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MAJOR ARTICLE

Influence of Acetylsalicylic Acid Use on Risk and Outcome of Community-Acquired *Staphylococcus aureus* Bacteremia: A Population-Based Study

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Objective: To investigate the influence of acetylsalicylic acid (ASA) use on risk and outcome of community-acquired *Staphylococcus aureus* bacteremia (CA-SAB).

Method: We used population-based medical databases to identify all patients diagnosed in northern Denmark with first-time CA-SAB and matched population controls from 2000–2011. Categories for ASA users included current users (new or long-term users), former users, and nonusers. The analyses were adjusted for comorbidities, comedication use, and socioeconomic indicators.

Results: We identified 2638 patients with first-time CA-SAB and 26 379 matched population controls. Compared with nonusers, the adjusted odds ratio (aOR) for CA-SAB was 1.00 (95% confidence interval [CI], 0.88–1.13) for current users, 1.00 (95% CI, 0.86–1.16) for former users, 2.04 (95% CI, 1.42–2.94) for new users, and 0.95 (95% CI, 0.84–1.09) for long-term users. Thirty-day cumulative mortality was 28.0% among current users compared with 21.6% among nonusers, yielding an adjusted hazard rate ratio (aHRR) of 1.02 (95% CI, 0.84–1.25). Compared with nonusers, the aHRR was 1.10 (95% CI, 0.87–1.40) for former users, 0.60 (95% CI, 0.29–1.21) for new users, and 1.06 (95% CI, 0.87–1.31) for long-term users. We observed no difference in the risk or outcome of CA-SAB with increasing ASA dose or by presence of diseases commonly treated with ASA.

Conclusions: Use of ASA did not seem to influence the risk or outcome of CA-SAB. The apparent increased risk among new users may relate to residual confounding from the circumstances underlying ASA treatment initiation. Our finding of no association remained robust with increasing ASA dose and across multiple patient subsets.

Key words: acetylsalicylic acid; aspirin; outcome; prognosis; risk; *Staphylococcus aureus* bacteremia.

INTRODUCTION

Staphylococcus aureus bacteremia (SAB) is a serious infection that continues to be associated with considerable morbidity and a 30-day mortality of 20%–30% [1, 2]. Acetylsalicylic acid (ASA) remains a critically important agent in the secondary prevention of atherosclerotic disease on a global scale [3]. In addition to its role in cardiovascular prophylaxis, an increasing number of studies have suggested that ASA has a number of effects on the immune system, which in turn may influence the risk and outcome of SAB. For example, in vitro data suggest that ASA mediates a direct antimicrobial effect against staphylococci [4]. Moreover, ASA has been shown to exert anti-inflammatory effects in sepsis [5–7] and, by inhibiting platelet activation, ASA may reduce the risk of thromboembolic complications associated with SAB [8, 9].

Nevertheless, there is a paucity of clinical data on the association between ASA use and SAB, and, to the best our knowledge, only 2 previous studies have elucidated the influence of ASA use on the risk and outcome of SAB, respectively [10, 11]. As SAB is associated with an adverse clinical impact on patients and substantial healthcare costs, any association with use of a widespread and inexpensive treatment, such as ASA, could have valuable potential for clinical care. We therefore conducted a combined population-based case-control and cohort study to investigate whether ASA treatment influenced the risk and the outcome of community-acquired (CA-)SAB when comparing users with nonusers. In addition, we examined whether the risk and outcome of CA-SAB differed by intensity of ASA use, by selected chronic medical conditions commonly treated with

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ASA, by duration of ASA use, and by age, gender, and comorbidity level.

METHODS

Design and Setting

We conducted this combined case-control and cohort study in northern Denmark (catchment population ~ 1.8 million inhabitants) between January 1, 2000, and December 31, 2011, using population-based medical registries with routinely recorded data. Denmark has a tax-supported healthcare system providing free medical care and partial reimbursement for the costs of most prescribed medications, including ASA. The unique 10-digit identification number assigned to all Danish citizens upon birth or immigration (the civil registration number) allows unambiguous electronic linkage of patient records across the data sources [12]. According to Danish legislation, individual consent is not required for registry-based studies. The project was approved by the Danish Data Protection Agency (record no. 2012-41-0942).

