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Statin Use and Risk of Community-Acquired *Staphylococcus aureus* Bacteremia: A Population-Based Case-Control Study

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Abstract

Objective: To ascertain whether persons treated with statins experience a decreased risk of community-acquired *Staphylococcus aureus* bacteremia (CA-SAB) as compared with nonusers.

Patients and Methods: Using population-based medical registries, we conducted a case-control study including all adults with first-time CA-SAB and population controls matched on age, sex, and residence in Northern Denmark from January 1, 2000, through December 31, 2011. Statin users were categorized as current users (new or long-term use), former users, and nonusers. We used conditional logistic regression to compute odds ratios (ORs) for CA-SAB according to statin exposure, overall and stratified by intensity (<20, 20-39, ≥40 mg/d) and duration of use (<365, 365-1094, ≥1095 days).

Results: We identified 2638 patients with first-time CA-SAB and 26,379 matched population controls. Compared with nonusers, current statin users experienced markedly decreased risk of CA-SAB (adjusted OR, 0.73; 95% CI, 0.63-0.84). The adjusted OR was 0.96 (95% CI, 0.60-1.51) for new users, 0.71 (95% CI, 0.62-0.82) for long-term users, and 1.12 (95% CI, 0.94-1.32) for former users as compared with nonusers. The CA-SAB risk decreased with increasing intensity of statin use; thus, compared with nonusers, the adjusted OR was 0.84 (95% CI, 0.68-1.04) for current users with daily dosages of less than 20 mg/d, 0.71 (95% CI, 0.58-0.87) for 20 to 39 mg/d, and 0.63 (95% CI, 0.49-0.81) for 40 mg/d or more. Conversely, we observed no differences in the risk of CA-SAB with successive increases in the duration of statin use.

Conclusion: Statin use was associated with a decreased risk of CA-SAB, particularly in long-term users.

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Staphylococcus aureus remains a leading cause of bacteremia associated with considerable morbidity and a 30-day mortality of 20% to 30% in Western countries.[1-3] Statins (3-hydroxy-3-methylglutaryl coenzyme A inhibitors) constitute the cornerstone of cholesterol-lowering therapy in patients at increased risk of cardiovascular events.[4] In addition to the well-known reduction in cholesterol levels, the results of in vitro studies have suggested that statins exert a number of so-called pleiotropic effects that may decrease the risk of *S aureus* bacteremia (SAB) in users.[5-8] First, statins have been reported to have direct antimicrobial effects against *S aureus*.[6,7] Second, statins inhibit host cell invasion by *S aureus*,[5,6] and third, use of statins has been observed to enhance the ability of phagocytes to kill *S aureus*.[8]

However, in spite of these interesting results, there is a paucity of in vivo data on the association between the use of statins and the risk of SAB, and to our knowledge, no previous clinical study has investigated whether the use of statins influence the risk of SAB. Given the detrimental clinical effects and considerable health care expenditure associated with SAB, any association with the use of statins would hold important health and clinical implications. Therefore, we conducted a population-based case-control study to ascertain whether persons treated with statins

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experienced decreased risk of community-acquired SAB (CA-SAB) as compared with nonusers. We assessed the risk of CA-SAB according to intensity and duration of statin treatment and explored whether the risk of CA-SAB differed by selected chronic diseases associated with statin use or according to sex, age, and comorbidity level.

PATIENTS AND METHODS

Setting

This case-control study was conducted in the North and Central Regions of Denmark (catchment population ~1.8 million inhabitants) between January 1, 2000, and December 31, 2011, using routinely recorded data from population-based medical registries. During the study period, a reform of local government merged 4 counties into 2 health regions: Central Denmark Region and North Denmark Region, collectively referred to as Northern Denmark. Denmark has a tax-supported health care system providing free and unrestricted access to general practitioners and hospitals and partial reimbursement of the costs of prescribed medication, including statins. The unique identification number assigned to all Danish citizens upon birth or immigration (the civil registration number) allowed unambiguous linkage of patient records across the data sources.[9] According to the Danish law, individual consent is not required for registry-based studies. The project was approved by the Danish Data Protection Agency (reference no. 2012-41-0942).

