ORIGINAL RESEARCH

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Bleeding Complications in Anticoagulated Patients With Atrial Fibrillation and Sepsis: A Propensity-Weighted Cohort Study

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***Background*—**Sepsis may adversely affect bleeding risk in anticoagulated patients with atrial fibrillation (AF), but the impact of warfarin treatment in such patients is poorly described. This registry-based nationwide cohort study examined safety of oral anticoagulant treatment (OAC) in patients with preexisting AF who were hospitalized because of incident sepsis in the period 2000–2015.

***Methods and Results*—**We identified 3030 AF patients who were warfarin users at the time of sepsis diagnosis, and we used inverse probability of treatment weighting to compare the rates of bleeding, thromboembolic events, and death within 90 days after sepsis diagnosis with a comparable cohort of 55721 patients without warfarin treatment and known AF. Weighted 90-day bleeding rates were slightly higher among warfarin users compared with nonusers (0.14 versus 0.12 per 100 person-years), yielding a weighted hazard ratio of 1.19 (95% confidence interval, 1.00–1.41). Thromboembolic event rates during the 90-days after sepsis were marginally higher among warfarin users versus nonusers (0.04 versus 0.03; hazard ratio: 1.25, 95% confidence interval, 0.89–1.76), while the 90-day all-cause mortality was substantially lower among warfarin users (hazard ratio: 0.64, 95% confidence interval, 0.58–0.69). Various sensitivity analyses conducted to challenge the robustness these findings yielded results that were consistent with the main findings.

***Conclusions*—**AF patients who are on warfarin therapy at sepsis diagnosis experienced an increase in bleeding rates within the 3 months following sepsis. Warfarin use was associated with lower mortality, despite virtually comparable thromboembolic event rates. **(*J Am Heart Assoc*. 2017;6:e007453. DOI: 10.1161/JAHA.117.007453.)**

Key Words: anticoagulation • atrial fibrillation • cohort study • complication

Sepsis is one of the most commonly encountered conditions among hospitalized patients and is associated with critical illness, high mortality, and healthcare costs.[1] The clinical presentation of sepsis is diverse, but coagulation abnormalities are almost invariably present.[1–4] Consequently, sepsis is associated with high mortality that may result from multiple organ failure due to microvascular thrombosis or bleeding due to depletion of coagulation factors and platelets. Indeed, bleeding risk with antithrombotic therapy in severe sepsis patients remains a concern.[5]

Concerns about anticoagulation therapy in sepsis patients underscore the importance of assessing bleeding risk in patients whose home medications include oral anticoagulant (OAC) therapy. Two prior studies have indicated that anticoagulant therapy is associated with an increased risk of bleeding in AF patients during sepsis.[5,6] However, there is a lack of large-scale, population-based assessments of outcomes in sepsis patients with preexisting atrial fibrillation (AF) on continuous anticoagulant therapy. In a prior US study of Medicare beneficiaries, AF occurred in 25% of patients with hospitalized sepsis, of which 18% had preexisting AF.[7]

We linked nationwide health registries to identify all sepsis patients with preexisting AF who were on warfarin therapy before hospital admission with sepsis. We conducted a

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/11/e007453/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In this nationwide cohort study, warfarin therapy in patients with preexisting atrial fibrillation during sepsis was associated with increased rates of bleeding complications, comparable rates of thromboembolic events, and significantly lower mortality during the 90-days after sepsis compared with sepsis patients who were not warfarin users and had no known atrial fibrillation.

What Are the Clinical Implications?

- Our results emphasize that cautious assessment of bleeding risk is warranted for patients with preexisting atrial fibrillation who are on continuous anticoagulant therapy after hospitalization with sepsis, but further research is needed to determine the optimal management of short- and long-term anticoagulation strategies in patients with atrial fibrillation and sepsis.

propensity-weighted analysis comparing the risk of bleeding, thromboembolic events, and 90-day mortality in this cohort with sepsis patients who were not warfarin users and who had no known AF.

Material and Methods

Setting and Data Sources

Our study was a propensity-weighted analysis of administrative registry data covering the entire Danish population, encompassing 5 659 715 inhabitants (as of January 1, 2015) in 2000–2015. Denmark has a tax-supported healthcare system providing free medical care and partial reimbursement of the costs of most prescribed medications, including warfarin. We identified all sepsis patients; their comorbidities; bleeding and thromboembolic outcomes in the Danish National Patient Register,[8] which includes admission/discharge date; and discharge *International Classification of Diseases* diagnoses for >99% of somatic hospital admissions in Denmark since 1977. Warfarin exposure and concomitant medications was ascertained from the Danish National Prescription Registry,[9] which holds purchase date, ATC (Anatomical Therapeutic Chemical) classification code, and package size for every prescription purchase in Denmark since 1994. Demographic information was obtained from the Danish Civil Registration System,[10] which contains information on sex, date of birth, and vital and emigration status. We linked all data sources by means of the unique personal civil registration numbers assigned to all Danish residents since 1968.[10] The study was approved by the Danish Data Protection Agency (2015-57-0001). Approval from an ethics committee is not required for anonymous registry-based studies in Denmark. Data were provided by Statistics Denmark.