Patients With *S. aureus* Bacteremia

We identified patients hospitalized with CA-SAB in the databases of the departments of clinical microbiology within the catchment area from 1995 onwards (information on blood culture practice and susceptibility testing is provided in the Supplementary Appendix 1). Eligible patients were defined as patients aged 15 years or older with 1 or more positive blood cultures in which *S. aureus* was the only isolate. Recurrence of SAB is strongly associated with outcome [13]. Therefore, we restricted the study to patients with first-time CA-SAB, defined as no previous SAB diagnosis within at least 5 years of the current hospitalization. If the first positive blood culture was obtained within 2 days of admission, SAB was defined as community-acquired. If the first positive blood culture was obtained >2 days after admission, the infection was considered hospital-acquired and the patient was excluded. Patients with CA-SAB and healthcare contacts within 30 days of the current hospitalization were classified as having healthcare-associated SAB (HCA-SAB) if 1 or more of the following criteria were fulfilled: hospital admission, contacts to hospital outpatient surgical clinics, or contacts to clinics of oncology, hematology, or nephrology [14]. We retrieved information on recent healthcare contacts from the Danish National Patient Registry (DNPR), which has tracked all admissions to Danish hospitals since 1977 and all visits to hospital outpatient clinics since 1995. The DNPR records log the dates of hospital admission and discharge, discharge diagnoses assigned by treating physicians, and data on surgical procedures [15].

Selection of Population Controls and Outcome

The Danish Civil Registration System (DCRS), which is updated daily, tracks age, gender, residence, marital status, and vital status for all Danish residents [12]. Using this registry, we randomly selected 10 population controls on the date the first positive blood culture was drawn and matched them to the CA-SAB cases by age, gender, and residence (northern Denmark region or central Denmark region). All controls were assigned an index date identical to the CA-SAB admission date for the matched case. The risk set sampling technique was applied [16], requiring that the population controls were alive and at risk of a first hospitalization with SAB on the date the corresponding case was admitted. In the cohort study, data on all-cause 30-day mortality were collected from the DCRS [12].

Use of Acetylsalicylic Acid

The Aarhus University Prescription Database (AUPD) contains data on all prescriptions dispensed in northern Denmark since 1998 [17]. Information in the AUPD includes the name and Anatomical Therapeutic Classification (ATC) code of the drug, date of dispensing, dosage, and number of packages dispensed. Using this database, we identified all prescriptions filled for ASA by the study participants prior to the SAB admission date. (ATC codes are provided in the Supplementary Appendix 2). We applied previously used methods [18] to define current users as patients who had filled a prescription for ASA within 125 days before the SAB admission date. In order to account for variations in duration of ASA use, the current user group was further subcategorized into new users, who filled their first-ever prescription within 125 days of their SAB admission date, and long-term users, who previously had redeemed a prescription for ASA. Former users were defined as patients whose last prescription redemption was more than 125 days predating their SAB admission date. Nonusers (ie, patients with no filled prescription for ASA recorded in the AUPD) served as the reference group for all comparisons. Furthermore, we defined the intensity of ASA use among current and former users as the number of pills filled multiplied by drug dosage in milligrams divided by the total duration of use in days. Duration of ASA use was determined by counting the number of days between the dates of the first and last prescription redemption before the SAB admission date.

Demographic Data, Coexisting Morbidities, and Comedications

The DCRS [12] provided data on gender, age, and marital status. We used the DNPR to identify all inpatient and outpatient diagnoses of comorbidities recorded up to 10 years before (but not on) the index date, and a Charlson Comorbidity Index (CCI) was computed for all patients and controls. The CCI assigns 1 to 6 points to 19 major disease categories and previously has been validated for use with hospital discharge registry data to predict mortality, including mortality after SAB [19, 20]. An aggregate score was calculated for each study participant, who then were classified as having a low (score = 0), intermediate (score = 1–2), or a high comorbidity level (score > 2). The

DNPR [15] also provided information on diagnoses of hypertension, alcohol-related conditions, and dialysis within 30 days of the index admission, which are not included in the CCI. Finally, we obtained data from the AUPD [17] on concomitant use of (1) vitamin K antagonists, thrombocyte inhibitors, angiotensin converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers (any previous use); (2) statins, NSAIDs, systemic glucocorticoids, antineoplastic, or immunosuppressive medication (used within 90 days of the index date); and (3) antibiotics (used within 30 days of the index date). All relevant diagnostic codes and ATC codes are provided in the Supplementary Appendix 2.

