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Impact of prior statin use on mortality in patients with type 2 diabetes mellitus and bloodstream infection

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Abstract

Objective: This study assessed the effect of prior statin use on the 28-day mortality of patients with type 2 diabetes mellitus (DM) who develop bloodstream infections.

Methods: This retrospective cohort study included all adult type 2 DM patients with bacteremia and verified prior medication history who visited the emergency department of a single tertiary hospital between January 2007 and December 2013. All major adverse consequences including septic shock events, use of mechanical ventilation, intensive care unit admission, and 28-day mortality were assessed.

Results: A total of 1,979 patients were enrolled in the study, of whom 507 were taking statins. Statin users had less severe disease presentation and lower levels of sepsis biomarkers such as bandemia (1.3 ± 3.1 vs 1.8 ± 4.2). After adjustment for confounding variables using a Cox regression model, only older age (adjusted hazard ratio [HR]: 1.04, 95% confidence interval [CI], 1.01–1.04), urinary tract infection (adjusted HR: 0.56, 95% CI, 0.43–0.75), and prior statin use (adjusted HR: 0.58, 95% CI: 0.42–0.85) were significantly associated with 28-day in-hospital mortality.

Conclusion: Prior statin treatment in patients with type 2 DM and bacteremia was associated with a lower 28-day in-hospital mortality rate.

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Introduction

The prevalence of diabetes mellitus (DM) has increased in recent decades[1,2] and is now considered a common metabolic disorder worldwide. Clinical studies have revealed that patients with diabetes have increased susceptibility to infections,[3,4] and that diabetes is associated with an increased risk of hospitalization due to infection.[5] Separately, the incidence of severe sepsis continues to rise,[6] and sepsis represents a major cause of mortality in patients with multiple comorbidities. Hence, it is important to identify factors that contribute to a lowering of mortality rates in patients with sepsis.

Statin therapy (i.e., use of 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors) has been incorporated into the treatment guidelines for patients with type 2 DM who are at risk of cardiovascular events.[7,8] In addition to lowering lower lipid levels, statins possess anti-inflammatory and immunomodulatory properties.[9,10] Given the pleiotropic effects of statins on multiple pathophysiologic determinants of sepsis, statin administration may represent an effective adjuvant therapy.[11] Previous studies have reported significantly lower mortality rates in patients with bacteremic episodes who take statins,[12–14] although other studies have failed to show an association between statin therapy and mortality in patients with bloodstream infections.[15–17] Whether prior statin use influences sepsis-related mortality specifically in patients with type 2 DM has not yet been established.

Bacterial infections are the most common cause of sepsis. Compared with blood culture-negative severe sepsis, blood culture-positive severe sepsis manifests with more intense symptoms and is associated with higher intensive care unit (ICU) and in-hospital mortality.[18] The aim of this retrospective study was to compare 28-day in-hospital mortality rates and inflammatory biomarker features among patients with type 2 DM and bacterial sepsis based on whether they took statins. We hypothesized that statin use can influence the risk of 28-day mortality after with the development of bacteremia in patients with type 2 DM.

Materials and methods

Study design

This was a single-center retrospective observational study of data collected between January 1, 2007 and December 31, 2013 from population-based registries in Kaohsiung City, Taiwan. The study protocol was approved by the Ethics Committee of Chang Gung Memorial Hospital, which waived the requirement for written informed patient consent because of the retrospective nature of the study.

Study setting and population

During the study period, all patients who met the inclusion criteria (age 18 years and older, diagnosed with type 2 DM, hospitalized for bacteremia in the emergency department [ED], and valid medication history available) were enrolled; their data were screened using a computer database.

Figure 1. Flowchart of patient selection. ED, emergency department; DM, diabetes mellitus.

Readmission of patients for disease caused by the same pathogen within 14 days of their last discharge was considered the same event, and the second episode was excluded from the study. The study flowchart is shown in Figure 1.

