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Anticoagulant Use and Risk of Ischemic Stroke and Bleeding in Patients With Secondary Atrial Fibrillation Associated With Acute Coronary Syndromes, Acute Pulmonary Disease, or Sepsis

Michael J. Quon, MD,[a] Hassan Behlouli, PhD,[b] Louise Pilote, MD, MPH, PhD[a,c]

ABSTRACT

OBJECTIVES The purpose of this study was to determine if anticoagulation of patients with new onset secondary atrial fibrillation (AF) occurring with acute coronary syndromes (ACS), acute pulmonary disease, or sepsis is associated with a reduction in ischemic stroke or an increase in bleeding risk.

BACKGROUND Studies evaluating the benefits and risks of anticoagulation in secondary AF are infrequent, and the optimal management of these patients is not well understood.

METHODS A retrospective study cohort was identified of 2,304 patients age 65 years or older, hospitalized with a primary diagnosis of ACS, acute pulmonary disease (chronic obstructive pulmonary disease, pneumonia/influenza, pulmonary embolism, or pleural effusion) or sepsis, and a complication of new-onset AF during admission from 1999 to 2015.

RESULTS Over a follow-up of ~3 years, we did not identify any association between anticoagulation and a lower incidence of ischemic stroke in patients with new-onset AF occurring with ACS, acute pulmonary disease, or sepsis (odds ratio [OR]: 1.22 [95% confidence interval (CI): 0.65 to 2.27], OR: 0.97 [95% CI: 0.53 to 1.77], and OR: 1.98 [95% CI: 0.29 to 13.47]), after adjusting for confounders. However, anticoagulation was associated with a higher risk of bleeding in patients with AF associated with acute pulmonary disease (OR: 1.72 [95% CI: 1.23–2.39]), but not in ACS or sepsis (OR: 1.42 [95% CI: 0.94–2.14], OR: 0.96 [95% CI: 0.29–3.21]).

CONCLUSIONS Our study demonstrates that the benefit of anticoagulation in secondary AF is not strong and can be associated with a higher risk of bleeding. Careful individual assessment regarding decisions on anticoagulation is warranted in these patients. (J Am Coll Cardiol EP 2017;■:■–■) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Whether paroxysmal, persistent, or permanent, AF increases the risk of ischemic stroke (1). When the arrhythmia is self-limited and caused by a reversible etiology, it has been defined as secondary AF (2,3). Secondary AF has been observed in multiple clinical conditions, including acute myocardial infarction, myocarditis, pericarditis, acute pulmonary disease, post-operative states, thyrotoxicosis, acute alcohol consumption, and sepsis (2–6).

Framingham Heart Study participants with new-onset, secondary AF showed that nearly 2 of 3 of individuals had long-term recurrence of AF; however,

From the [a]Division of General Internal Medicine, Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada; [b]Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada; and the [c]Divisions of General Internal Medicine and of Clinical Epidemiology, Department of Medicine, The Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada. This research was funded by a grant from the Canadian Institutes of Health Research. Dr. Pilote holds a James McGill chair at McGill University. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ACS = acute coronary syndrome

COPD = chronic obstructive pulmonary disease

$CHADS_2$ = congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or transient ischemic attack

CHF = congestive heart failure

CKD = chronic kidney disease

DOAC = direct oral anticoagulant

HASBLED = hypertension, abnormal renal function/ abnormal liver function, history of stroke/TIA, history of bleeding, labile INR, age >65, drug therapy (antiplatelet agents, NSAIDs), and alcohol intake

ICD = International Classification of Diseases

INR = international normalized ratio

NSAID = nonsteroidal anti-inflammatory drug

OR = odds ratio

TIA = transient ischemic attack

there were also similar rates of stroke and mortality when compared with individuals without precipitants (3). To date, most studies of secondary AF have focused on the precipitants of acute coronary syndrome (ACS) and cardiac surgery. In ACS, secondary AF has been observed in 6% of patients (7,8). Transient, new-onset AF in ACS is a predictor of higher rates of recurrent AF and future stroke (9–11). Anticoagulation has been associated with a decreased incidence of stroke in these patients in some reports (10,11). Pulmonary pathologies, such as pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD), are common primary diagnoses with secondary AF in the emergency department setting (12); however, documented AF-related outcomes in these patients are limited. The same is true for sepsis, another known precipitant of AF. One retrospective cohort study showed that new-onset AF was observed in 6% of patients admitted with severe sepsis (4). AF with severe sepsis has been associated with higher rates of in-hospital stroke and in-hospital mortality (4). Another study showed that patients with new-onset AF in sepsis have a higher risk for hospitalization with ischemic stroke over 5 years' post-discharge when compared with patients without AF (5). Meanwhile, in hospitalized patients with AF during sepsis, anticoagulation was not associated with reduced risk of ischemic stroke (6).