Statistical Analysis

In the case-control study, characteristics of cases and controls were first described in a contingency table. Next, conditional logistic regression was applied to compute crude and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) as a measure of the relative risks of CA-SAB among current, new, long-term, and former ASA users compared with nonusers. We adjusted for conditions included in the CCI score, marital status, alcohol-related conditions, treatment with statins, glucocorticoids, antineoplastic agents, or immunomodulating agents (within 90 days of the index date), and any previous use of other thrombocyte inhibitors and vitamin K antagonists. These potential confounding factors were carefully selected a priori based on the existing knowledge on risk and prognostic factors for CA-SAB.

In the cohort study, we followed patients from the date on which the patient´s first positive blood culture was drawn, until death, migration, or for 30 days, whichever came first. Characteristics of ASA users and nonusers were summarized in a contingency table, and a Cox proportional hazards model was used to compare 30-day cumulative mortality rates among ASA users and nonusers, including estimation of hazard ratios of death with 95% CIs. We adjusted for age, gender, CCI score, hypertension, alcohol-related conditions, marital status, use of statins or NSAIDs within 90 days of the index date, any previous use of other thrombocyte inhibitors, vitamin K antagonists, beta blockers, ACE inhibitors or calcium channel blockers, and use of antibiotics within 30 days of the index date.

In order to examine a potential dose-response relation between ASA use and CA-SAB, we stratified the analyses of risk and outcome according to intensity of ASA use, categorized as ≤75 mg/day, >75–150 mg/day, and >150 mg/day. We also examined risk and outcome of CA-SAB according to presence of selected chronic diseases associated with ASA use (previous myocardial infarction, chronic heart failure, peripheral arterial disease, chronic kidney disease, and diabetes).

To ascertain whether the potential association between ASA use and CA-SAB differed among various subsets of patients, we assessed the risk and outcome of CA-SAB according to duration of ASA use (categorized as <365 days, 365–1094 days, and ≥1095 days), and by age, gender, and CCI score. In addition, to investigate the potential influence of variations in exposure definitions, we repeated the analyses of risk and outcome using alternate definitions of current ASA use (prescription redemption within 60, 90, or 180 days). The assumption of proportional hazards in the Cox models was assessed graphically using log-minus-log plots and found appropriate. All statistical analyses were performed using Stata 11.2 for Windows (Stata Corp, College Station, TX).

RESULTS

Case-Control Study of the Risk of Community-Acquired *S. aureus* Bacteremia

Characteristics of cases and controls are shown in Table 1. Between 2000 and 2011, we identified 2 638 patients with incident CA-SAB and 26 379 population controls, of which 760 (28.8%) and 5 308 (20.1%) were current ASA users, respectively. Among patients with CA-SAB, 42% had recent health care system contacts (HCA-SAB). Methicillin-resistant *S. aureus* (MRSA) infections were rare during the study period (0.5%). The median age of the study participants was 69 years (interquartile range [IQR], 56–79 years) and 61% were men. Compared with controls, patients with CA-SAB used more medications prior to the index date and had more comorbidity, including a history of myocardial infarction (8.3% vs 3.9%), diabetes (18.1% vs 4.6%), and chronic kidney disease (16.5% vs 1.0%).

The unadjusted OR associating current ASA use with CA-SAB risk was 2.05 (95% CI, 1.85–2.28). Adjustment for potential confounders reduced the OR to 1.00 (95% CI, 0.88–1.13), mainly driven by the influence of coexisting morbidities. Compared with nonusers, the adjusted OR was 1.00 (95% CI, 0.86–1.16) for former users, 2.04 (95% CI, 1.42–2.94) for new users, and 0.95 (95% CI, 0.84–1.09) for long-term users (Table 2). We observed no notable difference in risk estimates for cases with and without recent healthcare system contacts (data not shown).

Cohort Study on the Outcome of Community-Acquired *S. aureus* Bacteremia

Table 3 presents characteristics of ASA users and nonusers in the cohort study. Of the 2 638 patients with CA-SAB, 760 (28.8%) were current users, 361 (13.7%) were former users, and 1 517 (57.5%) were nonusers. ASA users tended to be older than nonusers and had more coexisting morbidity, including a history of myocardial infarction (20.7% vs 0.7%), peripheral arterial disease (24.0% vs 4.0%), chronic heart failure (26.3% vs 4.8%), and chronic kidney disease (24.6% vs 10.6%). In addition, concomitant use of other types of medication was more common among ASA users than among nonusers.

