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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

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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,

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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