S aureus Bacteremia

We identified all patients 15 years or older hospitalized with CA-SAB in Northern Denmark through the laboratory information systems in the 4 departments of clinical microbiology from 1995 onward (identification and susceptibility testing of *S aureus* isolates are described in Supplemental Appendix 1, available online at http://www.mayoclinicproceedings.org). Inclusion was restricted to patients with presence of 1 or more positive blood cultures for *S aureus* as the sole isolate. Because patients with previous SAB are considered at increased risk of reinfection with SAB,[10] we included only patients with an *incident episode of CA-SAB*, defined as no previous SAB diagnosis within at least 5 years of the current hospitalization. *Community-acquired SAB* was defined as SAB in patients in whom 1 or more blood cultures had been drawn within 2 days of the current admission. We excluded patients with a first blood culture obtained more than 2 days after admission, because we considered these infections to be hospital acquired. The subset of patients with CA-SAB with recent preadmission health care contacts were further classified as health care–associated SAB if one or more of the following criteria were met within 30 days of the current hospitalization: hospital admission; visit to hospital outpatient surgical clinics; or visit to hospital hematology, oncology, or nephrology clinics.[11] Data on recent health care contacts were available in the Danish National Patient Registry (DNPR),[12] which has tracked all admissions to hospitals in Denmark since 1977 and all visits to hospital outpatient clinics since 1995. Records log admission and discharge dates, up to 20 discharge diagnoses, and data on surgical procedures.

Selection of Population Controls

For each case, we randomly selected 10 population controls and matched them to the CA-SAB cases by year of age (exact integer), sex, and residence (North Denmark Region or Central Denmark Region). Population controls were drawn from the Danish Civil Registration System,[9] which is electronically updated daily and keeps records of demographic characteristics and vital status for all Danish residents since 1968. Each control was assigned an index date identical to the CA-SAB admission date for the matched case. We used the risk set sampling technique[13]; thus, each population control had to be alive and at risk of a first hospitalization with CA-SAB on the date the corresponding case was admitted.

Use of Statins

Data on statin use were retrieved from the Aarhus University Prescription Database (AUPD).[14] This database contains detailed information on drug type coded according to the Anatomical Therapeutic Chemical (ATC) Classification System, fill date, number of packages redeemed, and dosage. Using this database, we identified all prescriptions filled for statins by cases and controls before the index date (ATC Classification

System codes are provided in Supplemental Appendix 2, available online at http://www.mayoclinicproceedings.org). Depending on the methods used previously,[15,16] *current users* were defined as patients whose most recent prescription redemption was within 90 days of the index date. To reduce the risk of bias associated with prevalent statin use,[15] we further subcategorized the current user group into new users, who redeemed their first-ever prescription within 90 days of the index date, and long-term users, if they had also previously redeemed such a prescription. We defined *former users* as patients who had redeemed their most recent prescription more than 90 days before the index date. *Nonusers* were defined as persons with no filled prescriptions for statins in the AUPD (the reference group in all comparisons). Moreover, we defined the *intensity of statin use* in current and former users as the number of pills prescribed multiplied by drug dosage (in milligrams) divided by the total duration of use (in days). Finally, we computed the *duration of statin* use for current and former statin users by counting the number of days between the date of the first and the last prescription redemption before the index date.

Demographic Characteristics, Coexisting Morbidity, and Comedications

Data on sex, age, and marital status were retrieved from the Danish Civil Registration System.[9] Using all diagnoses recorded in the DNPR up to 10 years before (but excluding) the index date, we identified coexisting morbidities included in the Charlson comorbidity index (CCI).[17] The CCI is a validated comorbidity scoring system covering the number and severity of 19 disease categories and has been adapted for use with hospital discharge registry data for the prediction of short- and long-term mortality, including after SAB.[18,19] We computed an aggregate score for all study participants, and 3 levels of comorbidity were defined as "low" (score, 0), "intermediate" (score, 1-2), and "high" (score, >2). The DNPR also provided information on hospital-diagnosed hypertension, alcohol-related conditions, and dialysis within 30 days of the index admission. Finally, we obtained information on the following filled prescriptions through the AUPD: systemic glucocorticoids, antineoplastic or immunomodulating agents, nonsteroidal anti-inflammatory drugs, and low-dose acetylsalicylic acid, all within 90 days of the index date. All diagnostic codes and ATC Classification System codes are provided in Supplemental Appendix 2.