Thirty-day cumulative mortality was 28.0% among current ASA users versus 21.6% among nonusers. This yielded

Table 1. Case-Control Study: Characteristics of Cases With Incident Community-Acquired *Staphylococcus aureus* Bacteremia and Population Controls in Northern Denmark 2000–2011

Characteristics	Cases n (%)	Controls n (%)
Numbers (%)	2638 (9.1)	26 379 (90.9)
Acetylsalicylic acid use		
Nonuse	1517 (57.5)	18 606 (70.5)
Former use	361 (13.7)	2465 (9.3)
Current use	760 (28.8)	5308 (20.1)
New use	56 (2.1)	216 (0.8)
Long-term use	704 (26.7)	5092 (19.3)
Age		
≥15–39 years	233 (8.8)	2 340 (8.9)
40–59 years	605 (22.9)	6009 (22.8)
60–79 years	1182 (44.8)	11 838 (44.9)
≥80 years	618 (23.4)	6192 (23.5)
Gender		
Men	1616 (61.3)	16 159 (61.3)
Women	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 solid cancer	655 (24.8)	1928 (7.3)
Alcohol-related conditions	235 (8.9)	398 (1.5)
Dialysis within 30 days 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		
ACE inhibitors[a]	1086 (41.2)	6768 (25.7)
Beta blockers[a]	1035 (39.2)	6470 (24.5)
Calcium channel blockers[a]	890 (33.7)	5488 (20.8)
Vitamin K antagonists[a]	429 (16.3)	1674 (6.4)
Other thrombocyte inhibitors[a]	242 (9.2)	1493 (5.7)
Statins[b]	368 (14.0)	3221 (12.2)
NSAIDs[b]	584 (22.1)	2662 (10.1)
Systemic glucocorticoids[b]	379 (14.4)	827 (3.1)
Immunomodulating agents[b]	40 (1.5)	128 (0.5)
Antibiotic treatment[c]	536 (20.3)	1252 (4.8)

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]Any previous use prior to the index date.

[b]Any previous use within 90 days of the index date.

[c]Any use within 30 days of the index date.

an unadjusted HRR of 1.37 (95% CI, 1.15–1.62) and an adjusted HRR of 1.02 (95% CI, 0.84–1.25) (Table 4). Compared with nonusers, the adjusted HRR was 1.10 (95% CI, 0.87–1.40) for former users, 0.60 (95% CI, 0.29–1.21) for new users, and 1.06 (0.87–1.31) for long-term users. Restricting the analyses to patients with and to patients without recent healthcare contacts did not materially influence the risk estimates (data not shown).

Additional Analyses

We observed no noteworthy difference in the risk or outcome of CA-SAB with successive increases in ASA dose (Table 5), nor did we see a clear association between selected diseases treated with ASA and CA-SAB risk or outcome (Table 6). Similarly, we found no consistent pattern or notable difference in risk or prognosis according to duration of ASA use (Supplementary Table 1) or according to age, gender, or CCI level (Supplementary

Table 2. Case-Control Study: Crude and Adjusted Odds Ratios for Incident Community-Acquired *Staphylococcus aureus* Bacteremia Associated With Use of Acetylsalicylic Acid

Characteristics	Cases n (%)	Controls n (%)	Unadjusted OR (95% CI)	Adjusted OR [a] (95% CI)
ASA use				
Nonuse	1517 (57.5)	18 606 (70.5)	1.0 (ref.)	1.0 (ref.)
Former use	361 (13.7)	2465 (9.3)	2.08 (1.83–2.37)	1.00 (0.86–1.16)
Current use	760 (28.8)	5308 (20.1)	2.05 (1.85–2.28)	1.00 (0.88–1.13)
New use	56 (2.1)	216 (0.8)	3.63 (2.68–4.90)	2.04 (1.42–2.94)
Long-term use	704 (26.7)	5092 (19.3)	1.98 (1.78–2.20)	0.95 (0.84–1.09)

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; OR, odds ratio; ref., reference.

[a]Adjusted for conditions included in the Charlson Comorbidity Index, marital status, alcohol-related conditions, use of statins, glucocorticoids or treatment with antineoplastic or immunomodulating agents (within 90 days of the index date), and any previous use of other thrombocyte inhibitors and vitamin K antagonists.