Bacteremia was defined as a clinical episode of infectious disease with at least two blood cultures yielding positive results for any pathogen at separate sites, or one culture set that was positive for a Gram-negative or Gram-positive pathogen in a patient with an intravascular device who showed features consistent with bacteremia.[19] Patients with pathogens considered to be contaminants, such as coagulase-negative *Staphylococci*, *Micrococcus spp.*, *Corynebacterium spp.*, and *Propionibacterium acnes*, were excluded from the study.[20,21]

Type 2 DM was diagnosed according to the American Diabetes Association guidelines in patients using at least one oral hypoglycemic agent; patients included in the study had been diagnosed with the disease at least 2 years previously. Comorbid underlying diseases were classified according to International Classification of Diseases (ICD-9)[22] coding based on recorded discharge summaries and included chronic renal insufficiency (582.00–589.99), congestive heart failure (428.0–428.9), cerebrovascular accident (430.00–438.99), and rheumatic diseases (714.0–714.9, 710.0–710.9). Major focuses of infection including respiratory tract infection (481.0–486.9), urinary tract infection (590.00–590.99, 601.0–601.9), skin and soft tissue infection (680.0–686.9, 728.86), biliary tract disease (574.0–574.8, 575.0–575.1, 576.1), liver abscess (572.0) and intra-abdominal infection (562.11, 567.0–567.9, 5761, 574.00–574.19, 574.30–574.49, 574.60–574.89) were also defined based on ICD-9 coding.

Patients were considered to be on statin therapy if they had been treated with any drug belonging to the statin class (including rosuvastatin, atorvastatin, and simvastatin) for at least 30 days and were still taking the statin at the time of diagnosis with bacteremia. Information on statin use was obtained from hospital records.

We retrospectively collected the following independent variables from all enrolled patients: demographic characteristics, vital signs at triage, biochemical characteristics, major preexisting comorbidities, quick sepsis-related organ failure assessment (qSOFA) scores, major infection source, microorganisms isolated from blood cultures, mechanical ventilation requirement, and ICU admission. Septic shock was defined as persistent sepsis-induced hypotension, despite adequate fluid resuscitation, that required the use of inotropic agents.[23] The primary endpoint of this analysis was 28-day in-hospital all-cause mortality.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as means ± standard deviations and compared using Student's t-test. Categorical variables, expressed as numbers and percentages, were compared using χ^2 or Fisher's exact tests, as appropriate. All variables found to be significant in univariate analyses were incorporated into a Cox regression model for survival analysis. P-values $<.05$ were considered statistically significant.

Results

During the 7-year study period, 3,472 episodes of definite bacterial sepsis in patients with type 2 DM were identified (Figure 1). Of these, 1,493 were excluded because of a lack of long-term medication history at our hospital, while another 13 were excluded because of readmission within 14 days for the same pathogen. A total of 1,979 patients with confirmed bacteremia comprised the final analysis dataset. Of these, 507 (25.6%) patients were taking statins prior to and during the bacteremic episode (the 'statin group'), while 1,472 (74.4%) were not (the 'non-statin group'). In the statin group, 227 (44.8%) patients were receiving rosuvastatin, 196 (38.7%) atorvastatin, and 84 (16.6%) simvastatin.

Demographic data and presentation at the ED

As shown in Table 1, statin users were slightly older (69.5 ± 10.6 vs 67.5 ± 12.4 years, $P < .001$) than non-statin users, and the statin group had a smaller percentage of male subjects (40.6% vs 47.8%, $P = .007$) compared with the non-statin group. There were no significant differences in the proportions of patients with renal insufficiency, congestive heart failure, cerebrovascular accidents, and rheumatic diseases between the groups. Upon presentation at the ED, statin users had relatively lower qSOFA scores as well as higher systolic blood pressure than their non-statin group counterparts. With less severe presentations at the ED, the statin group also had lower proportions of individuals with septic shock, those requiring mechanical ventilation, and those requiring ICU admission, although the differences between the groups were not statistically significant. However, patients in the statin group had a significantly lower 28-day mortality rate (6.3% vs 12.8%; $P < .001$) than those in the non-statin group.