The most recent American Heart Association/ American College of Cardiology/Heart Rhythm Society guidelines recommend anticoagulation with warfarin for patients with new-onset, transient AF in ACS with CHA_2DS_2-VASc score (congestive heart failure (CHF), hypertension, age >75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, female sex) ≥2 (13). These guidelines, however, fail to make specific anticoagulation recommendations for patients with AF secondary to acute pulmonary disease or a non-cardiac illness such as sepsis. Rather, these guidelines recommend treating the underlying cause and "considering the patient risk profile and duration of AF" in decisions regarding anticoagulation therapy. Acknowledging the limited long-term data, it is stated that "these patients should receive careful follow-up" (13). European and Canadian guidelines also fail to make clear recommendations in terms of thromboembolism prophylaxis in secondary AF (14–16). The outcomes of long-term anticoagulation in these clinical scenarios require further study.

This population based cohort study seeks to meet the following objectives: 1) determine the incidence of ischemic stroke and bleeding in patients with new-onset secondary AF associated with ACS, acute pulmonary disease, or sepsis; and 2) examine if anticoagulant use in these patient groups following discharge is associated with a reduction in ischemic stroke or an increase in bleeding risk.

METHODS

STUDY DESIGN. We conducted a retrospective cohort study of patients with secondary AF associated with ACS, acute pulmonary disease, or sepsis using administrative data with linkages between prescription drug claims, physician claims, and hospital discharge databases.

STUDY POPULATION. For cohort identification, the province of Quebec Hospital Discharge Database (Maintenance et Exploitation des Donnees pour l'Etude de la Clientèle Hospitalière [Med-Echo]) was used. Patients' encrypted health insurance numbers were used to link the Med-Echo database to the provincial physician and prescription claims database (la Regie de l'Assurance Maladie du Quebec) containing information on all outpatient prescriptions for patients 65 years or older as well as all inpatient and outpatient diagnostic and therapeutic procedures and outpatient visits in Quebec. We used the la Regie de l'Assurance Maladie du Quebec database to obtain information on medication prescriptions filled after discharge from index hospital admission.

Participants in our cohort were Quebec residents, 65 years or older, discharged alive from the hospital with a primary diagnosis of a known reversible cause of AF and a post-admission diagnosis of AF coded as a complication of the admission (Online Table 1). The primary diagnosis code indicates the main condition treated or investigated during the hospital stay. We identified primary diagnoses according to the International Classification of Diseases (ICD)-9 and -10 codes. Primary diagnoses that were included were ACS, acute pulmonary disease (COPD, pneumonia/influenza, pulmonary embolism, and pleural effusion) and sepsis. If there were multiple admissions with AF as a complication, only the first was included. The information was gathered between 1999 and 2015.

To identify new-onset AF only, we excluded: 1) patients who had a previous hospital admission or physician visit with either a primary or a major comorbid diagnosis of AF within the prior year; 2) patients who had a recent admission for either

coronary artery bypass graft or cardiac surgery (Online Table 1); and 3) patients who had an outpatient prescription for warfarin or any direct oral anticoagulant (DOAC) within the prior year. DOACs included dabigatran, rivaroxaban, and apixaban. Patients were also excluded if they were 105 years or older, did not have a valid health care number, or were admitted as a transfer from another institution. We also excluded residents of chronic care facilities because information on filled prescriptions is not available for these patients.