Table 3. Cohort Study: Characteristics of 2638 Patients Hospitalized With Incident Community-Acquired *Staphylococcus aureus* Bacteremia in Northern Denmark (2000–2011) According to Acetylsalicylic Acid Use

Characteristics	Current use	New use	Long-term use	Former use	Nonuse
Numbers (%)	760 (28.8)	56 (2.1)	704 (26.7)	361 (13.7)	1517 (57.5)
Age					
≥15–39 years	9 (1.2)	1 (1.8)	8 (1.1)	7 (1.9)	217 (14.3)
40–59 years	93 (12.2)	11 (19.6)	82 (11.7)	42 (11.6)	470 (30.9)
60–79 years	379 (49.9)	32 (57.1)	347 (49.3)	200 (55.4)	603 (39.8)
≥80 years	279 (36.7)	12 (21.4)	267 (37.9)	112 (31.0)	227 (15.0)
Gender					
Men	490 (64.5)	36 (64.3)	454 (64.5)	220 (60.9)	906 (59.7)
Women	270 (35.5)	20 (35.7)	250 (35.5)	141 (39.1)	611 (40.3)
Selected underlying conditions					
Previous myocardial infarction	157 (20.7)	7 (12.5)	150 (21.3)	52 (14.4)	11 (0.7)
Peripheral arterial disease	182 (24.0)	6 (10.7)	176 (25.0)	85 (23.6)	61 (4.0)
Chronic heart failure	200 (26.3)	7 (12.5)	193 (27.4)	75 (20.8)	73 (4.8)
Chronic kidney disease	187 (24.6)	15 (26.8)	172 (24.4)	88 (24.4)	160 (10.6)
Diabetes	226 (29.7)	11 (19.6)	215 (30.5)	80 (22.2)	171 (11.3)
Hypertension	328 (43.2)	14 (25.0)	314 (44.6)	137 (38.0)	186 (12.3)
Moderate to severe liver disease	6 (0.8)	1 (1.8)	5 (0.7)	7 (1.9)	45 (3.0)
Chronic pulmonary disease	137 (18.0)	10 (17.9)	127 (18.0)	60 (16.6)	171 (11.3)
Any solid cancer	150 (19.7)	16 (28.6)	134 (19.0)	96 (26.6)	409 (27.0)
Alcohol-related conditions	41 (5.4)	3 (5.4)	38 (5.4)	29 (8.0)	165 (10.9)
Dialysis within 30 days of the admission	111 (14.6)	9 (16.1)	102 (14.5)	46 (12.7)	94 (6.2)
Charlson Comorbidity Index score					
Low (0)	94 (12.4)	11 (19.6)	83 (11.8)	55 (15.2)	576 (38.0)
Intermediate (1–2)	283 (37.2)	20 (35.7)	263 (37.4)	124 (34.4)	534 (35.2)
High (>2)	383 (50.4)	25 (44.6)	358 (50.9)	182 (50.4)	407 (26.8)
Medication use					
ACE inhibitors[a]	497 (65.4)	27 (48.2)	470 (66.8)	207 (57.3)	382 (25.2)
Beta blockers[a]	460 (60.5)	26 (46.4)	434 (61.7)	208 (57.6)	367 (24.2)
Calcium channel blockers[a]	412 (54.2)	20 (35.7)	392 (55.7)	199 (55.1)	279 (18.4)
Vitamin K antagonists[a]	172 (22.6)	7 (12.5)	165 (23.4)	115 (31.9)	142 (9.4)
Other thrombocyte inhibitors[a]	169 (22.2)	7 (12.5)	162 (23.0)	56 (15.5)	17 (1.1)
Statins[b]	230 (30.3)	14 (25.0)	216 (30.7)	69 (19.1)	69 (4.6)
NSAIDs[b]	136 (17.9)	12 (21.4)	124 (17.6)	67 (18.6)	381 (25.1)
Systemic glucocorticoids[b]	109 (14.3)	12 (21.4)	97 (13.8)	53 (14.7)	217 (14.3)
Immunomodulating agents[b]	8 (1.1)	1 (1.8)	7 (1.0)	8 (2.2)	24 (1.6)
Antibiotic treatment prior to admission[c]	184 (24.2)	12 (21.4)	172 (24.4)	75 (20.8)	277 (18.3)

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs.

[a]Any previous use prior to the date of admission.

[b]Any previous use within 90 days of the date of admission.

[c]Any previous use within 30 days of the date of admission.