Study Population

We identified all patients hospitalized with an incident primary inpatient sepsis diagnosis between 2000 and 2015, excluding emergency department diagnoses and patients who had not been residents in Denmark for at least 1 year before sepsis diagnosis. We rationalized that patients with community-onset sepsis would more likely be taking their usual home medications at the time of sepsis hospitalization. Accordingly, we restricted the study population to patients with no hospital contact within the 30 days preceding admission, as done in other studies.[11]

Comedication status and comorbidities at baseline were ascertained by medication claims within 1 year before index date and/or history of primary or secondary hospital discharge diagnoses (excluding emergency room diagnoses) since 1994. Table S1 provides information on all codes for diagnoses and medications. We further combined baseline information into CHA_2DS_2-VASc stroke risk score[12] to summarize the perceived stroke risk at baseline and a HAS-BLED score[13] as a measure of bleeding risk at baseline (see score definitions in Table S2). Owing to the lack of data on sepsis severity, the length of hospital stay (calculated as the date for sepsis admission/diagnosis until discharge) was used as a proxy, with longer stays reflecting more complicated (and severe) conditions.

Exposure

To avoid bias from inclusion of users of non–vitamin K OACs (NOACs), we excluded all patients who filled a prescription for NOACs within 365 days before admission. Within the study population of patients with incident sepsis, we then identified all patients who had redeemed a prescription for warfarin within 90 days before the date of admission with sepsis. We restricted the cohort of warfarin users to patients with a prior hospital diagnosis for nonvalvular AF to limit confounding from the underlying indication for warfarin therapy.

We similarly defined a comparison cohort consisting of sepsis patients who were warfarin nonusers (defined as no redemption of warfarin in a 365-day period before date of sepsis diagnosis). Because AF patients not receiving warfarin or NOACs may represent selective channeling of treatments away from frail patients at increased risk of bleeding, we excluded patients with a prior hospital AF diagnosis; therefore, the comparison cohort comprised warfarin nonusers without AF.

To facilitate a balanced comparison of the 2 cohorts, we used an inverse probability of treatment weighted analysis with weights defined to obtain an estimate of the average treatment of the treated with the warfarin-exposed cohort in focus. The weights were based on the propensity score for being an AF patient on warfarin at baseline, estimated using logistic regression with the following potential confounders used as treatment predictors: age (continuous), binary indicators for sex, calendar period, ischemic stroke, systemic embolism or transient ischemic attack, congestive heart failure, vascular disease, prior bleeding, hypertension, diabetes mellitus, cancer, chronic pulmonary disease, renal disease, hospital diagnosed pneumonia within the year before index, alcohol-related disease, dementia, and depression, as well as recent prescriptions of digoxin, nonloop diuretics, beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, clopidogrel, antidiabetic medications, and/or statins (see Table S1 for codes). Balances between the 2 exposure groups were evaluated by the standardized differences of all baseline covariates, using a threshold of 0.1 to indicate an imbalance.[14]

Outcomes

The primary study end points were bleeding complications and thromboembolic events (ischemic stroke, systemic embolism, transient ischemic attack) within 90 days of the date of sepsis hospitalization. Bleeding events included intracranial bleeding, gastrointestinal bleeding, and major clinically relevant bleeding in various anatomic positions. All-cause mortality within 90 days of sepsis diagnosis was included as secondary end point. Hospital discharge diagnoses for all study outcomes were required to be primary in-hospital codes, excluding emergency room and ambulatory diagnoses, to ensure higher validity of the outcomes. The coding accuracy of the selected outcomes was validated previously and found to be sufficiently accurate for epidemiological research.[15]

Statistical Analyses

We followed all study participants from the date of sepsis diagnosis until the outcome of interest, death, emigration, or end of the study, whichever occurred first. We examined baseline characteristics at the time of sepsis diagnosis according to exposure and estimated absolute standardized differences to determine the extent to which the inverse probability of treatment weighting balanced baseline characteristics (considering an absolute standardized difference $\geq$0.2 to be critical).[16] We used time-to-event survival analyses to compare risk of end points according to warfarin exposure. Weighted incidence rates were calculated as number of events divided by person-time, whereas cumulative incidence functions (by means of the Aalen–Johansen estimator), assuming death as a competing risk, were used to depict the risk of the primary outcomes, bleeding and thromboembolic events, within 90 days. Finally, we used weighted Cox proportional hazards models to compare event hazard rates according to warfarin exposure.

