Incident Stroke and Mortality Associated With New-Onset Atrial Fibrillation in Patients Hospitalized With Severe Sepsis

Allan J. Walkey, MD, MSc

Renda Soylemez Wiener, MD, MPH

Joanna M. Ghobrial, MD

Lesley H. Curtis, PhD

Emelia J. Benjamin, MD, ScM

ATRIAL FIBRILLATION (AF) IS one of the most common arrhythmias among critically ill patients.[1,2] Previous studies have demonstrated that 6% to 20% of patients with severe sepsis develop new-onset AF, suggesting that severe sepsis may be a predisposing factor for new-onset AF.[2-5] Although chronic AF is a major contributor to long-term disability and mortality,[6] the relationship of new-onset AF in severe sepsis to prognosis is unknown.

Although new-onset AF appears to be relatively common in individuals with severe sepsis, data are sparse to risk stratify or prognosticate these often complicated and critically ill patients. Small, single-center studies suggest that new-onset AF is associated with higher mortality and prolonged hospitalization during severe sepsis.[5,7,8] However, a population-based assessment of the adverse outcomes associated with new-onset AF that occurs in the context of severe sepsis has not yet been undertaken.

Using a database of individuals hospitalized with severe sepsis identified via California State Inpatient Database

Context New-onset atrial fibrillation (AF) has been reported in 6% to 20% of patients with severe sepsis. Chronic AF is a known risk factor for stroke and death, but the clinical significance of new-onset AF in the setting of severe sepsis is uncertain.

Objective To determine the in-hospital stroke and in-hospital mortality risks associated with new-onset AF in patients with severe sepsis.

Design and Setting Retrospective population-based cohort of California State Inpatient Database administrative claims data from nonfederal acute care hospitals for January 1 through December 31, 2007.

Patients Data were available for 3 144 787 hospitalized adults. Severe sepsis (n=49 082 [1.56%]) was defined by validated *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code 995.92. New-onset AF was defined as AF that occurred during the hospital stay, after excluding AF cases present at admission.

Main Outcome Measures A priori outcome measures were in-hospital ischemic stroke (*ICD-9-CM* codes 433, 434, or 436) and mortality.

Results Patients with severe sepsis were a mean age of 69 (SD, 16) years and 48% were women. New-onset AF occurred in 5.9% of patients with severe sepsis vs 0.65% of patients without severe sepsis (multivariable-adjusted odds ratio [OR], 6.82; 95% CI, 6.54-7.11; $P<.001$). Severe sepsis was present in 14% of all new-onset AF in hospitalized adults. Compared with severe sepsis patients without new-onset AF, patients with new-onset AF during severe sepsis had greater risks of in-hospital stroke (75/2896 [2.6%] vs 306/46 186 [0.6%] strokes; adjusted OR, 2.70; 95% CI, 2.05-3.57; $P<.001$) and in-hospital mortality (1629 [56%] vs 18 027 [39%] deaths; adjusted relative risk, 1.07; 95% CI, 1.04-1.11; $P<.001$). Findings were robust across 2 definitions of severe sepsis, multiple methods of addressing confounding, and multiple sensitivity analyses.

Conclusion Among patients with severe sepsis, patients with new-onset AF were at increased risk of in-hospital stroke and death compared with patients with no AF and patients with preexisting AF.

Author Affiliations: The Pulmonary Center, Division of Pulmonary and Critical Care Medicine (Drs Walkey and Wiener), Department of Medicine (Drs Walkey, Wiener, and Benjamin), and Cardiology and Preventive Medicine, Whitaker Cardiovascular Institute (Dr Benjamin), Boston University School of Medicine, and Epidemiology Department, Boston University School of Public Health (Dr Benjamin), Boston, Massachusetts; Center for Health Quality, Outcomes, and Economic Research, Edith Nourse Rogers Memorial VA Hospital, Bedford, Massachusetts (Dr Wiener); Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School, Hanover, New Hampshire (Dr Wiener); Department of Medicine, Division of Cardiology, University of Washington School of Medicine, Seattle (Dr Ghobrial); Duke Clinical Research Institute and Department of Medicine, Duke University School of Medicine, Durham, North Carolina (Dr Curtis); and National Heart, Lung, and Blood Institute's and Boston University's Framingham Heart Study, Framingham, Massachusetts (Dr Benjamin).

Corresponding Author: Allan J. Walkey, MD, MSc, the Pulmonary Center, Boston University School of Medicine, R-304, Boston, MA 02118 (alwalkey@bu.edu).

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claims, we sought to determine the association of new-onset AF with adverse outcomes of in-hospital mortality and in-hospital ischemic stroke. We hypothesized that new-onset AF during severe sepsis would be associated with increased risks of in-hospital stroke and in-hospital mortality.

METHODS

Patients

We examined hospitalizations from adults (aged ≥18 years) using 2007 discharge data from the California State Inpatient Database, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (AHRQ).[9] The California State Inpatient Database contains data for all patients hospitalized in nonfederal acute care California hospitals during 2007. Data elements included demographics, admission and discharge status, length of stay, up to 25 *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnoses, and up to 21 *ICD-9-CM* procedure codes. Each diagnosis was coded with a separate identifier denoting whether it was present on admission, allowing discrimination between preexisting diagnoses and complications occurring after hospital admission.[10-12] All study procedures were approved by the Boston University Medical Campus Institutional Review Board, which waived informed consent for this study.