Statistical Analyses

Characteristics of cases and controls were first described in a contingency table. Next, using conditional logistic regression, we computed crude and adjusted odds ratios (ORs) with corresponding 95% CIs as a measure of the relative risks of CA-SAB in current, new, long-term, and former users as compared with nonusers. Furthermore, to examine a possible dose-response relation, we stratified the risk of CA-SAB by intensity of statin use (categorized as <20, 20-39, and ≥40 mg/d) and by duration of statin use (categorized as <365, 365-1094, and ≥1095 days). To assess whether the risk of CA-SAB differed among subsets of statin users, we applied conventional logistic regression with additional adjustment for the matching factors and stratified the results by the presence of selected chronic diseases related to statin use (previous myocardial infarction, peripheral arterial disease, chronic heart failure, chronic kidney disease, and diabetes). The potential confounding factors included in the multivariate adjustments were carefully selected a priori on the basis of the existing knowledge of risk factors for CA-SAB. They included marital status, CCI score, alcohol-related conditions, and use of systemic glucocorticoids and antineoplastic or immunomodulating agents within a 90-day window of the index date. In the analyses stratified by selected statin-associated diseases, the disease in question was excluded from the CCI before adjustment. In an additional stratified analysis, we explored the risk of CA-SAB according to sex, age group (≥15-39, 40-59, 60-79, and ≥80 years), and CCI score (0, 1-2, and >2). To assess whether the association differed by type of statin, we also reran all analyses stratified by simvastatin, atorvastatin, and other statins (including pravastatin, lovastatin, fluvastatin, cerivastatin, and rosuvastatin). Finally, to ascertain the potential influence of variations in exposure definitions, we conducted a sensitivity analysis using alternative definitions of current statin users (prescription redemption within 60, 120, and 180 days before the index date).

TABLE 1. Characteristics of Cases With Incident Community-Acquired *Staphylococcus aureus* Bacteremia and Population Controls in Northern Denmark, 2000-2011

Characteristic	n (%)	
	Cases	Controls
Number of participants	2638	26,379
Statin use		
Nonuse	2013 (76.3)	21,740 (82.4)
Former use	257 (9.7)	1418 (5.4)
Current use	368 (14.0)	3221 (12.2)
New use	27 (1.0)	179 (0.7)
Long-term use	341 (12.9)	3042 (11.5)
Age (y)		
≥15-39	233 (8.9)	2340 (8.9)
40-59	605 (22.9)	6009 (22.8)
60-79	1182 (44.8)	11,838 (44.9)
≥80	618 (23.4)	6192 (23.5)
Sex		
Male	1616 (61.3)	16,159 (61.3)
Female	1022 (38.7)	10,220 (38.7)
Selected underlying conditions		
Previous myocardial infarction	220 (8.3)	1037 (3.9)
Peripheral arterial disease	328 (12.4)	889 (3.4)
Chronic heart failure	348 (13.2)	960 (3.6)
Chronic kidney disease	435 (16.5)	273 (1.0)
Diabetes	477 (18.1)	1212 (4.6)
Hypertension	651 (24.7)	3016 (11.4)
Moderate to severe liver disease	58 (2.2)	32 (0.1)
Chronic pulmonary disease	368 (14.0)	1515 (5.7)
Any cancer	655 (24.8)	1928 (7.3)
Alcohol-related conditions	235 (8.9)	398 (1.5)
Dialysis within 30 d of the index date	251 (9.5)	21 (0.1)
Charlson comorbidity index score		
Low (0)	725 (27.5)	18,539 (70.3)
Intermediate (1-2)	941 (35.7)	6215 (23.6)
High (>2)	972 (36.9)	1625 (6.2)
Medication use before the index date[a]		
Systemic glucocorticoids	379 (14.4)	827 (3.1)
Immunomodulating agents	40 (1.5)	128 (0.5)
Nonsteroidal anti-inflammatory drugs	405 (15.4)	1226 (4.7)
Low-dose acetylsalicylic acid	640 (24.3)	4531 (17.2)

[a]Any use within 90 d of the index date.