To challenge the robustness of our findings, we did 3 preplanned sensitivity analyses. First, we repeated all analyses using an alternative definition of the cohort of warfarin users (prescription redemption within 120, 60, and 30 days before sepsis diagnosis, respectively). Second, to quantify the impact of "prevalent user bias,"[17] we restricted the warfarin cohort to new users of warfarin, defined as patients who redeemed their first-ever prescription of warfarin within 90 days of the date of sepsis diagnosis. Third, because restriction to new users can guard against "healthy adherer bias" but may not eliminate healthy user bias, we also compared outcomes among warfarin users with those of propensity-weighted warfarin nonusers who had redeemed prescriptions for other preventive medications (beta blockers, statins, calcium channel blockers, and/or angiotensin-converting enzyme inhibitors) in an active comparator design.[17]

Analyses were conducted using Stata/MP version 14 (StataCorp LP).

Results

Figure 1 shows the assembly of the study population. After exclusions, the study population included 3030 sepsis patients with nonvalvular AF who were warfarin users and 55 721 sepsis patients who were warfarin nonusers (Table 1). Warfarin users were substantially older than nonusers (mean age: 78 versus 67 years) and had more comorbidities, in particular, heart failure, prior stroke, and vascular disease, resulting in a mean CHA_2DS_2-VASc score 4.5 versus 2.7 in warfarin nonusers. After inverse probability of treatment weighting, all absolute standardized differences were <0.14, indicating that the weighted cohorts were comparable.

Figure 2 shows cumulative incidence curves of any bleeding complications and thromboembolic events 90 days after sepsis diagnosis for the crude and weighted populations. During the first 90 days after sepsis, crude bleeding rates were higher among patients on warfarin than among nonusers (0.14 versus 0.08; hazard ratio [HR]: 1.76; 95% confidence interval [CI], 1.56–1.99; Table 2, Figure 3). After propensity weighting, differences in 90-day bleeding rates between warfarin users and nonusers were attenuated, although rates remained higher among warfarin users (0.14 versus 0.12; HR: 1.19; 95% CI, 1.00–1.41; Figure 3).