The primary severe sepsis analytic cohort was defined by the presence of the *ICD-9-CM* code for severe sepsis (*ICD-9-CM* code 995.92).

Outcomes

Atrial fibrillation was defined by the presence of *ICD-9-CM* code 427.3x.[13] New-onset AF was defined as AF or atrial flutter that occurred during the hospital stay, excluding cases that were present on admission. In-hospital ischemic stroke was defined with *ICD-9-CM* codes 433, 434, or 436[14] that were not present on admission.

Figure. In-Hospital Stroke and Mortality Outcomes in Each Analytic Cohort
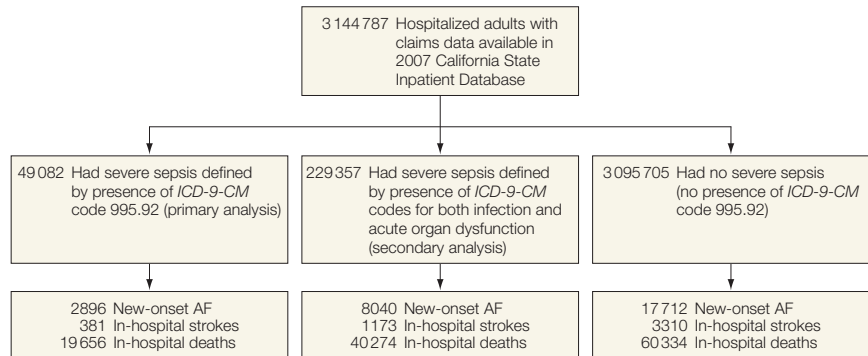
AF indicates atrial fibrillation; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*. The severe sepsis primary analysis group is a subset of the severe sepsis secondary analysis group defined by infection and organ dysfunction.

Covariates

Demographic data collected in the California State Inpatient Database included age, sex, and race/ethnicity (coded as white, black, Hispanic, or other). Previously described AF risk factors[15-18] were defined by *ICD-9-CM* codes[19,20] present on admission for heart failure, myocardial infarction, hypertension, obesity, diabetes mellitus, and chronic obstructive pulmonary disease (COPD). Acute factors were obtained from *ICD-9-CM* codes for acute organ dysfunction diagnoses,[21,22] electrolyte abnormalities, right heart catheterization, infectious pathogen type (gram-positive vs gram-negative bacteria vs fungal vs none reported), and infection source. The *ICD-9-CM* coding strategies are shown in eTable 1 (available at http://www.jama.com).

Sensitivity Analyses

We performed sensitivity and exploratory analyses to explore the temporality of severe sepsis, AF, and ischemic stroke events. We analyzed a cohort with severe sepsis (*ICD-9-CM* code 995.92) coded as "present on admission," in whom new-onset AF that was not "present on admission" occurred after the onset of severe sepsis. We performed 3 sensitivity analyses using increasingly narrow *ICD-9-CM* codes for embolic stroke, the putative mechanism for stroke associated with AF[6] (*ICD-9-CM* code 434 or 436 [cerebral artery occlusion or acute but ill-defined cerebrovascular disease]; *ICD-9-CM* code 434 [cerebral artery occlusion]; and *ICD-9-CM* code 434.1 [embolic stroke]). Because temporality between new-onset AF and new-onset stroke claims could not be established within the severe sepsis hospitalization, we performed an exploratory analysis investigating the risk of rehospitalization with a new ischemic stroke following the severe sepsis hospitalization (eAppendix).

We repeated mortality and stroke outcome analyses in an alternative severe sepsis cohort defined by the presence of *ICD-9-CM* codes for both infection and acute organ dysfunction, as previously described by Angus et al[22] (eTable 1). In addition, we investigated stroke and mortality risks adjusted for potential readmissions using the AHRQ Healthcare Cost and Utilization Project Supplemental Variables for Revisit Analyses to classify individual, deidentified patients as random effects. Because septic embolic disease may result in stroke, we performed a sensitivity analysis excluding all patients with septic emboli claims (*ICD-9-CM* code 449). Finally, indicators of intensive care unit admission are not available in the California State Inpatient Database. As a proxy for inten-

sive care, we performed a subgroup analysis in patients with claims for mechanical ventilation.

ICD-9-CM Validation

Validation of the severe sepsis *ICD-9-CM* code 995.92 at our institution (eAppendix) demonstrated moderate sensitivity (52%; 95% CI, 39%-65%) and high specificity (98%; 95% CI, 92%-100%), similar to validation findings in other hospitals.[23] Previous studies have demonstrated 95% sensitivity and 99% specificity for AF *ICD-9-CM* code 427.3x claims.[13] We validated present-on-admission modifiers (eAppendix) for severe sepsis and AF claims; agreement between severe sepsis present-on-admission status and blinded chart review was 91% (κ=0.77) and agreement between AF present-on-admission status and blinded chart review was 90% (κ=0.74), similar to previous findings.[24]