RESULTS

Descriptive Data

Table 1 presents characteristics of cases and controls. During the study period, we identified 2638 patients with CA-SAB and 26,379 population controls, of which 368 (14.0%) and 3221 (12.2%), respectively, were current users of statins. Among current statin users, 81.4% (4283) received simvastatin, 9.8% (514) atorvastatin, and 8.9% (467) other statins. Among patients with CA-SAB, 42.2% (1115) had recently been in contact with the health care system before admission (health care–associated SAB). Methicillin-resistant *S aureus* was rare (0.5%; 13). The median age of the study participants was 69 years (interquartile range, 56-79 years), and the majority (61.3%) were men. Patients with CA-SAB had considerably higher hospital-diagnosed comorbidity than did population controls, including peripheral arterial disease (12.4% [328] vs 3.4% [889]), chronic heart failure (13.2% [348] vs 3.6% [960]), diabetes mellitus (18.1% [477] vs 4.6% [1212]), and cancer (24.8% [655] vs 7.3% [1928]). In addition, cases were more likely to have filled prescriptions for systemic glucocorticoids, nonsteroidal anti-inflammatory drugs, and low-dose acetylsalicylic acid.

Risk of SAB

Compared with nonusers, the unadjusted OR for incident CA-SAB was 1.33 (95% CI, 1.17-1.50) for current users. Adjustment for potential confounders decreased the estimate (OR, 0.73; 95% CI, 0.63-0.84), which was primarily conveyed by the effect of comorbidities. The adjusted OR was 0.96 (95% CI, 0.60-1.51) for new users, 0.71 (95% CI, 0.62-0.82) for long-term users, and 1.12 (95% CI, 0.94-1.32) for former users as compared with nonusers (Table 2). The risk estimates did not differ notably among cases with and without recent health care contacts (data not shown).

The risk of CA-SAB decreased gradually with increasing intensity of current statin use (Table 3). Compared with nonusers, the adjusted OR was 0.84 (95% CI, 0.68-1.04) for current users with daily statin dosages of less than 20 mg/d, 0.71 (95% CI, 0.58-0.87) for current users with daily dosages of 20 to 49 mg/d, and 0.63 (95% CI, 0.49-0.81) for current users with daily dosages of 40 mg/d or more. In contrast, the risk of CA-SAB did not differ notably with successive increases in the duration of current statin use (Table 4). Thus, compared with nonusers, the adjusted OR was 0.77 (95% CI, 0.57-1.04) for persons who had received statins for less than 365 days, 0.48 (95% CI, 0.36-0.64) for persons treated for 365 to 1094 days, and 0.84 (95% CI, 0.71-0.99) for persons treated for 1095 days or longer. The Figure displays the risk of CA-SAB stratified by selected chronic diseases related to statin use. Compared with nonusers,

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TABLE 2. Crude and Adjusted Odds Ratios (ORs) for Community-Acquired *Staphylococcus aureus* Bacteremia Associated With the Use of Statins

Statin use	n (%)		OR (95% CI)	
	Cases	Controls	Unadjusted	Adjusted[a]
Nonuse	2013 (76.3)	21,740 (82.4)	1.00 (reference)	1.00 (reference)
Former use	257 (9.7)	1418 (5.4)	2.12 (1.83-2.46)	1.12 (0.94-1.32)
Current use	368 (13.9)	3221 (12.2)	1.33 (1.17-1.50)	0.73 (0.63-0.84)
New use	27 (1.0)	179 (0.7)	1.68 (1.12-2.53)	0.96 (0.60-1.51)
Long-term use	341 (12.9)	3042 (11.5)	1.30 (1.15-1.48)	0.71 (0.62-0.82)

