inclusion. Furthermore, patients demonstrating adherent statin use based on 90 days of continuous therapy prior to admission were included. We then compared those continuing statin therapy for at least the first 5 days after admission and those not continuing during the admission.

1 Department of Pharmacy Practice, College of Pharmacy, The University of Rhode Island, Kingston, RI, USA
2 Infectious Diseases Research Program, Veterans Affairs Medical Center, Providence, RI, USA
3 School of Public Health, Brown University, Providence, RI, USA

Corresponding author:

Aisling R Caffrey, Department of Pharmacy Practice, College of Pharmacy, The University of Rhode Island, 7 Greenhouse Road, Suite 265B, Kingston, RI 02881, USA.

Email: aislingcaffrey@uri.edu
Hospital data (1 October 2009–31 March 2013), which is an administrative claims database from a large commercial health plan (Optum Clinformatics) matched with hospital data (Premier). Included in the analysis were adult patients (>18 years) with a primary diagnosis of bacteremia (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 003.1, 020.2, 022.3, 036.2, 038.0, 038.1, 038.10–038.12, 038.19, 038.2, 038.3, 038.40–038.44, 038.49, 038.8, 038.9, 054.5, 449, 771.81, 995.91, 995.92, and 790.7). We only included patients with hospital admissions between 1 April 2010 and 31 March 2013, to allow for a continuous enrollment period of 6 months prior to admission. Antibiotic therapy for each patient during the hospital stay was assessed. Patients who received at least 2 consecutive days of at least one antibiotic therapy for bacteremia within the first 3 days of the admission were included. For patients with multiple admissions for bacteremia, only the first admission was included. Medication use was identified from both outpatient prescriptions and medications given during the hospital stay. Charlson and Elixhauser comorbidity scores were defined using diagnosis codes.

Using pharmacy claims, we identified prevalent statins users demonstrating adherence to their statin therapy, which was defined as patients who, irrespective of their statin initiation time, had at least 90 days of continuous statin exposure (i.e. atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) in the 90 days prior to hospitalization. In terms of adherence measures, the proportion of days covered was therefore 100% for all included patients, at least 90 days of supply dispensed in the 90 days prior to admission. The proportion of days covered (PDC) of ≥80% is commonly considered as good adherence for statins. Statin exposure was further categorized as statin continuation, with at least 5 days of statin therapy after admission, and non-continuation after admission. Inpatient mortality was defined as death occurring during the hospital stay.

To identify baseline differences between the statin continuation and non-continuation groups, we reviewed demographic and clinical data including current and prior comorbidities. For categorical variables, if the assumptions for the chi-square test were not met, the Fisher’s exact test was utilized. For continuous variables, the non-parametric Wilcoxon Rank Sum test was used.

We developed a propensity score for statin continuation versus non-continuation. The propensity score was therefore the predicted probability of statin therapy continuation, as calculated from the baseline covariates included in an unconditional logistic regression model which was built with manual backward elimination. Patients from the statin continuation and non-continuation groups were stratified by propensity score quintile to achieve homogeneity between exposure groups within quintiles of the predicted probability of statin continuation. To evaluate the association of continued statin use and in-hospital mortality, we used a Cox proportional hazards model. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and statistical significance was considered a p-value of ≤0.05. This study was reviewed and approved as exempt by the University of Rhode Island’s Institutional Review Board.

**Results**

We identified 633 patients who met our inclusion and exclusion criteria (Figure 1). This included 232 patients with statin continuation and 401 with non-continuation. In comparing the statin continuation and non-continuation groups (Table 1), age (median 62 vs 61 years) and gender (43% vs 44% females) were similar. The median Charlson comorbidity index during admission (2.0 vs 2.0, p=0.57; Table 2) and during the 6 months prior to admission (3.0 vs 3.0, p=0.97) was the same in both the groups. Admission from the emergency room occurred for 97% of patients with statin continuation and 95% with non-continuation (p=0.29). Marital status, race, region, and admitting physician specialty were also similar between the statin continuation versus non-continuation groups. Simvastatin (53.2%) and atorvastatin (33.8%) were the most commonly used statins. Inpatient mortality was significantly lower (2.59% vs 10.97%, p=0.0002) and length of stay was higher (median 6.0, interquartile range (IQR) 5.0–9.0 vs 5.0 days, IQR 3.0–9.0, p<0.0001) in those continuing statins compared with those not continuing. The final propensity score model c-statistic was 0.88, suggesting a strong model for predicting the probability of statin continuation. Among bacteremic patients with adherent statin use prior to...
admission, the propensity score adjusted Cox proportional hazards regression model evaluating time to inpatient mortality demonstrated significantly lower inpatient mortality among those continuing statin therapy (hazard ratio (HR) 0.25, 95% CI 0.08–0.79) compared with those not continuing after admission.