Prior validation of ischemic stroke *ICD-9-CM* codes has shown variable accuracy[14,25-27]; however, a strategy using *ICD-9-CM* codes 433, 434, and 436 at any diagnostic position previously demonstrated 86% sensitivity and 95% specificity (κ=0.82).[14] The *ICD-9-CM* code 434.11, used to indicate embolic stroke, has been demonstrated to be accurate in 73% of patients; patients with code 434.11 who did not have a clear embolic stroke on chart review were characterized as having ischemic stroke of atherothrombotic or uncertain etiology.[26]

Statistical Analyses

Severe Sepsis, New-Onset AF, and In-Hospital Stroke. Multivariable logistic regression models were used to determine the association between the presence of severe sepsis and new-onset AF or in-hospital stroke, adjusting for demographics (age, sex, and race/ethnicity) and claims for preexisting comorbidities (heart failure, stroke, myocardial infarction, diabetes, obesity, hypertension, and COPD).

Factors Associated With New-Onset AF During Severe Sepsis. We performed multivariable logistic regression models with forward stepwise selection to determine the factors associated with new-onset AF during severe sepsis. Because patients with preexisting AF are not at risk of new-onset AF, we excluded patients with preexisting AF from this model.

New-Onset AF During Severe Sepsis and Adverse Outcomes. We constructed 4 regression models to evaluate the association of new-onset AF during severe sepsis with in-hospital stroke and in-hospital mortality. Model 1 included demographics and comorbidities as model covariates (prior claims for history of heart failure, myocardial infarction, stroke, diabetes, obesity, hypertension, metastatic or hematologic malignancy, or COPD); model 2 included demographics and acute factors (number and type of organ dysfunction claims, electrolyte abnormality, right heart catheterization, sources of infection, and pathogen type); and model 3 was a combination of all covariates in model 1 and model 2.

Table 1. Characteristics of Patients With Severe Sepsis With and Without New-Onset AF[a]

Characteristics	No AF (n = 36 200)	Preexisting AF (n = 9986)	New-Onset AF (n = 2896)
Age, mean (SD), y	66 (17)	76 (12)	74 (12)
Female sex	17 690 (49.0)	4756 (47.7)	1280 (44.2)
Race/ethnicity			
White	19 006 (52.5)	6485 (64.9)	1861 (64.3)
Black	3547 (10.1)	671 (6.7)	209 (7.2)
Hispanic	8045 (22.2)	1397 (14.0)	384 (13.3)
Other	5502 (15.2)	1433 (14.4)	442 (15.3)
Comorbidities			
Hypertension	17 373 (48.0)	5751 (57.6)	1336 (46.1)
Diabetes mellitus	12 135 (33.5)	3546 (35.5)	800 (27.6)
Obesity	2914 (8.1)	711 (7.1)	208 (7.2)
Malignancy	4079 (11.3)	905 (9.1)	348 (12.0)
Congestive heart failure	2312 (6.4)	1365 (13.7)	306 (10.6)
COPD	1920 (5.3)	745 (7.5)	189 (6.5)
Myocardial infarction	1659 (4.6)	713 (7.1)	165 (5.7)
Stroke	880 (2.4)	317 (3.2)	126 (4.4)
Acute organ dysfunction			
Total organ failures, mean (SD)	2.44 (1.35)	2.51 (1.30)	3.10 (1.28)
Circulatory	23 264 (64.3)	6690 (67.0)	2049 (70.7)
Renal	21 343 (59.0)	6338 (63.5)	2048 (70.7)
Respiratory	20 833 (57.6)	6080 (60.1)	2385 (82.4)
Hematologic	7301 (20.2)	1974 (19.8)	933 (32.2)
Neurologic	5318 (14.7)	1414 (14.2)	526 (18.2)
Metabolic	7246 (20.0)	1933 (19.4)	706 (24.4)
Hepatic	3150 (8.7)	673 (6.7)	334 (11.5)
Electrolyte abnormality	23 963 (66.2)	6733 (67.4)	2051 (70.8)
Right heart catheterization	722 (2.0)	236 (2.4)	172 (5.9)
Source of infection			
Respiratory tract	14 178 (39.2)	4358 (43.6)	1419 (49.0)
Urinary tract	13 748 (38.1)	4025 (40.3)	950 (32.8)
Primary bacteremia	8910 (24.6)	2240 (22.4)	600 (20.7)
Abdominal	5532 (15.3)	1496 (15.0)	735 (25.4)
Skin or soft tissue	2888 (8.0)	729 (7.3)	229 (7.9)
Pathogen type			
Gram-positive bacteria	8675 (24.0)	2546 (25.5)	822 (28.4)
Gram-negative bacteria	8776 (24.2)	2342 (23.5)	677 (23.4)
Fungal	632 (1.8)	156 (1.6)	104 (3.6)
None specified	20 268 (56.0)	5530 (55.4)	1538 (53.1)

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.
[a] Data are expressed as No. (%) of participants unless otherwise specified.

Regression model 4 was performed on a separate cohort matched on the probability of new-onset AF. To construct the matched cohort, we calculated the probability of new-onset AF via multivariable logistic regression including measured covariates as independent variables. Nearest-neighbor matching to 4 decimal places[28] was used to match patients with new-onset AF with those without new-onset AF based on the calculated probability of new-onset AF.