[a]Adjusted for marital status, conditions included in the Charlson comorbidity index, alcohol-related conditions, and use of systemic glucocorticoids or treatment with antineoplastic or immunomodulating agents within 90 d of the index date.

the decreased risk of CA-SAB associated with current statin use was most pronounced in patients with chronic kidney disease (adjusted OR, 0.51; 95% CI, 0.34-0.76) and patients with diabetes (adjusted OR, 0.65; 95% CI, 0.50-0.85). No consistent pattern or notable differences in the risk of CA-SAB were observed according to sex, age, and CCI score (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

We observed no substantial difference in the risk of CA-SAB across different types of statins (Table 5), and altering the exposure window to define current statin use from 90 days to alternately 60, 120, and 180 days did not markedly affect our findings (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

DISCUSSION

In this population-based case-control study, the use of statins was associated with a decreased risk of CA-SAB, which appeared to be driven primarily by long-term use. Compared with nonusers, the risk of CA-SAB decreased with increasing intensity of statin use whereas successive increases in the duration of statin use did not markedly influence the CA-SAB risk. The association between statin use and decreased risk of CA-SAB remained consistent across strata of age, sex, comorbidity level, and statin types and was particularly prominent in patients with chronic kidney disease and patients with diabetes.

This is, to our knowledge, the first study to investigate whether the use of statins is associated with a decreased risk of bacteremia including SAB. However, the association between statin use and the risk of other types of infection has previously been assessed.[20-25] In a Danish combined population-based case-control and cohort study including 780,045 patients, the investigators observed

TABLE 3. Crude and Adjusted Odds Ratios (ORs) for Community-Acquired *Staphylococcus aureus* Bacteremia Associated With the Use of Statins, Stratified by Intensity of Use

Statin use	n (%)		OR (95% CI)	
	Cases	Controls	Unadjusted	Adjusted[a]
Nonuse	2013 (76.3)	21,740 (82.4)	1.00 (reference)	1.00 (reference)
Former use				
<20 mg/d	176 (6.7)	867 (3.3)	2.37 (1.99-2.82)	1.22 (1.00-1.49)
20-39 mg/d	68 (2.6)	452 (1.7)	1.77 (1.36-2.31)	0.97 (0.72-1.31)
≥40 mg/d	13 (0.5)	99 (0.4)	1.55 (0.87-2.77)	0.80 (0.42-1.52)
Current use				
<20 mg/d	125 (4.7)	1093 (4.1)	1.31 (1.08-1.59)	0.84 (0.68-1.04)
20-39 mg/d	150 (5.7)	1286 (4.9)	1.37 (1.14-1.64)	0.71 (0.58-0.87)
≥40 mg/d	93 (3.5)	842 (3.2)	1.29 (1.03-1.62)	0.63 (0.49-0.81)

[a]Adjusted for marital status, conditions included in the Charlson comorbidity index, alcohol-related conditions, and use of systemic glucocorticoids or treatment with antineoplastic or immunomodulating agents within 90 d of the index date.

TABLE 4. Crude and Adjusted Odds Ratios (ORs) for Community-Acquired *Staphylococcus aureus* Bacteremia Associated With the Use of Statins, Stratified by Duration of Use

Statin use	n (%)		OR (95% CI)	
	Cases	Controls	Unadjusted	Adjusted[a]
Nonuse	2013 (76.3)	21,740 (82.4)	1.00 (reference)	1.00 (reference)
Former use				
<365 d	23 (0.9)	145 (0.5)	1.82 (1.17-2.84)	1.39 (0.85-2.27)
365-1094 d	61 (2.3)	433 (1.6)	1.63 (1.14-2.14)	0.97 (0.72-1.32)
≥1095 d	173 (6.6)	840 (3.2)	2.46 (2.06-2.94)	1.15 (0.93-1.41)
Current use				
<365 d	61 (2.3)	536 (2.0)	1.29 (0.98-1.68)	0.77 (0.57-1.04)
365-1094 d	66 (2.5)	872 (3.3)	0.87 (0.67-1.12)	0.48 (0.36-0.64)
≥1095 d	241 (9.1)	1813 (6.9)	1.58 (1.36-1.84)	0.84 (0.71-0.99)