We then grouped ACS, acute pulmonary disease, and sepsis into 3 cohorts. We used the Med-Echo database to obtain information on patient characteristics and comorbid conditions (from the lists of secondary diagnoses in the hospital discharge records, using the specific ICD-9/ICD-10 codes). We calculated their $CHADS_2$ and HASBLED scores. $CHADS_2$ scores were calculated by assigning 1 point each for CHF, hypertension, age >75 years, diabetes mellitus and 2 points for previous stroke or TIA. Total possible $CHADS_2$ scores ranged between 0 and 6 points. HASBLED scores were calculated by assigning 1 point each for hypertension, liver disease, or chronic kidney disease (CKD), stroke or TIA, history of bleeding, age >65 years, and antiplatelet or NSAID use. Although a labile INR is also included in the HASBLED score, no patients in our study were previously treated with anticoagulation; thus, total HASBLED scores ranged from 1 to 6. The components of the $CHADS_2$ and HASBLED scores were defined using diagnoses coded within 1 year before the index admission with secondary AF, including the index admission. We obtained information on the first prescription filled for anticoagulant as well as antiplatelet medications. Initiation of anticoagulant use following admission with secondary AF was defined as prescription for warfarin or DOAC filled within 30 days of hospital discharge. Patients in each of the primary diagnoses were subsequently grouped into anticoagulant and no-anticoagulant users.

The primary outcomes were ischemic stroke and bleeding, documented at first hospital admission or emergency department visit following discharge. Ischemic stroke was defined as cerebral thrombosis, embolism, or artery occlusion, including TIA and retinal infarct. Bleeding was defined as intracerebral bleeding, gastrointestinal hemorrhage, intraocular hemorrhage, hematuria, hemoptysis, epistaxis, or hemorrhage (not otherwise specified) (Online Table 1). The Med-Echo database was used to obtain information on admissions until 2015.

STATISTICAL ANALYSES. Descriptive analyses were used to compare the ACS, acute pulmonary disease, and sepsis groups according to demographics, co-morbidities, and medication prescriptions. We presented continuous variables as mean ± SD and dichotomous variables as number (%). We calculated crude stroke and bleeding rates as well as incidence rates (per 100 person-years). We stratified stroke rates according to $CHADS_2$ score as well as anticoagulant use. Similar to prior studies (17,18), we grouped the $CHADS_2$ score using 0, 1, and >2, as low, moderate, and high risk, respectively. We stratified bleeding rates according to HASBLED score as well as anticoagulant use. Incidence stroke, and bleeding rates were compared in each group between anticoagulant use and no-anticoagulant use, using chi-square (or Fisher exact) testing. Multivariate regression analysis was performed to determine if anticoagulant use was associated with a lower incidence of stroke or higher incidence of bleeding. For the stroke outcome, we adjusted for all potential confounders of the $CHADS_2$ score (CHF, hypertension, age, diabetes, stroke/TIA). For the bleeding outcome, we adjusted for potential confounders of the HASBLED score (hypertension, liver disease or CKD, stroke/TIA, history of bleeding, age, antiplatelet or NSAID use). Results were then expressed as hazard ratios with 95% confidence intervals.

RESULTS

BASELINE CHARACTERISTICS. Our secondary AF cohort included a total of 2,304 patients (Table 1). ACS (n = 827) and acute pulmonary diseases (n = 1,375) represented most the primary diagnoses. With regard to acute pulmonary disease, most patients with secondary AF were admitted with COPD (n = 557) and influenza/pneumonia (n = 731) compared with smaller numbers of pulmonary embolism (n = 48) and pleural effusion (n = 39). Patients in our cohort were elderly (mean age: 77.1 to 79.3 years) and frequently had co-morbid illness including coronary artery disease, CHF, CKD, hyperlipidemia, and diabetes. Most patients had high $CHADS_2$ scores (≥2) (66.5%, 60.9%, and 65.9.3%), and high HASBLED scores (≥3) (59.5%, 47.4%, and 55.9%) seen in ACS, acute pulmonary disease, and sepsis, respectively.