Regarding the primary source of infection (Table 2), a higher proportion of statin users than non-stain users had urinary tract infection (46.9% vs 42.0%, $P = .03$). There were no significant differences between the two groups regarding other sources of infection.

Bloodstream infection pathogens

Overall, there were no differences in the distributions of Gram-negative and Gram-positive blood culture isolates between the

Table 1. Demographic data and clinical presentations in the statin and non-statin groups

	Non-statin users (n = 1,472)	Statin users (n = 507)	P-value
Age, years (mean ± SD)	67.5 ± 12.4	69.5 ± 10.6	<.001*
Sex, male (n%)	703 (47.8%)	206 (40.6%)	.007 *
Vital signs in the ED (mean ± SD)			
Body temperature (°C)	37.9 ± 2.0	37.9 ± 1.4	.09
Heart rate (beats per minute)	106.2 ± 23.9	105.8 ± 22.0	.31
Systolic blood pressure (mmHg)	137.5 ± 37.2	143.2 ± 37.0	.003*
Diastolic blood pressure (mmHg)	76.8 ± 27.5	77.2 ± 18.6	.88
Respiratory rate (breaths per minute)	19.7 ± 3.6	19.9 ± 3.2	.39
qSOFA score at ED triage (n%)			.01*
0	765 (51.9%)	316 (62.3%)	
1	454 (30.8%)	136 (26.8%)	
2	184 (12.5%)	47 (9.3%)	
3	26 (1.8%)	8 (1.6%)	
Major comorbidities (n%)			
Renal insufficiency	332 (22.6%)	110 (21.6%)	.66
Congestive heart failure	102 (6.9%)	34 (6.7%)	.68
Cerebrovascular accident	204 (13.9%)	85 (16.8%)	.08
Rheumatic diseases	28 (1.9%)	9 (1.8%)	.83
Septic shock[a] (n%)	158 (10.7%)	46 (9.1%)	.15
Mechanical ventilation (n%)	182 (12.3%)	49 (9.7%)	.10
ICU admission (n%)	139 (9.4%)	43 (8.5%)	.59
28-day mortality (n%)	188 (12.8%)	32 (6.3%)	<.001*

Abbreviations: SD, standard deviation; ED, emergency department; qSOFA, quick sepsis-related organ failure assessment; ICU, intensive care unit

[a]Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation and inotropic agent use.

*P <.05

Table 2. Major sources of infection and laboratory data among statin and non-statin users

	Non-statin users (n = 1,472)	statin users (n = 507)	P-value
Major source of infection (n%)			
Respiratory tract	318 (21.6%)	101 (19.9%)	.52
Urinary tract	618 (42.0%)	238 (46.9%)	.03*
Skin and soft tissue	176 (12.0%)	58 (11.4%)	.68
Biliary tract	112 (7.6%)	43 (8.5%)	.48
Liver abscess	61 (4.1%)	15 (3.0%)	.20
Intra-abdomen	220 (14.9%)	74 (14.6%)	.79
Laboratory data in the ED (mean ± SD)			
WBC (1,000/μL)	13.4 ± 8.6	13.2 ± 5.9	.68
Segment (%)	83.5 ± 12.6	84.3 ± 10.6	.06

(continued)

Table 2. Continued

	Non-statin users (n = 1,472)	statin users (n = 507)	P-value
Bandemia (%)	1.8 ± 4.2	1.3 ± 3.1	.001*
Glucose (mg/dL)	284.9 ± 194.9	293.7 ± 188.2	.52
BUN (mg/dL)	35.6 ± 30.9	35.3 ± 26.8	.42
Cr (mg/dL)	2.0 ± 2.0	2.0 ± 2.0	>.99
AST (U/L)	128.9 ± 682.2	118.5 ± 345.6	.75
Total bilirubin (mg/dL)	3.0 ± 4.2	2.1 ± 3.2	.003*
Lactate (mmol/L)	4.1 ± 3.5	4.1 ± 3.3	.96
CRP (mg/L)	141.9 ± 116.5	136.6 ± 115.6	.29
HbA1c (%)	7.3 ± 1.2	7.4 ± 1.5	.79