[a]Adjusted for marital status, conditions included in the Charlson comorbidity index, alcohol-related conditions, and use of systemic glucocorticoids or treatment with antineoplastic or immunomodulating agents within 90 d of the index date.

an adjusted OR of 0.80 (95% CI, 0.77-0.83) for pneumonia associated with statin use.[20] In contrast, a US population-based control study including 3360 patients reported an adjusted OR of 1.26 (95% CI, 1.01-1.56) for pneumonia associated with the use of statins.[21] Moreover, preoperative use of statins has been associated with a decreased risk of infections after cardiac surgery.[22,23] In a US cohort study including 6253 patients, statin use was associated with a decreased risk of any postoperative infection (adjusted OR, 0.74; 95% CI, 0.60-0.90).[22] In line, another US cohort study of 1934 patients reported an adjusted OR of 0.67 (95% CI, 0.46-0.99) for any postoperative infection associated with statin use.[23] Furthermore, there is evidence that statins are associated with a decreased risk of sepsis, which is often caused by *S aureus*.[2,3,24,25] In a Canadian population-based cohort study of 69,168 patients with atherosclerotic disease, the investigators observed a decreased risk of sepsis associated with the use of statins (adjusted hazard ratio, 0.81; 95% CI, 0.72-0.90).[24] In line with our results, the risk reduction was most pronounced in patients with diabetes and patients with chronic kidney disease (specific estimates were not provided in the article). In addition, a US cohort study including 1041 patients with chronic kidney disease reported an unadjusted incidence rate of sepsis of 41 per 1000 patient-years in statin users as compared with 110 per 1000 patient-years in nonusers.[25]

A number of different pathophysiological mechanisms may underlie our findings. Statins have been observed to exhibit a direct antimicrobial effect against *S aureus* in vitro.[6,7] Nevertheless, in previous studies the minimal inhibitory concentrations for simvastatin against *S aureus* ranged from 15 to 32 mg/L, which is considerably higher than the concentration of 0.02 mg/L attained in adults with daily simvastatin dosages of 40 mg/d.[7] Thus, it seems less likely that the decreased risk of CA-SAB observed in vivo is conveyed primarily by a direct antimicrobial effect of statins. Moreover, *S aureus* is conventionally considered an extracellular pathogen, yet there is increasing evidence suggesting that it may also survive intracellularly in endothelial cells and neutrophils offering protection from the immune system and extracellular antibiotics.[26] However, in vitro results have indicated that statins deplete important isoprenoid intermediates within the cholesterol pathway and attenuate host cell actin stress fiber disassembly, which, collectively, leads to the inhibition of endocytic *S aureus* invasion.[5] In addition, statins have been reported to boost the production of antibacterial DNA-based extracellular traps by human and murine neutrophils and macrophages, which may further facilitate the killing of *S aureus*.[8] The action mechanisms of statins are likely to be the same in patients with different chronic diseases; still compared with nonusers, the decreased risk of