We used generalized estimating equations to calculate odds ratios for stroke in all models. Individual hospitals were defined as random effects due to potentially correlated physician coding practices and patient characteristics within a single hospital. Differences in per-patient stroke rates according to AF status were analyzed with Wilcoxon-Mann-Whitney tests. We used Poisson regression with robust estimates[29,30] to calculate relative risks for mortality associated with AF status.

A 2-sided $\alpha = .05$ was selected for statistical significance for analyses of outcomes. SAS software, version 9.0 (SAS Institute Inc) was used for all analyses.

RESULTS

The 2007 California State Inpatient Database contained claims data from 3 144 787 hospitalized adults who had a mean age of 55 (SD, 21) years and of whom 62% were women, with a racial/ethnic composition of 57% white, 26% Hispanic, 8% black, and 9% other. The FIGURE demonstrates the number of patients with or without severe sepsis and outcomes associated with each severe sepsis classification category.

Severe sepsis was present during 49 082 hospitalizations (1.56%; 95% CI, 1.55%-1.57%). Patients with severe sepsis were a mean of 69 (SD, 16) years old and 48% were women, with a racial/ethnic composition of 56% white, 20% Hispanic, 9% black, and 15% other/missing. TABLE 1 displays the characteristics of the severe sepsis cohort stratified by AF status. eTable 2 dem-

onstrates that imbalances in measured covariates between AF groups were substantially attenuated in the cohort matched on the calculated probability of new-onset AF.

Severe Sepsis and New-Onset AF

New-onset AF occurred during 20 608 hospitalizations (0.65%; 95% CI, 0.65%-0.66%) (including sepsis and nonsepsis) and during 2896 hospitalizations (5.9%; 95% CI, 5.7%-6.1%) of patients with severe sepsis. Therefore, 14% (95% CI, 13.6%-14.5%) of all hospital-associated new-onset AF occurred in the context of severe sepsis. Compared with hospitalized patients without severe sepsis, patients with severe sepsis had an increased risk of new-onset AF (demographics- and comorbidity-adjusted odds ratio, 6.82; 95% CI, 6.54-7.11; $P < .001$).

Factors Associated With New-Onset AF During Severe Sepsis

Results of the multivariable analysis of factors associated with new-onset AF during severe sepsis are shown in TABLE 2. Factors associated with increased risk of new-onset AF during severe sepsis included demographics (increasing age, male sex, and white race), comorbidities (history of heart failure, obesity, malignancy, and stroke), and acute factors (increasing number of organ failures, respiratory failure, hematologic failure, renal failure, use of right heart catheter, pulmonary or abdominal source of infection, and gram-positive or fungal organisms).

In-Hospital Ischemic Stroke

In-hospital stroke claims occurred during 3310 adult hospitalizations (0.11%; 95% CI, 0.10%-0.11%) (both sepsis and nonsepsis) and 381 hospitalizations (0.78%; 95% CI, 0.70%-0.86%) of patients with severe sepsis. Thus, 11% (95% CI, 10%-13%) of in-hospital strokes occurred in patients with severe sepsis. Compared with hospitalized patients without severe sepsis, patients with severe sepsis had an increased risk of in-hospital ischemic

Table 2. Factors Associated With New-Onset Atrial Fibrillation Among Patients With Severe Sepsis[a]

Variables	Odds Ratio (95% CI)
Age, per 10 y	1.52 (1.47-1.56)
Female sex	0.83 (0.76-0.90)
Race/ethnicity	
White	1 [Reference]
Black	0.67 (0.58-0.78)
Hispanic	0.58 (0.50-0.63)
Other	0.78 (0.69-0.87)
Comorbidities[b]	
Hypertension	0.88 (0.81-0.95)
Diabetes mellitus	0.82 (0.75-0.90)
Obesity	1.20 (1.03-1.40)
Congestive heart failure	1.61 (1.41-1.83)
Metastatic or hematologic malignancy	1.23 (1.09-1.39)
Prior stroke	1.64 (1.35-2.01)
Acute organ dysfunction[b]	
Per organ failure	1.12 (1.05-1.19)
Respiratory failure	2.81 (2.48-3.19)
Renal failure	1.40 (1.26-1.56)
Hematologic failure	1.50 (1.34-1.68)
Acidosis	0.87 (0.77-0.97)
Right heart catheterization[b]	2.25 (1.87-2.70)
Source of infection[b]	
Respiratory tract	1.27 (1.14-1.40)
Urinary tract	0.89 (0.81-0.99)
Abdominal	1.77 (1.59-1.97)
Primary bacteremia	1.17 (1.02-1.36)
Skin or soft tissue	1.33 (1.14-1.55)
Pathogen type[b]	
Gram-positive bacteria	1.29 (1.18-1.55)
Fungal	1.59 (1.27-2.00)

[a] C statistic=0.760.
[b] The reference group for these variables is none present.

stroke (demographic and comorbidity-adjusted odds ratio, 6.0; 95% CI, 5.38-6.69; $P < .001$).

In patients with severe sepsis, in-hospital ischemic stroke occurred in 75 of 2896 individuals (2.6%; 95% CI, 2.0%-3.2%) with new-onset AF compared with 57 of 9986 (0.57%; 95% CI, 0.43%-0.74%) with preexisting AF and 249 of 36 200 (0.69%; 95% CI, 0.61%-0.78%) without AF. The average stroke rate was 0.15% (SD, 1.21%) per hospital day for patients with new-onset AF compared with 0.05% (1.01%) for patients with no AF or preexisting AF ($P < .001$).