MEDICATIONS FOLLOWING DISCHARGE. A prescription for anticoagulant within the first 30 days following discharge was 38.4%, 34.1%, and 27.7% in ACS, acute pulmonary disease, and sepsis cohorts, respectively. Most of these patients were prescribed warfarin. DOACs represented a minority of prescribed anticoagulants, and included dabigatran (n = 32) and rivaroxaban (n = 48). Patients with ACS were more likely to be prescribed dual antiplatelet therapy

TABLE 1 Baseline Characteristics of Patients With Secondary AF With ACS, Acute Pulmonary Disease, or Sepsis

	ACS (n = 827)	Pulmonary Disease (n = 1375)	Sepsis (n = 102)
Age at admission	78.5 ± 7.3	79.3 ± 7.6	77.1 ± 7.8
Male	447 (54.1)	689 (50.1)	47 (46.1)
Co-morbidities, 1 yr before admission			
Valvular heart disease	143 (17.3)	169 (12.3)	16 (15.7)
Coronary artery disease	827 (100.0)	536 (39.0)	37 (36.3)
CKD	176 (21.3)	319 (23.2)	26 (25.5)
Hyperlipidemia	407 (49.2)	453 (33.0)	30 (29.4)
Liver disease	18 (2.2)	52 (3.8)	8 (7.8)
History of bleeding event	33 (4.0)	71 (5.2)	3 (2.9)
Specific components of $CHADS_2$ score			
CHF	258 (31.2)	278 (20.2)	17 (16.7)
Hypertension	540 (65.3)	857 (62.3)	66 (64.7)
Age >75 yrs	545 (65.9)	958 (69.7)	56 (54.9)
Diabetes	239 (28.9)	353 (25.7)	30 (29.4)
History of stroke/TIA	15 (1.8)	24 (1.8)	2 (2.0)
$CHADS_2$ score			
Low ($CHADS_2$ score 0)	93 (11.3)	128 (9.3)	11 (10.8)
Moderate (CHADS2 score 1)	184 (22.3)	410 (29.8)	34 (33.3)
High ($CHADS_2$ score ≥2)	550 (66.5)	837 (60.9)	57 (65.9)
HASBLED score			
Low and moderate (1-2)	335 (40.5)	723 (52.6)	45 (44.1)
High (≥3)	492 (59.5)	652 (47.4)	57 (55.9)
Medications, prescriptions filled within 30 days of discharge			
NSAIDs	11 (1.3)	20 (1.5)	3 (3.0)
Single antiplatelet*	272 (32.9)	439 (31.9)	35 (34.3)
Dual antiplatelet†	149 (18.0)	36 (2.6)	1 (0.9)
Anticoagulant‡ only	85 (10.2)	317 (23.1)	18 (17.6)
Single antiplatelet and anticoagulant	149 (18.0)	139 (10.1)	10 (9.8)
Dual antiplatelet and anticoagulant	82 (9.9)	7 (0.5)	0 (0.0)
Anticoagulant prescription filled within 30 days of admission	316 (38.4)	463 (34.1)	28 (27.7)
Primary treating physician during hospitalization			
General practitioner	319 (38.5)	846 (61.5)	54 (52.9)
Internist	43 (5.2)	239 (17.4)	22 (21.6)
Cardiologist	454 (54.9)	30 (2.2)	2 (2.0)

Values are mean ± SD or n (%). *Single antiplatelet indicates discharge with either aspirin or clopidogrel. †Dual antiplatelet indicates discharge with combination of aspirin and clopidogrel. ‡Anticoagulant indicates discharge with warfarin or direct oral anticoagulant (dabigatran, rivaroxaban, or apixaban).

ACS = acute coronary syndrome; AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or TIA; CKD = chronic kidney disease; HASBLED = hypertension, abnormal renal function, abnormal liver function, history of stroke/TIA, history of bleeding, labile international normalized ratio, age >65, drug therapy [antiplatelet agents, NSAIDs], and alcohol intake; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation; TIA = transient ischemic attack.

without anticoagulant (18.0% compared with 2.6% and 0.9%), single antiplatelet and anticoagulant (18.0% compared with 10.1% and 9.8%), and triple therapy of dual antiplatelet therapy and anticoagulant (9.9% compared with 0.5% and 0.0%).