Abbreviations: SD, standard deviation; ED, emergency department; WBC, white blood cell; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; CRP, C-reactive protein; HbA1c, glycated hemoglobin.
*P < .05

Table 3. Distributions of Gram-negative and Gram-positive bloodstream infections among statin and non-statin users

Variable	Non-statin users (n = 1,472)	Statin users (n = 507)	Total (n = 1,979)	P-value
Gram-negative bacteria	1,018 (69.2%)	359 (70.8%)	1,377 (69.6%)	.43
Escherichia coli	506 (34.4%)	216 (42.6%)	722 (36.5%)	<.001*
Klebsiella pneumonia	242 (16.4%)	64 (12.6%)	306 (15.5%)	.03*
Proteus species	37 (2.5%)	13 (2.6%)	50 (2.5%)	.78
Pseudomonas aeruginosa	34 (2.3%)	8 (1.6%)	42 (2.1%)	.28
Salmonella enterica species	31 (2.1%)	8 (1.6%)	39 (0.0%)	.58
Bacteroides fragilis	20 (1.4%)	7 (1.4%)	27 (1.4%)	.83
Others	148 (10.1%)	43 (8.5%)	191 (9.7%)	.26
Gram-positive bacteria	454 (30.8%)	148 (29.2%)	602 (30.4%)	.43
Staphylococcus aureus	199 (13.5%)	50 (9.9%)	249 (12.6%)	.03*
Streptococcus species	115 (7.8%)	56 (11.0%)	171 (8.6%)	.03*
Enterococcus species	50 (3.4%)	17 (3.3%)	67 (3.4%)	.88
Others	90 (6.1%)	25 (5.0%)	115 (5.8%)	.32

Data are presented as number of patients (%)
*P < .05

two groups (69.1% vs 70.8%, P =.43). The distributions of microbial agents in relation to statin use are shown in Table 3. Gram-negative bacteria accounted for most of the reported pathogens (69.6%), with Gram-positive bacteria representing only approximately one-third (30.4%). The most prevalent pathogens among statin and non-statin users were *Escherichia coli* (42.6% vs 34.4%; P < .001), *Klebsiella pneumoniae* (12.6% vs 16.4%; P = .03), *Staphylococcus aureus* (9.9% vs 13.5%; P = .03), and *Streptococcus spp.* (11.0% vs 7.8%; P = .03).

Sepsis and organ dysfunction biomarkers

Patients taking statins had lower bilirubin (2.1 mg/dL vs 3.0 mg/dL; P = .003) and bandemia (1.3% vs 1.8%; P < .001) levels

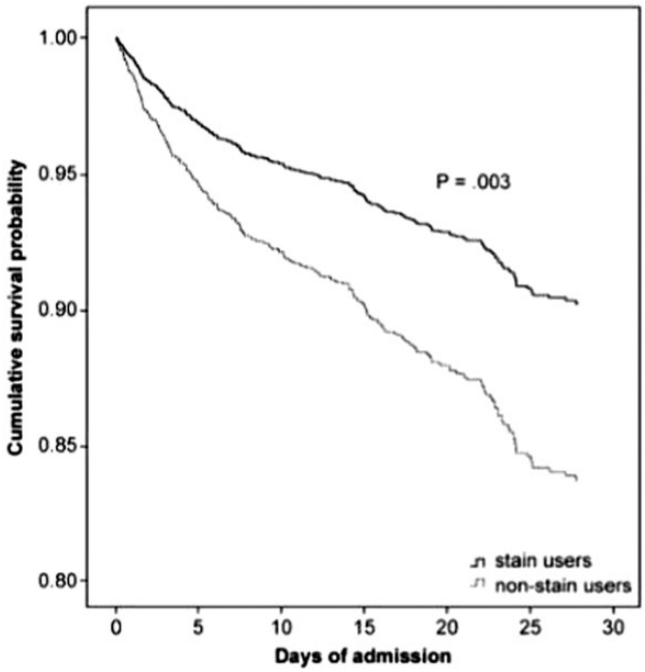

Figure 2. Adjusted 28-day in-hospital survival curve of patients with type 2 diabetes mellitus and bacteremia according to prior statin use

than those in non-statin users. There were no significant differences observed between the groups in the levels of other biomarkers such as lactate, C-reactive protein, white blood cell count, segment percentage, serum creatinine, and blood urea nitrogen.