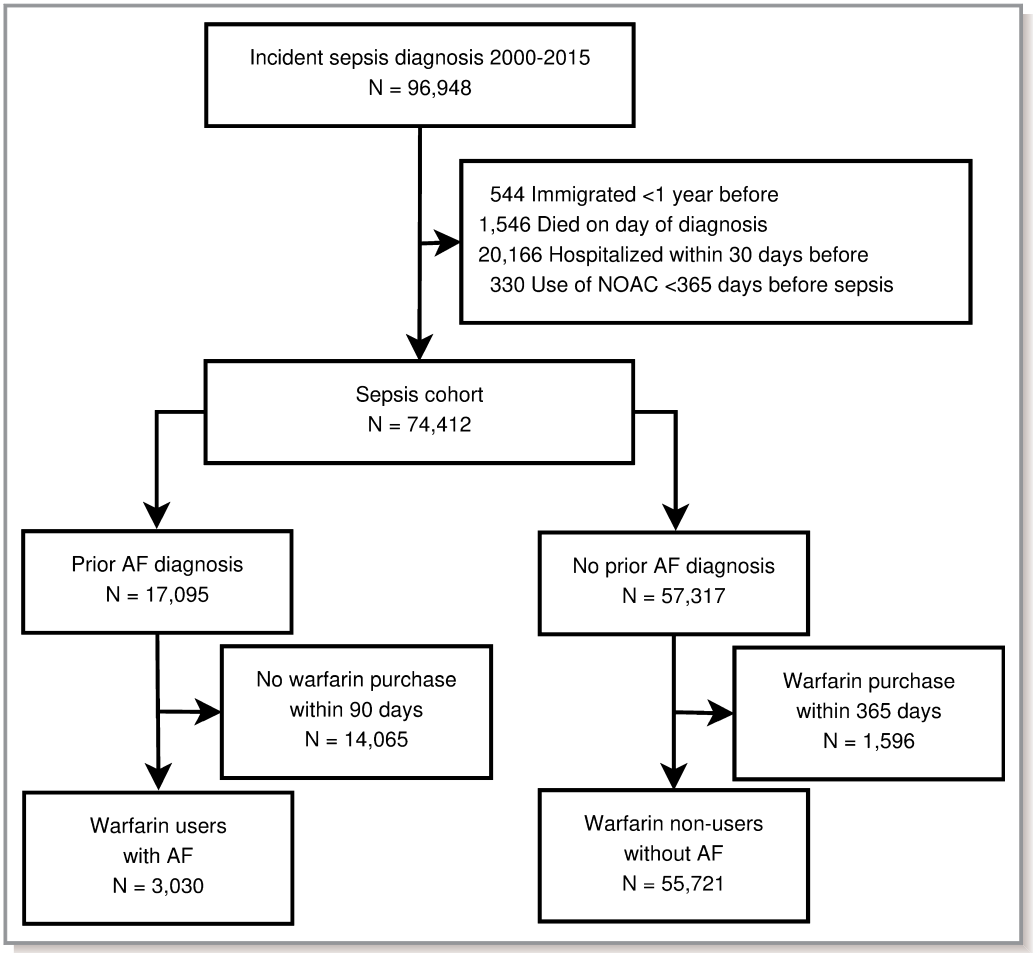

Figure 1. Patient inclusion flowchart. AF indicates atrial fibrillation; NOAC, non–vitamin K oral anticoagulant.

Crude 90-day rates of ischemic stroke or systemic thromboembolic events were low but higher in warfarin users than in nonusers (0.04 versus 0.02; HR: 1.81; 95% CI, 1.43–2.30; Figure 3). Weighted 90-day rates were marginally higher among warfarin users versus nonusers (0.04 versus 0.03; HR: 1.25; 95% CI, 0.89–1.76), with the CI including unity. The 90-day mortality rate was higher among warfarin users compared with nonusers before weighting (0.44 versus 0.33) but was significantly lower following propensity weighting (0.40 versus 0.66 [Table 2]), with a weighted HR of 0.64 (95% CI, 0.58–0.69).

Sensitivity Analyses

Sensitivity analyses using different time windows for ascertaining warfarin usage lead to similar conclusions as the main analyses (Figure 3). The sensitivity analyses restricted to new users of warfarin included 128 warfarin users in the weighted cohorts, and the modest sample size yielded low precision. Accordingly, the estimates were accompanied with very wide CIs. Compared with the main analyses, restriction to new users indicated slightly higher rates of bleeding and thromboembolic events among warfarin users compared with nonusers; however, the estimate of thromboembolic events should be interpreted with caution, given the very few events (only 5). Finally, restricting the comparison cohort to users of other preventive medications did not alter the conclusions of the main analyses. The finding of lower 90-day mortality among warfarin users versus nonusers remained consistent across all sensitivity analyses (Figure 3).

Discussion

First, among AF patients with an incident sepsis diagnosis, we saw an increase in bleeding rates within 90 days of sepsis diagnosis compared with propensity-weighted warfarin nonusers without AF. Second, concurrent rates of thromboembolic events were marginally higher among warfarin users versus nonusers. Third, mortality rates during the 90 days after sepsis were lower among AF patients who were taking

Table 1. Descriptive Characteristics of Patients With Incident Sepsis in Denmark According to Use of OAC Therapy