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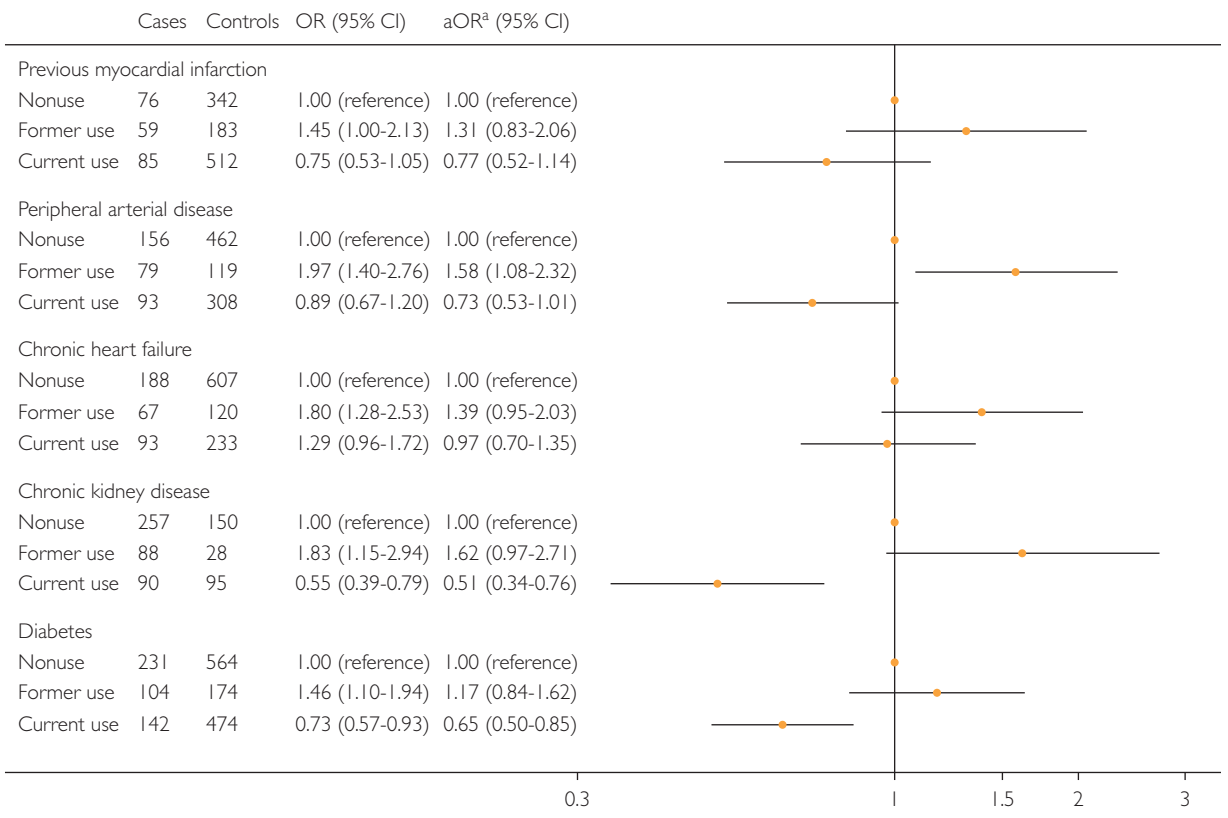

FIGURE. Crude and adjusted odds ratios (ORs) for incident community-acquired *Staphylococcus aureus* bacteremia stratified by selected diseases associated with the use of statins. aOR = adjusted odds ratio; OR = odds ratio. [a]Adjusted for sex, age, residence, marital status, conditions included in the Charlson comorbidity index (excluding the morbidity in question), alcohol-related conditions, and use of systemic glucocorticoids or treatment with antineoplastic or immunomodulating agents within 90 days of the index date.

CA-SAB was particularly pronounced in patients with chronic kidney disease and patients with diabetes. Although it cannot be entirely precluded that the pathophysiological mechanisms differ among patients with these diseases, the findings most likely reflect the particularly high baseline risk of CA-SAB associated with chronic kidney disease and diabetes.[27,28]

Strengths of our study include the population-based design and setting within a free tax-supported universal health care system that reduces the potential risk of selection and referral bias considerably. The AUPD provided virtually complete and comprehensive data on statin prescriptions with no risk of recall bias. Moreover, we restricted the study population to patients with CA-SAB, thereby decreasing the risk of confounding from surgical procedures and concurrent diseases associated with hospital-acquired SAB.