Table 3. Association Between New-Onset AF and Adverse Outcomes

	Outcomes	
Model	In-Hospital Ischemic Stroke, Odds Ratio (95% CI)	In-Hospital Mortality, Relative Risk (95% CI)
Age-, sex-, and race/ethnicity–adjusted	4.05 (3.09-5.30)	1.36 (1.32-1.41)
Demographics- and comorbidity-adjusted[a]	3.84 (2.93-5.04)	1.33 (1.28-1.37)
Demographics- and acute factor–adjusted[b]	2.84 (2.15-3.76)	1.09 (1.06-1.13)
Combined multivariable-adjusted[c]	2.70 (2.05-3.57)	1.07 (1.04-1.11)
New-onset AF, probability-matched[d]	2.75 (1.76-4.29)	1.13 (1.08-1.19)

Abbreviation: AF, atrial fibrillation.
[a] Adjusted for age, sex, race/ethnicity, and history of diabetes mellitus, hypertension, obesity, heart failure, stroke, myocardial infarction, chronic obstructive pulmonary disease, and metastatic or hematologic malignancy.
[b] Adjusted for age, sex, race/ethnicity, and sepsis-associated factors including number of organ failures, presence of electrolyte disturbances, source of sepsis, type of organ failure, type of pathogenic organism, and use of right heart catheterization.
[c] Adjusted for all variables from both the comorbidity-adjusted and sepsis-associated factor-adjusted models.
[d] Cohorts matched on calculated probability of risk of new-onset AF.

Among individuals with severe sepsis, new-onset AF was associated with increased adjusted risks of in-hospital ischemic stroke (**TABLE 3**). In contrast, patients with severe sepsis and preexisting AF did not have an increased risk of in-hospital ischemic stroke compared with those with severe sepsis and no AF (multivariable-adjusted odds ratio, 0.74; 95% CI, 0.55-1.01; $P=.054$). Furthermore, individuals with new-onset AF had greater stroke risk than those with preexisting AF (multivariable-adjusted odds ratio, 3.63; 95% CI, 2.51-5.25; $P<.001$). A sensitivity analysis using different ischemic stroke *ICD-9-CM* definitions demonstrated increasing strength of association between new-onset AF and in-hospital stroke in severe sepsis as *ICD-9-CM* codes increased in specificity for embolic stroke (**TABLE 4**). Additional sensitivity analyses in patients meeting the alternative severe sepsis definition, in patients with severe sepsis present on admission, in patients without septic emboli claims, and in patients who required mechanical ventilation did not result in substantially different estimates of stroke risk associated with new-onset AF (Table 4).

To establish a temporal relationship between new-onset AF during severe sepsis and new stroke, we performed an exploratory analysis investigating the risk of incident stroke occurring after the severe sepsis hospitalization. We identified 27 325 severe sepsis survivors without a prior stroke claim. Rehospitalization with a new ischemic stroke occurred in 23 of 1171 (2.0%) with new-onset AF during severe sepsis, 81 of 5300 (1.5%) with preexisting AF during sepsis, and 261 of 20 854 (1.3%) without AF during severe sepsis. Compared with patients with no AF, patients with new-onset AF during the severe sepsis hospitalization had a nonsignificantly increased risk of rehospitalization with incident ischemic stroke (multivariable-adjusted hazard ratio, 1.51; 95% CI, 0.98-2.33; $P=.06$).

In-Hospital Mortality

In patients with severe sepsis, 1629 (56.3%; 95% CI, 54.4%-58.1%) with new-onset AF died in the hospital compared with 4375 (43.8%; 95% CI, 42.8%-44.8%) with preexisting AF and 13 652 (37.7%; 95% CI, 37.2%-38.2%) without AF. Thus, compared with patients without new-onset AF, individuals with new-onset AF during severe sepsis experienced increased in-hospital mortality (Table 3). Sensitivity analyses did not show substantially different effect estimates for mortality (eTable 3). The eFigure demonstrates that the increased mortality risk for patients with severe sepsis and new-onset AF persisted regardless of the number of severe sepsis–associated organ failures.

COMMENT

Our investigation of new-onset AF during severe sepsis presents a number of clinically relevant findings. First, severe sepsis was associated with increased risk of both new-onset AF and in-hospital ischemic stroke. In addition, we identified multiple demographic and clinical factors associated with new-onset AF during severe sepsis. Importantly, patients with new-onset AF during severe sepsis had increased risks of both in-hospital ischemic stroke and mortality. The increased stroke and mortality risks observed with new-onset AF were robust across 2 definitions of severe sepsis, multiple methods of addressing confounding, and multiple sensitivity analyses.

Consistent with previous reports of increased stroke risk following infection,[31-35] our study demonstrates that patients with severe sepsis had a 6-fold increased risk of in-hospital stroke compared with hospitalized patients without severe sepsis. Importantly, patients with severe sepsis who developed new-onset AF had a greater risk of in-hospital stroke than patients with preexisting AF and individuals without a history of AF. As far as we are aware, the increased risk of ischemic stroke in patients with severe sepsis and new-onset AF has not been previously reported.