Table 4. Cohort Study: Unadjusted and Adjusted 30-day Mortality in Patients With Community-Acquired Incident *Staphylococcus aureus* Bacteremia According to Acetylsalicylic Acid Use

Characteristics	n	30-day Mortality (95% CI)	HRR (95% CI)	aHRR[a] (95% CI)
Nonuse	1517	21.6 (19.6–23.8)	1.00 (ref.)	1.00 (ref.)
Former use	361	30.8 (26.3–35.8)	1.53 (1.23–1.89)	1.10 (0.87–1.40)
Current use	760	28.0 (25.0–31.4)	1.37 (1.15–1.62)	1.02 (0.84–1.25)
New use	56	14.3 (7.4–26.5)	0.65 (0.32–1.30)	0.60 (0.29–1.21)
Long-term use	704	29.12 (25.9–32.6)	1.43 (1.20–1.70)	1.06 (0.87–1.31)

Abbreviations: aHRR, adjusted hazard rate ratio; CI, confidence interval; HRR, hazard rate ratio.

[a]Adjusted for age, gender, Charlson Comorbidity Index score; hypertension; alcohol-related conditions; marital status; use of statins, NSAIDs (within 90 days of the index date), and any previous use of other thrombocyte inhibitors; vitamin K antagonists; beta blockers; ACE inhibitors; calcium channel blockers, and use of antibiotics within 30 days of the admission.

Table 2). Finally, changing the exposure window used to define current ASA use from 125 days to 60, 90, and 180 days did not markedly affect our results (Supplementary Tables 3 and 4, respectively).

DISCUSSION

In this combined case-control and cohort study, persons who used ASA did not experience a decreased risk of CA-SAB or a difference in 30-day CA-SAB all-cause mortality, compared with nonusers. We observed no notable differences in the risk or outcome of CA-SAB with increasing intensity of ASA use, and our estimates remained consistent across subgroups with various diseases often treated with ASA. As well, no substantial differences in risk or prognosis of CA-SAB were found by duration of ASA use, age, gender, or CCI level.

To the best of our knowledge, only 1 previous study has specifically investigated the association between ASA use and SAB risk. In a US historical cohort study of 872 patients receiving hemodialysis, Sedlacek et al reported a lower rate of catheter-associated SAB in patients treated with ASA versus those not treated with ASA (0.17 vs 0.34 events per patient-catheter-year) [10]. The association was dose-dependent and was observed most often with the 325 mg dose. However, a Canadian population-based case-control study of 449 patients and 4 156 controls receiving hemodialysis reported no association between ASA use and risk of vascular access-related infections and sepsis (OR, 1.03; 95% CI, 0.82–1.28), which remained unchanged with increasing ASA dose [21]. Also in support of our findings, a recent US historical cohort study of 30 239 patients reported an aHRR of 0.99 (95% CI, 0.88–1.12) for hospitalization with sepsis associated with ASA use [22].

Regarding prognosis, a Swiss single-center propensity score-matched cohort study of 314 patients with SAB examined the influence of ASA use on 30-day all-cause mortality, employing patients with *E. coli* bacteremia as an additional control group [11]. The investigators found that ASA use was associated with decreased mortality among patients with SAB (aHRR, 0.38; 95% CI, 0.21–0.69); however, the association reduced towards the null among patients with *E.coli* bacteremia (aHRR, 0.78; 95% CI, 0.40–1.55). To our knowledge, this represents the only previous study to focus specifically on SAB, still a number of prior studies have ascertained the association between ASA use and sepsis outcome with conflicting results. An Australian historical propensity score-matched cohort study examining 7 945 intensive care unit admissions, reported an absolute risk difference of

Table 5. Risk and Outcome of Incident Community-Acquired *Staphylococcus aureus* Bacteremia According to Intensity of Acetylsalicylic Acid Treatment

Characteristics	Risk of Incident CA-SAB		30-day Mortality After Incident CA-SAB	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI) [a]	Unadjusted HRR (95% CI)	Adjusted HRR (95% CI)[b]
Nonuse	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Former use				
≤75 mg/day	1.89 (1.63–2.20)	0.95 (0.90–1.13)	1.54 (1.20–1.97)	1.13 (0.87–1.48)
>75–150 mg/day	2.71 (2.16–3.40)	1.15 (0.89–1.49)	1.44 (0.98–2.10)	1.05 (0.71–1.56)
>150 mg/day	2.41 (1.22–4.36)	1.12 (0.58–2.17)	1.94 (0.80–4.70)	0.96 (0.39–2.36)
Current use				
≤75 mg/day	2.19 (1.84–2.61)	1.09 (0.89–1.34)	1.37 (1.03–1.84)	1.12 (0.81–1.54)
>75–150 mg/day	1.99 (1.76–2.25)	0.98 (0.84–1.14)	1.40 (1.14–1.71)	1.07 (0.84–1.36)
>150 mg/day	1.85 (1.50–2.28)	0.93 (0.73–1.18)	1.23 (0.85–1.79)	1.07 (0.73–1.58)

Abbreviations: CA-SAB, community-acquired *Staphylococcus aureus* bacteremia; CI, confidence interval; HRR, hazard rate ratio; OR, odds ratio.