Our study also has limitations. The population-based design allowed the inclusion of all incident CA-SAB cases in the study period; still, we may have missed some cases if the patient had been hospitalized outside the catchment area, if the patient had received antibiotic treatment before the admission, or if the patient had died before blood culture sampling. We used filled prescriptions as a proxy for actual statin use and any nonadherence would thus bias our estimates toward unity. Still, a previous validation study from our study group reported a close correspondence between general practitioner–reported medication use and timing of prescription dispensation,[29] and furthermore, the sensitivity analysis in which we changed the split date

TABLE 5. Influence of Statin Type on the Association Between Statin Use and Risk of Community-Acquired *Staphylococcus aureus* Bacteremia

Statin use	Adjusted[a] OR (95% CI)		
	Simvastatin	Atorvastatin	Other[b]
Nonuse	1.00 (reference)	1.00 (reference)	1.00 (reference)
Former use	1.17 (0.97-1.41)	1.16 (0.68-1.99)	1.03 (0.62-1.72)
Current use	0.72 (0.62-0.84)	0.78 (0.55-1.13)	0.57 (0.36-0.90)
New use	0.97 (0.60-1.58)	1.07 (0.19-5.99)	0.36 (0.03-3.79)
Long-term use	0.70 (0.60-0.83)	0.77 (0.53-1.12)	0.58 (0.36-0.92)

[a]Adjusted for marital status, conditions included in the Charlson comorbidity index, alcohol-related conditions, and use of systemic glucocorticoids or treatment with antineoplastic or immunomodulating agents within 90 d of the index date.
[b]Including pravastatin, lovastatin, fluvastatin, cerivastatin, and rosuvastatin.

for current and former users did not materially change the effect estimates. We lacked data on infective foci, and this could have potentially influenced our results if the foci were unevenly distributed among users and nonusers of statins. Moreover, we did not have detailed data on education level and personal income. Yet, although socioeconomic status may be associated with statin use and risk of CA-SAB,[3] severe confounding from this factor seems less likely as statins are relatively inexpensive, prescriptions are partially reimbursed, and cost-free, unfettered access to health care is available to all Danish citizens. We were able to adjust for a wide range of potentially confounding factors including comorbidities and a number of comedications. Still, it cannot be entirely precluded that part of the observed protective association might reflect bias from "healthy user" effects; that is, statin users are characterized by better functional status and less severe comorbidity and are more likely to exert other healthy behaviors than nonusers. Although data on smoking and body mass index (calculated as the weight in kilograms divided by the height in meters squared) were unavailable, part of these factors' potential effects may be accounted for by the adjustment for lifestyle-related comorbidities including cardiovascular disease, chronic pulmonary disease, diabetes, and hypertension. Also, a Danish cross-sectional study found that statin users have a slightly higher body mass index than do nonusers whereas there were no differences in smoking or alcohol consumption.[30] Furthermore, although our design accounted for differences in duration of statin use, the particularly pronounced decreased risk associated with long-term statin use may partly be explained by prevalent user bias.[15]

Our study was carried out in an area with low prevalence of methicillin-resistant *S aureus* bacteremia (0.5%), which may hinder the extrapolation of our results to other settings with substantial methicillin-resistant *S aureus* prevalence. Nevertheless, we consider it likely that our results are generalizable to other settings and countries with similar lifestyle and cost-free, unfettered access to health care and prescription drugs, including statins.

CONCLUSION

Current users of statins experienced an almost 30% decreased risk of CA-SAB as compared with nonusers. The risk decreased gradually with increasing intensity of use, revealing a distinct dose-response relation, and the association was most pronounced in patients with concomitant chronic kidney disease and patients with diabetes. Statins may have a place in the prevention of CA-SAB, particularly in patients with these common chronic diseases and in other persons at high risk of CA-SAB. Nevertheless, our results warrant confirmation in other settings and study designs, and the biological mechanisms by which statin treatment may protect against CA-SAB should be explored further.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ATC** = Anatomical Therapeutic Chemical; **AUPD** = Aarhus University Prescription Database; **CA-SAB** = community-acquired *Staphylococcus aureus* bacteremia; **CCI** = Charlson comorbidity index; **DNPR** = Danish National Patient Registry; **OR** = odds ratio; **SAB** = *Staphylococcus aureus* bacteremia

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