INCIDENCE OF STROKE. Mean follow-up time was 3.6, 3.1, and 3.1 years in ACS, acute pulmonary disease, and sepsis groups, respectively. Overall incidence of ischemic stroke was 5.4% in ACS (1.37 per 100 person-years), 3.9% in acute pulmonary disease (1.10 per 100 person-years), and 5.9% in sepsis (1.63 per 100 person-years) (Table 2). Anticoagulant use, in comparison to no-anticoagulant use, did not lower crude stroke rates in any of the groups (5.7 vs. 5.3%, p = 0.83; 4.3 vs. 3.7%, p = 0.57; 7.1 vs. 5.5%, p = 0.75) in ACS, acute pulmonary disease, and sepsis, respectively. In multivariate regression analysis, we failed to identify any association with a lower risk of stroke in ACS, acute pulmonary disease, and sepsis (OR: 1.22 [95% CI: 0.65 to 2.27], OR: 0.97 [95% CI: 0.53 to 1.77], OR: 1.98 [95% CI: 0.29 to 13.47]), respectively, after adjusting for potential confounders (CHF, hypertension, age, diabetes, stroke/TIA) (Figure 1).

INCIDENCE OF BLEEDING. Overall incidence of bleeding was 13.5% (3.67 per 100 person-years) in ACS, 13.4% (4.17 per 100 person-years) in acute pulmonary disease, and 19.6% (6.23 per 100 person-years) in sepsis (Table 3). Anticoagulant use, in comparison to no-anticoagulant use, increased crude bleeding rates in acute pulmonary disease (16.8 vs. 11.8%, p < 0.05) but did not significantly increase crude bleeding rates in ACS or sepsis (16.1 vs. 12.1%, p = 0.10; 17.9 vs. 20.5%, p = 0.76). After controlling for potential confounders (hypertension, CKD or liver disease, history of stroke/TIA, NSAID use or antiplatelet use, history of bleeding) in multivariate regression analysis, anticoagulant use was associated with a higher risk of bleeding in acute pulmonary disease (OR: 1.72 [95% CI: 1.23 to 2.39], but was inconclusive in ACS or sepsis (OR: 1.42 [95% CI: 0.94 to 2.14]; OR: 0.96 [95% CI: 0.29 to 3.21]) (Figure 1).

DISCUSSION

With follow-up of ~3 years, our study found that anticoagulant use was not associated with a lower risk of ischemic stroke in patients with new-onset AF associated with ACS, acute pulmonary disease, and sepsis. Meanwhile, anticoagulant use was associated with a higher risk of bleeding in patients with acute pulmonary disease.

We observed that only one-third of patients who developed secondary AF were discharged on anticoagulation. These treatment rates were lower when compared with similar retrospective cohort studies examining new-onset AF as a primary diagnosis in which anticoagulation proportion rates of 46% to 60% were observed (17-19). During most of the years included in our study (1998 through 2015), there were no guideline-based anticoagulation recommendations in patients who developed AF secondary to these primary diagnoses. Our study suggests that, during this period, clinicians were less likely to

TABLE 2 Incidence of Ischemic Stroke Following Discharge With Secondary AF With ACS, Acute Pulmonary Disease, or Sepsis

	ACS (n = 827)*		Pulmonary Disease (n = 1,375)†		Sepsis (n = 102)‡	
Primary Diagnosis	No. of Events (%)	Incidence Rate per 100 Person-yrs§	No. of Events (%)	Incidence Rate per 100 Person-yrs§	No. of Events (%)	Incidence Rate per 100 Person-yrs§
Ischemic stroke‖	45 (5.4)	1.37	53 (3.9)	1.10	6 (5.9)	1.63
Treated with anticoagulant (within 30 days of discharge)	18 (5.7)	1.50	20 (4.3)	1.19	2 (7.1)	2.68
Low ($CHADS_2$ score = 0)	2 (6.3)	1.61	0 (0)	0	0 (0)	0
Moderate ($CHADS_2$ score = 1)	4 (5.6)	1.18	4 (3.3)	0.71	0 (0)	0
High ($CHADS_2$ score = 2)	12 (5.7)	1.64	16 (5.3)	1.67	2 (11.1)	4.77
Not treated with anticoagulant (within 30 days of discharge)	27 (5.3)	1.29	33 (3.7)	1.06	4 (5.5)	1.36
Low ($CHADS_2$ score = 0)	0 (0.0)	0	2 (2.3)	0.48	0	0
Moderate ($CHADS_2$ score = 1)	7 (6.3)	1.25	10 (3.6)	0.97	2 (8.7)	2.28
High ($CHADS_2$ score = 2)	20 (6.0)	1.62	21 (4.0)	1.26	2 (5.1)	1.24