[a]Adjusted for conditions included in the Charlson Comorbidity Index; marital status; alcohol-related conditions; use of statins, glucocorticoids with antineoplastic, or immunomodulating agents (within 90 days of the index date); and any previous use of other thrombocyte inhibitors and vitamin K antagonists.

[b]Adjusted for age, gender, Charlson Comorbidity Index score, hypertension, alcohol-related conditions, marital status, use of statins, NSAIDs (within 90 days of the index date), any previous use of other thrombocyte inhibitors, vitamin K antagonists, beta blockers, ACE inhibitors, calcium channel blockers, and use of antibiotics within 30 days of the admission.

Table 6. Risk and Outcome of Incident Community-Acquired *Staphylococcus aureus* Bacteremia According to Selected Diseases Associated With the Use of Acetylsalicylic Acid

Characteristics	Risk of Incident CA-SAB		30-day Mortality After Incident CA-SAB	
	Adjusted OR (95% CI)[a]		Adjusted HRR (95% CI)[b]	
	Former ASA use	Current ASA use	Former ASA use	Current ASA use
Previous myocardial infarction	1.34 (0.59–3.05)	1.00 (0.46–2.18)	1.11 (0.87–1.43)	1.02 (0.83–1.26)
Chronic heart failure	0.93 (0.60–1.44)	1.04 (0.72–1.51)	1.11 (0.60–2.05)	1.12 (0.67–1.87)
Peripheral arterial disease	1.34 (0.85–2.10)	1.13 (0.75–1.69)	1.02 (0.79–1.33)	1.01 (0.81–1.26)
Chronic kidney disease	1.20 (0.71–2.02)	1.06 (0.69–1.63)	1.21 (0.64–2.28)	0.90 (0.51–1.60)
Diabetes	0.73 (0.50–1.08)	0.77 (0.57–1.04)	1.33 (0.77–2.29)	1.15 (0.72–1.84)

Nonusers served as reference for all comparisons.

Abbreviations: CA-SAB, community-acquired *Staphylococcus aureus* bacteremia; CI, confidence interval; HRR, hazard rate ratio; OR, odds ratio.

[a]Adjusted for conditions included in the Charlson Comorbidity Index, marital status, alcohol-related conditions, use of statins, glucocorticoids or treatment with antineoplastic or immunomodulating agents (within 90 days of the index date), and any previous use of other thrombocyte inhibitors and vitamin K antagonists.

[b]Adjusted for age, gender, Charlson Comorbidity Index, hypertension, alcohol-related conditions, marital status, use of statins, NSAIDs (within 90 days of the index date), any previous use of other thrombocyte inhibitors, vitamin K antagonists, beta blockers, ACE inhibitors, calcium channel blockers, and use of antibiotics within 30 days of the admission.

-14.8% (95% CI, -18.9% to -8.6%) for sepsis-related in-hospital mortality, comparing patients treated with ASA versus those not treated [23]. A German single-center historical cohort study of 886 patients who were admitted with sepsis to a surgical intensive care unit reported a decreased risk of in-hospital death associated with ASA use (aOR, 0.56; 95% CI, 0.37–0.84) [24]. Furthermore, a US historical propensity score-matched cohort study of 651 patients with sepsis or septic shock being treated in an intensive care unit reported an adjusted odds ratio of in-hospital death of 0.73 (95% CI, 0.46–1.16) associated with chronic antiplatelet treatment, including ASA [25]. In line with our results, a Dutch prospective propensity score-matched cohort study of 972 patients admitted with sepsis to an intensive care unit found no association between chronic antiplatelet therapy (>95% received ASA) and clinical presentation or 30-day all-cause mortality (adjusted hazard ratio, 1.21; 95% CI, 0.79–1.84) [26].

A number of limitations should be taken into account interpreting these earlier studies. In contrast to our population-based setting, several previous studies were conducted in tertiary single centers focusing on selected groups of patients (eg, patients receiving dialysis) [10, 23, 24], which increases the risk of selection bias. The majority of previous studies did not access microbiological data to identify infections, including sepsis [21–23]. Thus, misclassification cannot be entirely ruled out, and some lacked complete follow-up [22, 25]. Moreover, information on ASA exposure use was in some cases collected exclusively from medical charts that may be incomplete [10, 25], and variations in the duration of ASA use were not taken into account [10, 21, 24, 25].

