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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

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