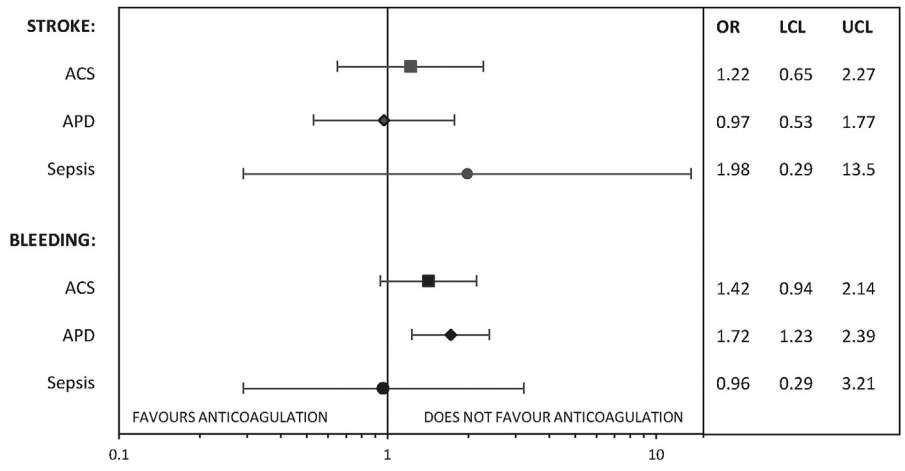
*Patients with ACS treated with anticoagulant (n = 316) and not treated with anticoagulant (n = 506). †Patients with acute pulmonary disease treated with anticoagulant (n = 463) and not treated with anticoagulant (n = 895). ‡Patients with sepsis treated with anticoagulant (n = 28) and not treated with anticoagulant (n = 73). §Incidence rates were calculated with the following formula: number of events/total follow-up time (100 person-years). ‖Ischemic stroke was defined as first hospital admission or emergency department visit for cerebral thrombosis, embolism, or artery occlusion, including TIA and retinal infarct.

Abbreviations as in Table 1.

anticoagulate patients with secondary AF compared with patients with a primary diagnosis of AF.

After adjusting for confounders (the individual components of $CHADS_2$ score), the use of anticoagulation was not associated with a lower risk of ischemic stroke in the primary diagnoses. Crude bleeding rate was higher in the acute pulmonary disease cohort. After adjusting for confounders (the individual components of HASBLED score), the use of anticoagulation was associated with a higher risk of bleeding in acute pulmonary disease, with a trend toward an association with ACS as well. We also observed that bleeding rates in the ACS patients, although often frequently also treated with antiplatelet agents, were not higher than acute pulmonary disease and sepsis cohorts.

FIGURE 1 Anticoagulant Use and the Risk of Ischemic Stroke and Bleeding in Patients With Secondary Atrial Fibrillation Associated With Acute Coronary Syndrome, Acute Pulmonary Disease, and Sepsis



Multivariate regression analysis for stroke outcome was controlled for potential confounders of the CHADS score (congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack [TIA]). Multivariate regression analysis for bleeding outcome was controlled for potential confounders of the HASBLED score (hypertension, abnormal renal function/abnormal liver function, history of stroke/TIA, history of bleeding, age >65 years, drug therapy [antiplatelet agents, NSAIDs]), ACS = acute coronary syndrome; APD = acute pulmonary disease.

TABLE 3 Incidence of Bleeding Following Discharge With Secondary AF With ACS, Acute Pulmonary Disease, or Sepsis