Survival analysis

We performed Cox regression analysis incorporating factors related to underlying diseases and major infection sources that were significantly different between statin and non-statin users to analyze the influence of prior statin use on 28-day mortality. We found that older age was associated with higher 28-day in-hospital mortality (adjusted hazard ratio [HR], 1.04; 95% confidence interval [CI]: 1.01–1.04). However, prior statin use was associated with a significantly lower 28-day in-hospital mortality from bloodstream infection (adjusted HR, 0.58; 95% CI: 0.42–0.85), as was urinary tract infection (adjusted HR, 0.56, 95% CI: 0.43–0.75). The adjusted 28-day in-hospital survival curve was significantly different between statin and non-statin users as shown in Figure 2. Subgroup analysis of 28-day in-hospital mortality among statin users compared with non-statin users revealed that the three most common pathogens infecting these patients were *S. aureus* (5.6% vs 13.4%; P <.159), *K. pneumonia* (5.9% vs 10.6%; P <.359), and *E. coli* (2.1% vs 7.3%; P <.004).

Discussion

Our retrospective observational study found that prior statin use reduced 28-day mortality in patients with type 2 DM and bloodstream infections. Previous observational studies also found a significantly lower mortality rate associated with statin

therapy in patients with severe infections and sepsis.[12–14] However, there were major differences in subject comorbidities, definitions of sepsis, and other confounding factors among these previous studies. Since the prevalence of DM has been increasing in recent decades,[1–2] our study limited patient enrollment to those with type 2 DM. Moreover, our criteria for included bloodstream infections ruled out some etiologies that may mimic sepsis. To the best of our knowledge, this is the first study to evaluate the impact of prior statin use on mortality from bloodstream infection in patients with type 2 DM. A previous systematic review found that the use of statins did not significantly improve in-hospital or 28-day mortality rates in patients with sepsis.[16] However, the randomized controlled trials included in this systematic review included participants with systemic inflammatory response syndrome or acute lung injury. Instead, our study restricted patients to those with bloodstream infections to rule out some etiologies that mimic sepsis.

The sources of infection observed in our study were similar between the statin and non-statin groups, except for a higher proportion of urinary tract infection in the former group. While our analysis focused on bloodstream infections, urinary tract infections are more likely than other types of infections to lead to Gram-negative bacteremia. Whether statin use is associated with micturition disorders remains controversial, as some studies have found an association between statin use and lower urinary tract storage symptoms (increased daytime frequency, nocturia, urgency, and urinary incontinence).[24,25] However, a previous retrospective study by St. Sauver et al.[26] found that statin use decreased the risk of benign prostatic enlargement and lower urinary tract symptoms. Our results might be explained by the observation that people taking statins develop lower urinary tract symptoms more frequently, whereupon they receive medical care. Another infection source was liver abscess; although the difference in its incidence was not significant between statin and non-statin users, the former group experienced fewer liver abscesses than did the latter. DM and liver abscess are strongly correlated in Taiwan;[27,28] however, larger cohorts are necessary to evaluate the effect of statin use on preventing liver abscess.