Discussion

In this retrospective cohort study among privately insured patients with bacteremia, we observed higher survival among the statin continuation group compared with the non-continuation group. These results support statin continuation through the period of inflammation, as the inflammatory response has been found to be lower among patients taking statins around the time the infection develops.25,26 The specific mechanism by which mortality is reduced among statin users with bacteremic infections still remains undefined, however, a proposed mechanism has been the moderation of the overall inflammatory response.27 Other previously observed anti-inflammatory effects with statins have included lowering of C-reactive protein (CRP), chemokine release (MCP-1, RANTES), cytokines (IL-1β, TNF α, IL-6, IL-8), and adhesion molecules (P-selectin, VLA 4, CD11a, CD11b, CD18).28,29 Statins may also have a direct antimicrobial effect,30 and possible antibacterial activity of statins against a variety of pathogens may be attributed to their ability to suppress cell growth, and to promote apoptosis.31–33

Contrary to our findings, a recent randomized controlled trial (RCT) did not observe benefits of statin continuation on inflammatory parameters and sepsis among adherent statin users.34 However, the aforementioned study has several
methodological issues as pointed out in a correspondence by Bostock and Vizcaychipi, including a vague primary end-point, lack of information regarding previous statin therapy duration, and use of the Mann–Whitney test to evaluate the matched groups. The limitations of a number of previous studies evaluating protective effects of statins were (a) control for few confounders, (b) lack of information about pre-hospitalization medication use, (c) combined incident and adherent statin use, and (d) combined pre-hospital and post-hospital use. These limitations may explain the conflicting findings between studies in regard to the impact of statin use on mortality among patients with infections.

In terms of contrasting results between studies assessing the effects of statin continuation, a prospective cohort study conducted in Spain evaluated the survival benefits with statin use in *S. aureus* bacteremic (SAB) patients with at least 30 days prior statin use and continuation until SAB