Characteristic	Warfarin Nonusers	Warfarin Users	Standardized Differences*	
			Before	After
Participants, n	55 721	3030		
Female, % (n)	47.0 (26 196)	35.3 (1071)	0.239	0.067
Age, y, mean (SD)	66.9 (20.4)	78.2 (8.7)	0.717	0.059
Year of diagnosis, % (n)				
2000–2003	14.4 (8017)	6.4 (194)	0.264	0.045
2004–2007	19.1 (10 670)	15.9 (481)	0.086	0.125
2008–2011	28.9 (16 127)	30.5 (923)	0.033	0.020
2012–2015	37.5 (20 907)	47.3 (1432)	0.198	0.139
Days in hospital, mean (SD)	19.2 (41.9)	18.1 (21.9)	0.033	0.015
Severe sepsis, % (n)	2.5 (1386)	3.3 (100)	0.049	0.072
Comorbidity, % (n)				
Prior bleeding	27.8 (15 489)	47.1 (1426)	0.406	0.026
HAS-BLED score, mean (SD)	2.2 (1.5)	3.2 (1.3)	0.711	0.115
CHA_2DS_2-VASc score, mean (SD)	2.7 (1.8)	4.5 (1.6)	1.040	0.080
Prior stroke	13.6 (7582)	27.6 (836)	0.351	0.016
Heart failure or LVD	26.0 (14 506)	69.4 (2104)	0.965	0.105
Hypertension	40.6 (22 604)	80.3 (2434)	0.890	0.048
Vascular disease	13.5 (7523)	28.5 (865)	0.376	0.067
Renal dysfunction	10.7 (5959)	18.8 (569)	0.230	0.033
Diabetes mellitus	17.2 (9586)	29.5 (895)	0.295	0.025
Chronic pulmonary disease	15.4 (8581)	26.1 (792)	0.267	0.037
Cancer	23.3 (13 002)	24.9 (753)	0.036	0.032
Alcohol-related disease	8.8 (4918)	4.0 (122)	0.197	0.015
Osteoporosis	7.1 (3948)	8.2 (247)	0.040	0.004
Dementia	6.8 (3806)	4.9 (147)	0.085	0.017
Depression	25.2 (14 018)	23.2 (702)	0.047	0.009
Pneumonia within previous 365 days	19.1 (10 649)	25.7 (780)	0.160	0.019
Ulcer disease	7.5 (4164)	8.8 (268)	0.050	0.075
Medications used, % (n)				
Digoxin	1.7 (971)	45.6 (1383)	1.206	0.058
Nonloop diuretics	28.9 (16 117)	45.0 (1365)	0.339	0.020
Loop diuretics	23.3 (13 009)	61.4 (1860)	0.834	0.096
Beta blocker	18.3 (10 170)	63.6 (1927)	1.039	0.090
Calcium channel blocker	18.6 (10 352)	32.6 (989)	0.326	0.051
Renin–angiotensin inhibitor	28.8 (16 075)	56.5 (1713)	0.583	0.100
Aspirin	28.8 (16 052)	32.1 (974)	0.073	0.126
Clopidogrel	4.6 (2541)	3.6 (110)	0.047	0.013
Statins	23.0 (12 823)	44.8 (1356)	0.472	0.015
NSAID	27.8 (15 491)	21.6 (655)	0.144	0.081
Systemic corticosteroids	14.1 (7834)	17.7 (536)	0.100	0.008
Proton pump inhibitors	28.8 (16 053)	33.1 (1003)	0.093	0.007

LVD indicates left ventricular dysfunction; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant.
*Standardized difference, before and after inverse probability of treatment weighting.