Several potential mechanisms might explain the increased ischemic stroke risk in patients with severe sepsis and new-onset AF. Severe sepsis alone may be associated with an increased risk of stroke through hemodynamic collapse, increased systemic inflammation, and coagulopathy.[36,37] New-onset AF may simply be a marker for greater severity of illness and, thus, greater stroke risk. However, within the limitations of claims data, adjustment for clinical and demographic factors associated with severity of illness did not eliminate the strong associations of new-onset AF claims with incident stroke claims.

Alternatively, new-onset AF may be a potential source of cardioembolic

stroke. In fact, we identified an almost 4-fold increased risk of in-hospital embolic stroke claims associated with new-onset AF during the severe sepsis hospitalization. Although new-onset AF in critically ill patients is often transient,[2] prior studies have shown that atrial thrombi may form within 2 days of the onset of AF.[38] Of note, individuals with severe sepsis and preexisting AF did not have an increased stroke risk compared with patients without AF. Potential differences in anticoagulation practice patterns between patients with preexisting and new-onset AF could not be ascertained from the California administrative data. Whether anticoagulation practices differ between patients with preexisting AF and new-onset AF and whether benefits of systemic anticoagulation for AF during severe sepsis outweigh risks cannot be ascertained from our data source and warrant further investigation.

New-onset AF was associated with a 7% increase in the adjusted risk of in-hospital death. The hospital mortality of patients with new-onset AF during severe sepsis was similar to the mortality of those without AF, but with 1 additional acute organ failure. Whether new-onset AF functions as a marker for increased illness severity and poor prognosis (eg, new-onset AF represents an additional "organ dysfunction") or directly contributes to mortality (eg, through refractory hypotension, stroke, or heart failure) cannot be elucidated from observational claims data and also warrants further investigation.

Our results expand on those of prior studies[2-4] demonstrating severe sepsis to be strongly associated with new-onset AF. Severe sepsis was associated with 14% of all episodes of new-onset AF occurring in hospitalized adults. Standard demographic risk factors for community-acquired AF such as older age, male sex, and white race[15,16] and previously described AF-associated comorbidities such as heart failure, obesity,[15,16] and malignancy[39-41] were also associated with new-onset AF during

severe sepsis. In addition, prevalent stroke was associated with new-onset AF, a finding that suggests that some patients with new-onset AF may have had undiagnosed paroxysmal AF.[42] Our seemingly paradoxical findings that hypertension and diabetes were associated with reduced risk of new-onset AF in severe sepsis may be an artifact of less frequent coding of chronic comorbid conditions such as hypertension and diabetes in patients with critical illness and warrant prospective study. Multiple acute factors were also associated with increased risk of first-

diagnosed AF during severe sepsis. Whether these acute factors serve as markers of illness severity or represent other potential mechanisms for AF is unclear, though the increased risk of arrhythmias associated with use of right heart catheters in critically ill patients has been previously reported.[43,44]

Our study has several limitations. First, the incidence of severe sepsis–associated, new-onset AF in our study (5.9%) was on the lower end of previously reported rates (6%-20%).[2-5] Incidence of AF in our study may be lower because claims data are less sensitive for

Table 4. Sensitivity Analyses of Association Between New-Onset Atrial Fibrillation and In-Hospital Stroke in Patients With Severe Sepsis[a]

Group	Severe Sepsis Defined by *ICD-9-CM* Code 995.92	Severe Sepsis Defined by Infection Plus Acute Organ Dysfunction[22]
Severe sepsis		
Defined by *ICD-9-CM* codes 433, 434, or 436[b]	2.70 (2.05-3.57)	2.85 (2.41-3.37)
No. of patients in model	48 961	228 677
No. of stroke events	381	1172
Defined by *ICD-9-CM* codes 434 or 436[c]	3.04 (2.26-4.10)	3.44 (2.86-4.13)
No. of patients in model	48 961	228 677
No. of stroke events	327	814
Defined by *ICD-9-CM* code 434[d]	3.10 (2.30-4.17)	3.46 (2.86-4.15)
No. of patients in model	48 961	228 677
No. of stroke events	324	809
Defined by *ICD-9-CM* code 434.11[e]	3.94 (2.21-7.01)	4.81 (3.38-6.87)
No. of patients in model	48 961	228 677
No. of stroke events	70	182
Severe sepsis, excluding septic emboli[b]	2.70 (2.06-3.54)	2.84 (2.40-3.37)
No. of patients in model	47 290	228 649
No. of stroke events	376	1169
Severe sepsis with mechanical ventilation[b]	2.47 (1.79-4.42)	2.50 (2.05-3.03)
No. of patients in model	23 335	52 595
No. of stroke events	284	668
Severe sepsis, patient random effect, accounting for multiple sepsis admissions[b]	2.86 (2.16-3.78)	NA
No. of patients in model	45 037	NA
No. of stroke events	353	NA
Severe sepsis present on admission[b]	2.17 (1.37-3.42)	NA
No. of patients in model	38 591	NA
No. of stroke events	196	NA