### Table 2. Clinical characteristics and health service utilization among adherent statin users prior to admission.

| Characteristics                                      | Statin continuation (N = 232) | Non-continuation (N = 401) | p value |
|------------------------------------------------------|-------------------------------|-----------------------------|---------|
| Comorbidities (during admission)                     |                               |                             |         |
| Charlson score (median and IQR)                      | 2                             | 2                           | 0.5708  |
| Elixhauser score (median and IQR)                    | 4                             | 4                           | 0.3973  |
| Chronic renal disease                                | 61                            | 78                          | 0.0451  |
| Coagulation and hemorrhagic disorders                | 27                            | 84                          | 0.0030  |
| Coagulopathy                                         | 25                            | 75                          | 0.0084  |
| Congestive heart failure nonhypertensive             | 64                            | 60                          | 0.0001  |
| Coronary atherosclerosis and other heart diseases    | 87                            | 115                         | 0.0218  |
| Diabetes mellitus with complication                  | 61                            | 69                          | 0.064   |
| Dyslipidemia including hyperlipidemia                | 161                           | 208                         | <0.0001 |
| Infective arthritis                                  | 15                            | 11                          | 0.0230  |
| Liver disease                                        | 12                            | 47                          | 0.0063  |
| Malignant neoplasm                                   | 6                             | 54                          | <0.0001 |
| Metastatic cancer                                    | 3                             | 30                          | 0.0003  |
| Mild liver disease                                   | 11                            | 40                          | 0.0197  |
| Obesity                                              | 69                            | 83                          | 0.0103  |
| Poisoning by medication and drugs                    | 20                            | 69                          | 0.0027  |
| Solid tumor without metastasis                       | 5                             | 49                          | <0.0001 |
| Weight loss                                           | 22                            | 68                          | 0.0095  |
| Medication use (during admission)                    |                               |                             |         |
| Anti-hypertensive medication                         | 207                           | 274                         | <0.0001 |
| Comorbidities (6 months prior to admission)          |                               |                             |         |
| Charlson score (median and IQR)                      | 3                             | 3                           | 0.9720  |
| Elixhauser score (median and IQR)                    | 6                             | 5                           | 0.7992  |
| History of any cancer                                | 35                            | 102                         | 0.0023  |
| History of chronic kidney disease                    | 47                            | 57                          | 0.048   |
| History of condition with dizziness or vertigo       | 32                            | 25                          | 0.0014  |
| History of dyslipidemia including hyperlipidemia     | 175                           | 263                         | 0.0097  |
| History of history of other Immunocompromise         | 14                            | 46                          | 0.0244  |
| History of maintenance chemotherapy radiotherapy     | 8                             | 43                          | 0.0012  |
| History of malignant neoplasm                        | 24                            | 76                          | 0.0042  |
| History of metastatic cancer                         | 7                             | 37                          | 0.0031  |
| History of other and ill-defined cerebrovascular     | 15                            | 12                          | 0.0372  |
| diseases                                             |                               |                             |         |
| History of other eye disorder                        | 27                            | 28                          | 0.0451  |
| History of solid tumor without metastasis            | 24                            | 74                          | 0.0066  |
| Medication use history (6 months prior to admission) |                               |                             |         |
| History of diabetic medication                       | 74                            | 112                         | 0.0081  |
| History of anti-hypertensive medication              | 199                           | 317                         | 0.0357  |

Data are median and interquartile range (IQR) or number and percent of patients.
having received an antibiotic which may be used for bactere-
type and we were only able to use general inclusion criteria of
pathogen, but we identified organisms using ICD-9 codes,
Microbiology data was not available for a potential causative
exactly known and it may vary for different pathogens.
causative pathogen, since the mechanism of action is not
having a different impact on clinical outcomes based on the
assumed outpatient statin exposure to be equivalent to filling
sizes. In our review of statin doses, dispensing quantity in
incident users mostly reflected moderate to high doses. As we
used an administrative claims database for our analysis, we
assumed outpatient statin exposure to be equivalent to filling
prescription. Furthermore, there is a possibility of statins
having a different impact on clinical outcomes based on the
causative pathogen, since the mechanism of action is not
exactly known and it may vary for different pathogens.
Microbiology data was not available for a potential causative
pathogen, but we identified organisms using ICD-9 codes,
where available. Bacteremic treatment varies by organism
type and we were only able to use general inclusion criteria of
having received an antibiotic which may be used for bactere-
ia.15–18 Since we only evaluated a general bacteremic popu-
lation, our results may not be generalized to pathogen-specific
bacteremias. Despite using propensity scores to control for
confounding, we could not control for unmeasured confounding.
Specifically, bacteremia severity scores and bacteremia
source were not available from the data source, although we
did control for ventilation status and sepsis severity using
diagnosis-related groups (DRG).

In conclusion, our retrospective cohort study quantified
the effect of adherent statin continuation on clinical out-
comes such as inpatient mortality and hospital length of stay
among bacteremic patients in a real-world clinical popula-
tion. We observed significant reduction in inpatient morality
among adherent statin continuation for at least the first few
days after hospitalization compared with non-continuation
during admission. Our results possibly hint at the necessity
of statin exposure through the period of inflammation devel-
opment as the inflammatory response has been found to be
decreasing among patients consuming statins at the same
time as developing infection.25,26 Further unaddressed ques-
tions related to this research question include appropriate
statin exposure time and duration needed for the maximum
clinical benefits, and differences in the magnitude of each
statin’s protective effects.

Authors’ note
Tristan T Timbrook is now affiliated with Department of Pharmacy,
University of Utah Health, Salt Lake City, Utah, USA.

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Ethical approval
This study, which used existing de-identified data, was determined to
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ORCID iD
Aisling R Caffrey https://orcid.org/0000-0002-4180-027X
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