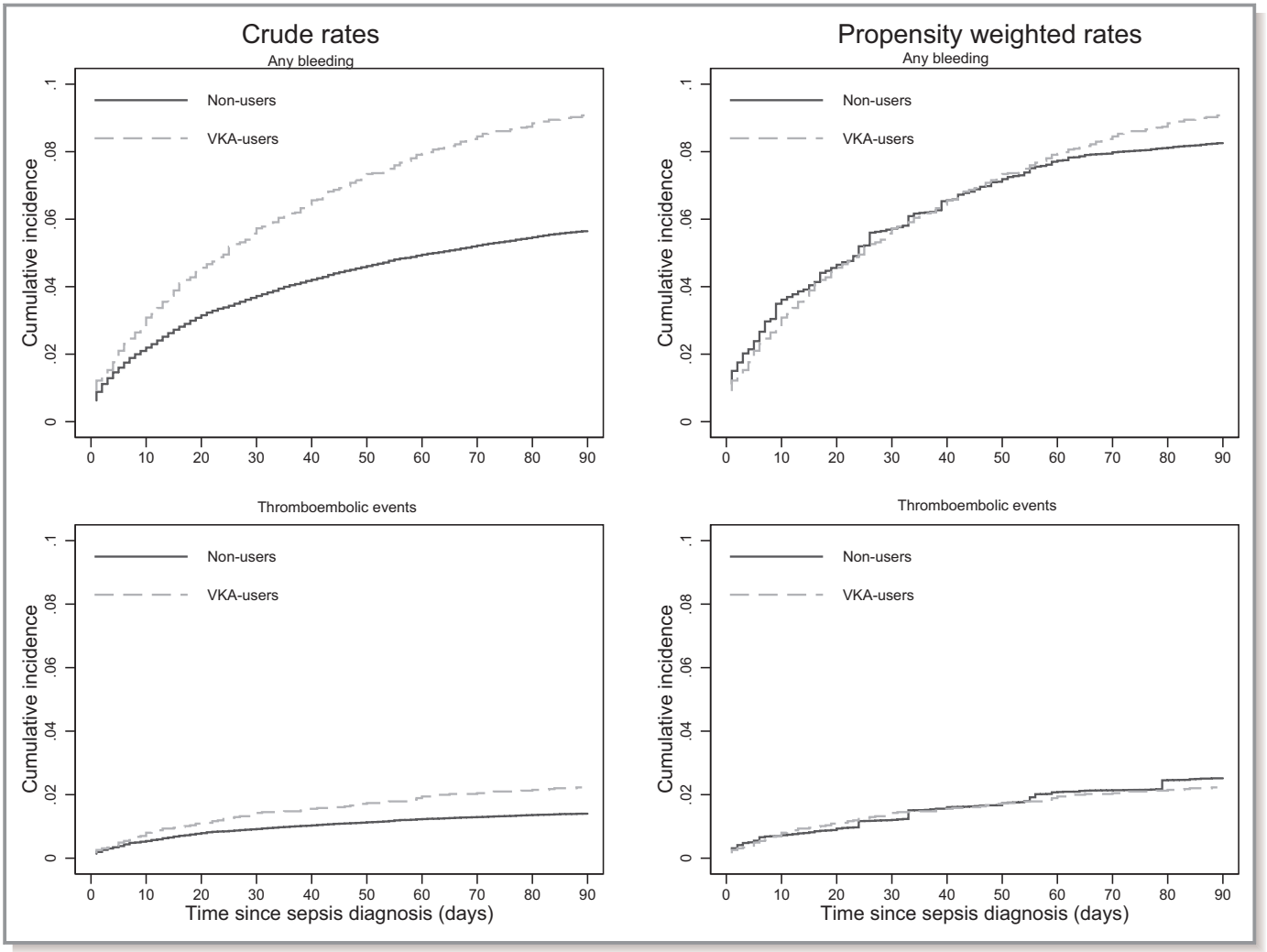

Figure 2. Cumulative incidence curves for the primary end points bleeding and thromboembolic events, according to use of oral anticoagulant therapy. VKA indicates Vitamin K antagonist.

warfarin compared with warfarin nonusers. These findings persisted through various sensitivity analyses conducted to challenge the robustness of our findings.

Prior studies have shown that patients with severe sepsis are at high risk of developing new-onset AF,[18,19] which in turn can put them at a higher risk of stroke and death than patients with preexisting AF.[20] Nevertheless, there is a paucity of studies on patients with preexisting AF who are taking continuous OACs. In a small study of 115 older adult patients with preexisting AF, Darwish et al[5] observed no ischemic strokes and only 3 bleeding events in 35 patients with OACs versus none in patients without OACs. Recently, Walkey et al[6] showed an increased risk of in-hospital bleeding events in AF patients receiving parenteral anticoagulation during sepsis compared with propensity-matched patients receiving no anticoagulation (8.6% versus 7.2%; relative risk: 1.21; 95% CI, 1.10–1.32). In this study, ≈80% of the patients had preexisting AF, in whom bleeding risk was lower than in patients with new-onset AF (6.7% versus 12.6%).[6] Nonetheless, it is difficult to determine whether this bleeding risk is substantial enough to warrant concern; some excess bleeding among warfarin users would be expected compared with warfarin nonusers. In line with our findings, Walkey et al[6] reported comparable rates of thromboembolic events among AF patients with anticoagulation compared with matched comparisons with no anticoagulation.

Experimental studies have shown that coumarin derivatives may be able to blunt sepsis-induced thrombin formation and disseminated intravascular coagulation.[21] Nonetheless, although it would seem tempting to pursue a causal interpretation of the significantly lower mortality rates among warfarin users with AF, caution must be exercised because prevalent user bias could also explain the lower mortality.[17] Our study included a substantial number of prevalent warfarin users, and longer term medication usage may be a surrogate for unmeasured factors associated with better prognosis.[22]

Table 2. Number of Events and Event Rates Within 90 Days After Sepsis Diagnosis According to Baseline Use of OAC Therapy

	Warfarin Nonusers Without AF			Warfarin Users With AF		
Outcomes	Events	Crude Rate	Weighted Rate	Events	Crude Rate	Weighted Rate
Primary outcomes						
Any bleeding event	3067	0.08	0.12	282	0.14	0.14
Thromboembolic events	791	0.02	0.03	76	0.04	0.04
Secondary outcome						
All-cause mortality	13 484	0.33	0.66	847	0.40	0.40

AF indicates atrial fibrillation; OAC, oral anticoagulant.

Nonetheless, a sensitivity analysis restricted to new users yielded results that were virtually consistent with the main findings, although CIs were too wide to permit reliable conclusions. Furthermore, restricting the comparison cohort to users of other preventive medications to avoid healthy adherer bias[17] also yielded results consistent with the main findings. In addition, the lower mortality in warfarin users could stem from surveillance bias if physicians have a lower threshold for hospitalizing AF patients on warfarin than other patients presenting with signs and symptoms of sepsis. A conservative interpretation of our mortality estimates is that there is no markedly higher mortality among AF patients on warfarin therapy. This observation is clinically important because it suggests that AF patients who are on warfarin at the time of sepsis diagnosis are not at a higher risk of fatal bleeding.