The mechanisms underlying our results are not entirely clear. It remains possible that the observed lack of association between ASA use and CA-SAB risk and prognosis may be explained by insufficient ASA dosage. Still, our estimates remained robust across all dose categories, and further dose escalations would likely be inadvisable due to increased risk of adverse events, including gastrointestinal bleeding [27]. Our patient cohort was population-based and well-defined. Nevertheless, patients with CA-SAB remain inherently heterogeneous in terms of personal and genetic background, disease presentation and severity, and distribution of the infective foci, which might partly explain the lack of impact by ASA therapy. Moreover, most patients in our study were over 65 years old and suffered from multiple chronic diseases. Thus, the overall risk and outcome of CA-SAB could be influenced primarily by the accumulated burden of advanced age, comorbidity, and reduced functional status, and less so by individual types of drugs, such as ASA.

Surprisingly, our study suggests that new use of ASA is associated with increased risk of CA-SAB, but with a protective impact on outcome. We speculate that in fact these observations are not explained by ASA use, but rather by the circumstances underlying recent ASA treatment initiation (eg, hospitalization due to cardiovascular disease), which influence baseline risk and prognosis of CA-SAB. Combined with the limited number of new users yielding imprecise estimates, these results warrant cautious clinical interpretation.

Our study has several strengths, including its considerable size and our unfettered access to routinely recorded clinical data at the individual level. The study design allowed us to assess ASA use both as a potential risk as well as a prognostic factor for CA-SAB. By excluding patients with hospital-acquired SAB, we reduced the risk of bias associated with concurrent medical conditions and with invasive procedures. We also had detailed data on ASA use, and the comprehensive data on ASA prescriptions available from the AUPD eliminated the risk of recall bias.

However, a number of limitations should be considered in the interpretation of our results. The study´s population-based design ensured capture of all incident CA-SAB cases during the study period. Still, we may have missed some cases in which the patient was hospitalized outside the study area, was treated

with antibiotics prior to admission, or died before blood could be cultured. Data on the infective foci were not available and this might have influenced our findings if the foci were unevenly distributed among ASA users and nonusers. Moreover, clinical care for patients with CA-SAB may have varied during the study period. Yet, we did not have detailed information on clinical work-up and in-hospital treatment, which would have strengthened the study.

In addition, records of filled prescriptions were used as a proxy for actual ASA use, but the AUPD does not include data on adherence. Nevertheless, a close correspondence between general practitioner-reported drug use and timing of prescription dispensation was demonstrated in a previous validation study from our study area [28]. Moreover, we observed no notable difference in effect estimates when the date used to distinguish current and former use was changed in a sensitivity analysis. We lacked data on ASA treatment during hospitalization and long-term rehabilitation facilities, which might have introduced some misclassification. As well, in Denmark, ASA is available either by prescription from a physician or over-the-counter (OTC), but unfortunately we did not have data on OTC use. Still, as the percentage of ASA sales based on a prescription increased notably during the study period (77% in 2002, 89% in 2006, and 91% in 2011) [29], it is unlikely that underreporting of ASA treatment notably influenced our estimates of risk or prognosis. Along with increasing ASA use [30], the incidence of CA-SAB also rose in Denmark during the study period [31]. Such changes could be speculated to inflate the estimates; still, we find it unlikely that they explain the consistent null-findings across risk and prognosis in our study. We also lacked detailed information on educational level and personal income. Although socioeconomic status may be associated with ASA use and risk or prognosis of CA-SAB, we do not consider substantial confounding from this factor likely, because ASA is inexpensive, prescriptions are partially reimbursed, and free unlimited access to healthcare is available to all Danish residents. Finally, although we included hospital diagnoses of alcohol-related conditions, these diagnoses are likely to capture only the most severe cases.

In conclusion, use of ASA did not seem to influence the risk and prognosis of CA-SAB. The observed increased risk among new users may be related to residual confounding from the circumstances underlying ASA treatment initiation and a limited subsample size; cautious interpretation, therefore, is warranted. Although our results argue strongly against a beneficial effect of ASA on the risk and outcome of CA-SAB, it should be noted that previous observational studies have suggested otherwise. Hopefully, further clinical studies, including randomized controlled trials [32], will provide further clarification.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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