A notable difference between statin and non-statin users in our study was the relative underrepresentation of *S. aureus* and overrepresentation of *E. coli* in the former group. A previous in vitro study found that statins exerted their greatest antibacterial effects against *S. aureus*, but were not effective against *E. coli*.[29] Chow et al.[30] showed that statins modulate extracellular traps in host macrophages, thereby improving *S. aureus* clearance. A previous cohort study revealed that the continuation of statin therapy was associated with significant beneficial effects on mortality among statin users with *S. aureus* bacteremia.[31] However, another observational cohort study reported that prior statin use was associated with lower 90-day total mortality rates attributable to Gram-negative, but not Gram-positive, bacteremia.[32] Our subgroup analysis of 28-day in-hospital mortality revealed that death rates were higher among non-statin users infected with both *S. aureus* and *E. coli*, although our data for the former were not statistically significant.

While an elevated white blood cell count is widely recognized as evidence of infection and an important criterion for the evaluation of systemic inflammatory response syndrome, there are reports of normal white blood cell counts upon presentation in a significant percentage of patients admitted to the ED with blood culture-verified bacteremia.[33] However, recent studies indicate that bandemia is highly predictive of a serious infection.[33–35] In our study, patients taking statins had similar white blood cell

counts to those in the non-statin group but had a significantly lower band form count. This indicated that statin users had less severe bacteremia than non-statin users, which was consistent with the patients' course from initial presentation through final outcome as evaluated using various methods.

Previous studies found that elevated serum bilirubin levels are associated with an increased risk of mortality in patients with severe sepsis and septic shock.[36,37] Elevated bilirubin levels were also found to be associated with longer hospital stays as well as increased durations of vasopressor support and mechanical ventilation.[37] The pathogenesis of jaundice is multifactorial, and includes an increased bilirubin load from hemolysis, hepatocellular injury, and decreased basolateral and canalicular transport of bile acid owing to the septic condition.[38] Our present study found that patients in the statin group had lower bilirubin levels. Elevated bilirubin is a marker of illness severity that may be counteracted by statins; this is supported in our study by the observation that the qSOFA scores at the time of ED triaging were lower among statin users.

Underlying illness may also contribute to differences in mortality rates among patients with bacteremia. In our study, patients in the statin group were older and had more documented cardiovascular disease. However, the results of our Cox regression analysis implied that statin users had significantly lower hazard ratios for bacteremia-related in-hospital mortality than non-statin users did.

Various experimental and pathophysiological pieces of evidence regarding the anti-inflammatory and anti-infection roles of statins have been reported; however, their effect on sepsis remains unclear.[39,40] This may be because sepsis is a heterogeneous disease, and small subgroup analyses are required to detect the potential benefits of statins. Although our study was observational with some confounding variables, the results convincingly showed that prior statin use was associated with lower mortality in patients with type 2 DM and bloodstream infections.

Our study had several limitations. First, it was a retrospective study, and the accuracy and completeness of patient medical records varied among different attending physicians. However, as we reviewed all patient treatment histories and excluded patients who did not receive long-term medication, selection bias was minimized. Second, the study was conducted at one institution in a single city, and the results may not be generalizable to other countries. Third, various statins are available on the market, and we did not obtain information on the equivalent dosages or lipid-lowering effects of the different types of statins administered to each patient. Further large-scale prospective cohort studies are therefore necessary to verify our findings.

Conclusions

Prior statin use reduces 28-day mortality in patients with type 2 DM and bloodstream infection. In our study cohort, the severity of bloodstream infections remained lower among statin users throughout the period between triaging in the ED and final outcome.

Abbreviations

CI, confidence interval; DM, diabetes mellitus; ED, emergency department; HR, hazard ratio; ICD, International Classification of Diseases; ICU, intensive care unit; qSOFA, quick sepsis-related organ failure assessment

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Author contributions

Conceptualization: C-M. Su.
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Methodology: C-Y. Cheng
Supervision: C-M. Su.
Validation: C-T. Kung
Writing – original draft: C-Y. Cheng
Writing – review & editing: C-M. Su.
All authors have approved the final version of the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Data availability

The raw data for this study are available upon reasonable request to the corresponding author.

Ethics approval and informed consent

The study protocol was approved by the Ethics Committee of Chang Gung Memorial Hospital, which waived the requirement for written informed patient consent because of the retrospective nature of the study.

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