At present, little is known regarding bleeding complications in AF patients using anticoagulation during sepsis. Current guidelines for management of AF do not address sepsis, despite the frequency with which these patients are encountered in clinical practice.[7,23–25] In the light of this lack, this study may provide support for a randomized trial of anticoagulation in severe sepsis accompanied by AF stratified by newly diagnosed versus prevalent AF.

Although our study has the strength of a large number of observations included in a relatively homogeneous population setting, it also has limitations. Because we used prescription redemption as a proxy for medication usage, some patients might not have been using warfarin therapy at the time of sepsis, for example, because of physician intervention. We lacked information about the international normalized ratio on admission and on how anticoagulation was managed during hospitalization; however, we restricted the study to patients with primary sepsis diagnoses and performed exclusions, which, at least heuristically, should ensure better specificity for community-acquired sepsis, during which we suspect that patients would likely be taking their usual home medications at the time of admission. Moreover, warfarin has a long half-life, and when therapy is discontinued, it takes ≈4 days for the international normalized ratio to reach 1.5 in almost all patients.[26] We lacked clinical data on sepsis severity, presence of disseminated intravascular coagulation,

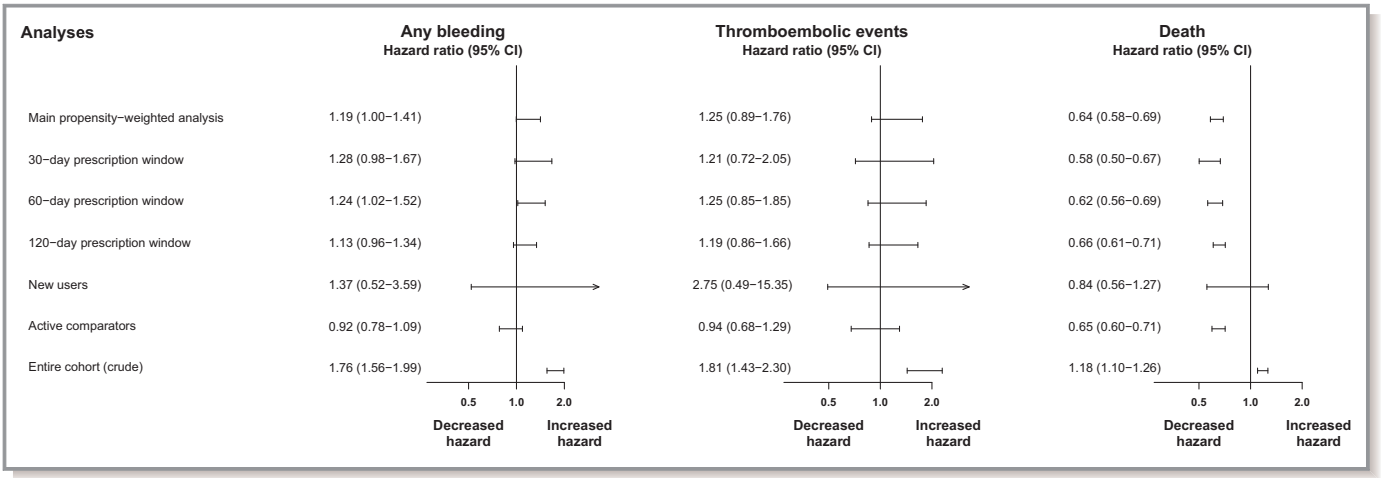

Figure 3. Hazard rates for the association between use of oral anticoagulant therapy and sepsis outcomes. CI indicates confidence interval.

and platelet counts; however, the mean length of hospital stay and the proportion of patients with severe sepsis or septic shock was comparable among warfarin users and nonusers. In addition, we included a number of frailty predictors in our propensity-weighted analysis such as cancer, chronic lung disease, prior pneumonia, osteoporosis, dementia, and depression.[27,28] Another potential limitation is our reliance on administrative coding to identify patients with sepsis. According to prior validation studies, hospital diagnoses show good specificity but poor sensitivity for sepsis.[29,30] Finally, there is the possibility of residual and unmeasured confounding, including prevalent user bias and healthy adherer bias, which we addressed in various sensitivity analyses.