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; NA, not applicable (analysis not performed).
[a]Data are odds ratios (95% CIs) unless otherwise specified. Models adjusted for age; sex; race/ethnicity; history of diabetes mellitus, hypertension, obesity, heart failure, myocardial infarction, stroke, chronic obstructive pulmonary disease, and metastatic or hematologic malignancy; and sepsis-associated factors including number of organ failures, presence of electrolyte disturbances, source of sepsis, type of organ failure, type of pathogenic organism, and use of right heart catheterization.
[b]Not present on admission. Codes 433, 434, or 436: occlusion and stenosis precerebral arteries, cerebral artery occlusion, or acute, ill-defined cerebrovascular disease.
[c]Not present on admission. Codes 434 or 436: cerebral artery occlusion or acute, ill-defined cerebrovascular disease.
[d]Not present on admission. Code 434: cerebral artery occlusion.
[e]Not present on admission. Code 434.11: embolic stroke.

detecting new-onset AF compared with the chart abstraction or prospective identification used in prior studies. Additionally, new-onset AF that occurred on hospital admission in the setting of severe sepsis may be classified as "preexisting AF" by the "present on admission" coding strategy used in our study, which might falsely lower the observed incidence of AF or bias outcome analyses.

Second, because new-onset AF during critical illness is often self-limited,[2] clinicians may not record episodes of AF that are deemed clinically insignificant. Thus, "circular coding" may be present in which new-onset AF is preferentially coded when it is thought to be associated with an adverse outcome such as stroke. However, we did not find associations between stroke and preexisting AF, which would theoretically be susceptible to a similar circular coding bias.

Third, because our definition of new-onset AF necessitated that AF occur after hospital admission, an "immortal time" bias[45] may exist in which patients had to survive long enough to be diagnosed as having AF. Immortal time bias may have falsely lowered the risk of mortality associated with new-onset AF; thus, the mortality risk associated with new-onset AF during severe sepsis may actually be greater than reported in our study. Death may be considered as a competing risk for in-hospital stroke; however, we could not ascertain time to in-hospital stroke, which would be necessary to perform competing risk analyses. The composite vector of these potential biases is not clear.

Fourth, though sensitivity analyses suggest a temporal order among severe sepsis, AF, and in-hospital stroke, the administrative data used for the present study are limited in ascertaining the timing of clinical events. However, an exploratory analysis of incident ischemic stroke occurring after the severe sepsis hospitalization suggests that stroke risks may remain elevated up to 1 year following severe sepsis. Finally, because of the observational nature of our study and the possibility for unmeasured confounding, we cannot prove a causal relation between new-onset AF in the setting of severe sepsis and increased risk of stroke and death.

Given projected estimates of severe sepsis incidence in 1 million Americans in 2011,[22] it is likely that new-onset AF occurs in more than 60 000 patients with severe sepsis in the United States each year. Our findings suggest that new-onset AF during severe sepsis is associated with especially high short-term nosocomial stroke and mortality risks; most patients with new-onset AF during a hospitalization with severe sepsis did not survive. Current guidelines do not address AF that occurs in the setting of severe sepsis or acute infection,[6,46] suggesting that new-onset AF that occurs during severe sepsis is an underrecognized public health problem. If our findings of increased stroke and death in the setting of AF and severe sepsis are replicated in other data sets, then it will be important to examine management strategies that might diminish the risk of adverse outcomes associated with AF during severe sepsis.

REFERENCES

1. Artucio H, Pereira M. Cardiac arrhythmias in critically ill patients: epidemiologic study. *Crit Care Med*. 1990;18(12):1383-1388.
2. Annane D, Sébille V, Duboc D, et al. Incidence and prognosis of sustained arrhythmias in critically ill patients. *Am J Respir Crit Care Med*. 2008;178(1):20-25.
3. Goodman S, Shirov T, Weissman C. Supraventricular arrhythmias in intensive care unit patients: short and long-term consequences. *Anesth Analg*. 2007;104(4):880-886.
4. Arora S, Lang I, Nayyar V, Stachowski E, Ross DL. Atrial fibrillation in a tertiary care multidisciplinary intensive care unit—incidence and risk factors. *Anaesth Intensive Care*. 2007;35(5):707-713.
5. Meierhenrich R, Steinhilber E, Eggermann C, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. *Crit Care*. 2010;14(3):R108.
6. Fuster V, Rydén LE, Cannom DS, et al; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123(10):e269-e367.
7. Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. *J Crit Care*. 2008;23(4):532-536.
8. Salman S, Bajwa A, Gajic O, Afessa B. Paroxysmal atrial fibrillation in critically ill patients with sepsis. *J Intensive Care Med*. 2008;23(3):178-183.
9. Agency for Healthcare Research and Quality. Overview of the state inpatient databases (SID). http://www.hcup-us.ahrq.gov/sidoverview.jsp. Accessed January 6, 2011.
10. Glance LG, Dick AW, Osler TM, Mukamel DB. Accuracy of hospital report cards based on administrative data. *Health Serv Res*. 2006;41(4 pt 1):1413-1437.
11. Glance LG, Dick AW, Osler TM, Mukamel DB. Does date stamping *ICD-9-CM* codes increase the value of clinical information in administrative data? *Health Serv Res*. 2006;41(1):231-251.
12. Coffey R, Milenkovic M, Andrews RM. The case for the present-on-admission (POA) indicator. HCUP Methods Series report 2006-01. http://www.hcup-us.ahrq.gov/reports/methods/2006_1.pdf. June 26, 2006. Accessed July 7, 2011.
13. Glazer NL, Dublin S, Smith NL, et al. Newly detected atrial fibrillation and compliance with antithrombotic guidelines. *Arch Intern Med*. 2007;167(3):246-252.
14. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke*. 2002;33(10):2465-2470.
15. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet*. 2009;373(9665):739-745.
16. Chamberlain AM, Agarwal SK, Folsom AR, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol*. 2011;107(1):85-91.
17. Winkelmayer WC, Patrick AR, Liu J, Brookhart

MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol*. 2011;22(2):349-357.

18. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J*. 2003; 21(6):1012-1016.

19. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of *ICD-9-CM* codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005;43(5):480-485.

20. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in *ICD-9-CM* and *ICD-10* administrative data. *Med Care*. 2005;43 (11):1130-1139.

21. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348(16):1546-1554.

22. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303-1310.

23. Poulose JT, Cartin-Ceba R, Shoja A, et al. Comparison of *International Classification of Diseases—Ninth Revision* (*ICD-9*) coding with retrospective case review for the diagnosis of septic shock [abstract]. *Am J Respir Crit Care Med*. 2009;179: A4691.

24. Quan H, Parsons GA, Ghali WA. Assessing accuracy of diagnosis-type indicators for flagging complications in administrative data. *J Clin Epidemiol*. 2004; 57(4):366-372.

25. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; 285(22):2864-2870.

26. Goldstein LB. Accuracy of *ICD-9-CM* coding for the identification of patients with acute ischemic stroke: effect of modifier codes. *Stroke*. 1998;29(8):1602-1604.

27. Benesch C, Witter DM Jr, Wilder AL, Duncan PW, Samsa GP, Matchar DB. Inaccuracy of the *International Classification of Diseases* (*ICD-9-CM*) in identifying the diagnosis of ischemic cerebrovascular disease. *Neurology*. 1997;49(3):660-664.

28. Parsons LS. *Proceedings of the 25th Annual SAS Users Group International Conference.* Using SAS software to perform a case-control match on propensity score in an observational study. In: Cary, NC: SAS Institute Inc; 2000:1166-1171.

29. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

30. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol*. 2005;162(3):199-200.

31. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004;351(25):2611-2618.

32. Syrjänen J. Central nervous system complications in patients with bacteremia. *Scand J Infect Dis*. 1989;21(3):285-296.

33. Syrjänen J, Valtonen VV, Iivanainen M, Kaste M, Huttunen JK. Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. *BMJ (Clin Res Ed)*. 1988; 296(6630):1156-1160 . Clin Res Ed.

34. Zurrú MC, Alonzo C, Brescacín L, et al. Recent respiratory infection predicts atherothrombotic stroke: case-control study in a Buenos Aires healthcare system. *Stroke*. 2009;40(6):1986-1990.

35. Elkind MS, Carty CL, O'Meara ES, et al. Hospitalization for infection and risk of acute ischemic stroke: the Cardiovascular Health Study. *Stroke*. 2011; 42(7):1851-1856.

36. Zeerleder S, Hack CE, Wuillemin WA. Disseminated intravascular coagulation in sepsis. *Chest*. 2005; 128(4):2864-2875.

37. Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Viral respiratory tract infections increase platelet reactivity and activation: an explanation for the higher rates of myocardial infarction and stroke during viral illness. *J Thromb Haemost*. 2005;3(9): 2108-2109.

38. Stoddard MF, Dawkins PR, Prince CR, Ammash NM. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transesophageal echocardiographic study. *J Am Coll Cardiol*. 1995;25(2):452-459.

39. Fatema K, Gertz MA, Barnes ME, et al. Acute weight gain and diastolic dysfunction as a potent risk complex for post stem cell transplant atrial fibrillation. *Am J Hematol*. 2009;84(8):499-503.

40. Gibbs HR, Swafford J, Nguyen HD, Ewer MS, Ali MK. Postoperative atrial fibrillation in cancer surgery: preoperative risks and clinical outcome. *J Surg Oncol*. 1992;50(4):224-227.

41. Hidalgo JD, Krone R, Rich MW, et al. Supraventricular tachyarrhythmias after hematopoietic stem cell transplantation: incidence, risk factors and outcomes. *Bone Marrow Transplant*. 2004;34(7):615-619.

42. Elijovich L, Josephson SA, Fung GL, Smith WS. Intermittent atrial fibrillation may account for a large proportion of otherwise cryptogenic stroke: a study of 30-day cardiac event monitors. *J Stroke Cerebrovasc Dis*. 2009;18(3):185-189.

43. Harvey S, Harrison DA, Singer M, et al; PAC-Man Study Collaboration. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet*. 2005;366(9484): 472-477.

44. Wheeler AP, Bernard GR, Thompson BT, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network. Pulmonary-artery vs central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006; 354(21):2213-2224.

45. Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med*. 2003;168(1):49-53.

46. Camm AJ, Kirchhof P, Lip GY, et al; European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; ESC Committee for Practice Guidelines; Document Reviewers. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace*. 2010; 12(10):1360-1420.