	ACS (n = 827)*		Pulmonary Disease (n = 1,375)†		Sepsis (n = 102)‡	
Primary Diagnosis	No. of Events (%)	Incidence Rate per 100 Person-yrs§	No. of Events (%)	Incidence Rate per 100 Person-yrs§	No. of Events (%)	Incidence Rate per 100 Person-yrs§
Bleeding‖	112 (13.5)	3.67	184 (13.4)	4.17	20 (19.6)	6.23
Treated with anticoagulant (within 30 days of discharge)	49 (16.3)	4.77	74 (18.1)	5.13	5 (20.0)	7.66
Low and moderate risk (HASBLED = 0–2)	23 (17.6)	4.85	42 (17.3)	4.22	1 (9.1)	2.83
High risk (HASBLED ≥3)	26 (15.3)	4.71	32 (19.2)	7.14	4 (28.6)	13.38
Not treated with anticoagulant (within 30 days of discharge): total	63 (12.1)	3.11	110 (11.6)	3.70	15 (19.7)	5.88
Low and moderate risk (HASBLED = 0–2)	20 (10.0)	2.30	46 (9.9)	3.05	8 (24.2)	7.33
High risk (HASBLED ≥3)	43 (13.4)	3.67	64 (13.3)	4.38	7 (16.3)	4.79

*Patients with ACS treated with anticoagulant (n = 301) and not treated with anticoagulant (n = 521). †Patients with acute pulmonary disease treated with anticoagulant (n = 410) and not treated with anticoagulant (n = 948). ‡Patients with sepsis treated with anticoagulant (n = 25) and not treated with anticoagulant (n = 76). §Incidence rates were calculated with the following formula: number of events/total follow-up time (100 person-years). ‖Bleeding was defined as intracerebral bleeding, gastrointestinal bleeding, intraocular bleeding, hematuria, hemoptysis, epistaxis, and unspecified location of bleeding.

Abbreviations as in Table 1.

Our study included patients who were all older adults (age >65 years), who also had frequent comorbidities. Thus, ~45% to 60% of patients had high HASBLED scores (≥3) and ~60% to 65% of patients had high CHADS score (≥2) (Table 1). Net clinical benefit of anticoagulation in primary AF has been shown to be highest in patients with highest risk scores in both $CHADS_2$ and HAS-BLED scores. In this patient population, a wider gap between stroke risk and bleeding risk has been observed; thus, more is to be gained from anticoagulation treatment (20). However, despite our high-risk patient populations, we did not observe this benefit to anticoagulation.

One possibility for the lack of observed benefit in anticoagulation is that risk of stroke and bleeding may be different in secondary AF compared with primary AF. In our secondary AF cohorts, we observed higher bleeding risks (3.6 to 6.2 per 100 person-years) than stroke risks (1.1 to 1.6 per 100 person-years). These observed stroke risks in our secondary AF cohorts were lower when compared with stroke risks in similar primary AF study cohorts (1.6 to 2.5 per 100 person-years) (17-19). In contrast, the bleeding risks in our secondary AF patients were higher than bleeding risks in primary AF patients (1.5 to 4.3 per 100 person-years) (18,21).

The lack of observed benefit in anticoagulation in our study also contrasts prior retrospective studies examining new-onset, transient AF in ACS (10,11). Zusman et al. (10) found warfarin use to be a significant predictor of stroke-free survival. This study, however, reported a much higher baseline history of stroke of 17% in the AF group, suggesting that perhaps a higher number of these patients may have experienced undiagnosed AF before presentation. Asanin et al. (11) found that patients who received anticoagulation therapy at hospital discharge had a significantly decreased risk of ischemic stroke. Meanwhile, this study showed that 34% of the patients without AF were discharged on anticoagulation. This might suggest alternative, unmeasured reasons for anticoagulation that also would increase risk of cardioembolic stroke, such as an anterior myocardial infarction or cardiomyopathy.

Prior studies have shown that AF in sepsis is associated with both higher in-hospital and 5-year stroke risk when compared with patients with no AF (4,5). Meanwhile, outcomes of anticoagulation following hospital discharge have not been studied in these patients. Stroke risk in new-onset AF associated with pulmonary disease, and subsequent outcomes from anticoagulation, also has not been studied. Thus, our study is the first designed to determine if these patient populations would benefit from long-term anticoagulation.