In conclusion, in this nationwide cohort study, warfarin therapy in patients with AF during sepsis was associated with increased rates of bleeding complications, comparable rates of thromboembolic events, and significantly lower mortality during the 90 days after sepsis. Nevertheless, in the absence of a randomized trial, we cannot establish whether our findings are attributable to a causal effect, residual confounding, or bias.

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Disclosures

Associate Professor Larsen has served as an investigator for Janssen Scientific Affairs, LLC and Boehringer Ingelheim, and has been on the speaker bureaus for Bayer, BMS/Pfizer, Roche Diagnostics, Boehringer Ingelheim and Takeda Pharma. Professor Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and has been on the speakers bureau for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Micro- life, Roche, and Daiichi-Sankyo. Senior statistician Skjøth has been consultant for Bayer. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Definitions on comorbidity and concomitant medication according to ICD-10 codes and ATC-codes.

Diagnoses	**International Classification of Diseases 10th revision (ICD-10) code**	**Anatomical Therapeutic Chemical (ATC) code**
Atrial fibrillation	I48	
Sepsis	A02.1 A28.2B A267 A327 A392 A394 A40 A41 A42.7 A49.9A B37.7 B49.9A R572	
Severe sepsis	A419C R572	
Ischemic stroke	I63 I64	
Systemic embolism	I74	
Prior bleeding	K250 K252 K254 K260 K262 K264 K270 K272 K274 K280 K282 K290 K920 K921 K922 D62 J942 H113 H356 H431 N02 R04 R31 R58	
Prior stroke		
Heart failure or LVD	I110 I130 I132 I420 I50	
Hypertension		See specified definition[a]
Vascular disease	I702 I703 I704 I705 I706 I707 I708 I709 I71 I739	
Renal dysfunction	I12 I13 N00 N01 N02 N03 N04 N05 N07 N11 N14 N17 N18 N19 Q61	
Diabetes	E100 E101 E109 E110 E111 E119	A10
Chronic pulmonary disease	J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J67 J684 J701 J703 J841 J920 J961 J982 J983	
Cancer	C	
Alcohol-related disease	E224 E529A F10 G312 G621 G721 I426 K292 K70 K860	

	L278A O354 T51 Z714 Z721	
Osteoporosis		
Dementia	F00 F01 F02 F03 G30	
Depression	F32 F33	
Pneumonia within last 365 days	J12 J13 J14 J15 J16 J17 J18 A481 A709	
Ulcer disease	K221 K25 K26 K27 K28	
Medications within 365 days before index date		
Coumarin		B01AA
NOAC		B01AF01 B01AF02 B01AE07
Digoxin		C01AA05
Non-loop diuretics		C02DA C02L C03A C03B C03D C03E C03X C07C C07D C08G C09BA C09DA C09XA52
Loop diuretics		C03C
Beta-blocker		C07
Calcium channel blocker		C07F C08 C09BB C09DB
Renin-angiotensin inhibitor		C09
Aspirin		B01AC06
Clopidogrel		B01AC04
Statins		C10
NSAID		M01A
Systemic corticosteroids		H02
Proton pump inhibitors		A02BC

Abbreviations: NOAC, Non-vitamin K oral anticoagulant; NSAID, Non-steroidal anti-inflammatory drugs.

[a]We identified subjects with hypertension from combination treatment with at least two of the following classes of antihypertensive drugs:

I· Alpha adrenergic blockers (C02A, C02B, C02C)

II· Non-loop diuretics (C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52)

III· Vasodilators (C02DB, C02DD, C02DG, C04, C05)

IV· Beta blockers (C07)

V· Calcium channel blockers (C07F, C08, C09BB, C09DB)

VI· Renin-angiotensin system inhibitors (C09)

Table S2. Risk score definitions.

Risk score	Points if present
CHA_2DS_2VASc*	
Congestive heart failure or Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 65 years	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke (ischemic stroke, transient ischemic disease or systemic embolism)	2
Vascular disease (myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Sex category (female)	1
HAS-BLED**	
Hypertension	1
Abnormal renal function	1
Abnormal hepatic function	1
Stroke (ischemic stroke or transient ischemic attack)	1
Bleeding	1
Labile international normalized ratio***	1
Elderly age (≥ 65 years)	1
Drugs (aspirin, clopidogrel, or non-steroidal anti-inflammatory drugs)	1
Alcohol intake	1

*Reflects stroke risk in atrial fibrillation patients not in anticoagulant therapy (Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263-72.

**Reflects bleeding risk in atrial fibrillation patients undergoing anticoagulant therapy (Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100.

***Not included due to unavailable information

Bleeding Complications in Anticoagulated Patients With Atrial Fibrillation and Sepsis: A Propensity–Weighted Cohort Study

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