STUDY LIMITATIONS AND STRENGTHS. The main limitations of our study are due to its reliance on administrative data. Our inclusion and exclusion criteria were designed to capture only those patients with new-onset, transient AF resulting from a reversible primary etiology. In efforts to create this cohort, we required that AF was both reported and then subsequently coded as an admission complication. The true incidence of patients who developed transient AF during a hospital admission is likely higher given the known risk of brief, self-terminated episodes of AF that may be undetected or

underreported. This failure to capture all secondary AF likely limited our sample size. Meanwhile, we used varied strategies in attempt to exclude pre-existing AF; however, we were unable to determine that our cohort included only patients with *transient* AF. Unlike the previous smaller, retrospective studies, we were unable to systematically review both hospitalized electrocardiography to confirm true AF and discharge electrocardiography to document sinus rhythm for inclusion in the study. For example, if AF was coded as a complication, but then persisted at discharge, it would be included in our cohort. Meanwhile, capturing patients with either primary AF or persistent AF in our cohort would not explain the lack of observed stroke reduction given the known benefits of anticoagulation in primary AF. Lack of observed benefit in anticoagulation in our study could be attributed to further unadjusted, confounding variables. Clinical variables that both increase the likelihood of being anticoagulated and increase the risk of stroke could confound any observed benefit of anticoagulation. For example, variables such as disease severity of the primary diagnosis as well as the duration of AF have been shown to increase stroke risk in ACS (11). Although these variables were not measurable in our study, they might have influenced clinical decision-making regarding anticoagulation as well as stroke risk following discharge. Finally, our study cohort was designed in efforts to include primary diagnoses that were frequently associated with new-onset AF based on the literature. Given the low incidence of stroke, our study may be underpowered to detect a significant risk reduction. However, no trends toward stroke reduction were observed. In the ACS cohort, bleeding rates were increased in the anticoagulation cohort, but the sample size may have not been large enough to show a significant difference. In addition, based on the years of our study cohorts (1999 through 2015), there was infrequent use of DOACs (n = 80) in our overall study population. Clinical interpretation of our study results should be interpreted accordingly, given the improved efficacy and safety of these agents compared with warfarin observed in large randomized trials.

Our study has several strengths. It is the largest retrospective study examining anticoagulation use and ischemic stroke incidence in patients with new-onset AF in ACS. It is the first study assessing post-discharge rates of ischemic stroke and anticoagulation outcomes in patients who develop new-onset AF secondary to acute pulmonary disease or sepsis. It is also the first study that examines bleeding risk following discharge in patients who develop secondary AF associated with any of these primary diagnoses.

CONCLUSIONS

The benefits of anticoagulation in patients who develop secondary AF associated with ACS, acute pulmonary disease, or sepsis remains unclear. We have demonstrated that when considering anticoagulation for stroke prevention, clinicians view these patients differently from patients with primary AF. It is possible that the risk of ischemic stroke in secondary AF should be considered differently than primary AF. Our study did not demonstrate benefit of anticoagulation therapy in stroke reduction; however, it may have been underpowered to detect a significant benefit. Anticoagulation therapy led to a higher risk of bleeding in patients with acute pulmonary disease with a trend toward an association with ACS as well. Our results do not support routine anticoagulant use for ischemic stroke reduction in these patients; rather, careful individual assessment regarding decisions on anticoagulation is warranted. Although most research has been focused on AF secondary to ACS, our study demonstrates the relative importance of AF secondary to acute pulmonary disease, particularly hospitalizations due to COPD, influenza, and pneumonia. Randomized trials examining the role of anticoagulation in these clinical scenarios are needed.

ADDRESS FOR CORRESPONDENCE: Dr. Louise Pilote, Division of Clinical Epidemiology, McGill University Health Centre, 1001 Decarie Boulevard, Room D05.5021, Montreal, Quebec H4A 3J1, Canada. E-mail: louise.pilote@mcgill.ca.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Medical Knowledge: The benefits of anticoagulation in secondary AF associated with ACS, acute pulmonary disease, or sepsis is not strong and may be associated with increased bleeding risk, particularly in patients admitted with acute pulmonary disease (including COPD, pneumonia/influenza, pulmonary embolism, or pleural effusion).

Patient Care: Benefits of anticoagulation at discharge is not strong in patients who develop new-onset, transient secondary AF associated with ACS, acute pulmonary disease, or sepsis.

TRANSLATIONAL OUTLOOK: Randomized controlled trials examining the role of anticoagulation in patients with new-onset, transient secondary AF are required.

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KEY WORDS cerebrovascular accident, myocardial infarction, new onset, warfarin

APPENDIX For a supplemental table, please see the online version of this article.