Comparative Risks of Ischemic Stroke in Atrial Flutter versus Atrial Fibrillation

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Introduction: The aim of this study was to compare the risk of ischemic stroke in patients who have atrial fibrillation and patients who have atrial flutter. *Methods:* Using inpatient and outpatient Medicare claims data from 2008 to 2014 for a 5% sample of all beneficiaries 66 years of age or older, we identified patients diagnosed with atrial fibrillation and those diagnosed with atrial flutter. The primary outcome was ischemic stroke. In the primary analysis, patients with atrial flutter were censored upon converting to fibrillation; in a secondary analysis, they were not. Survival statistics were used to compare incidence of stroke in patients with flutter and patients with fibrillation. Cox proportional hazards analysis was used to compare the associations of flutter and fibrillation with ischemic stroke after adjustment for demographics and risk factors. *Results:* We identified 14,953 patients with flutter and 318,138 with fibrillation. During a mean follow-up period of 2.8 (±2.3) years, we identified 18,900 ischemic strokes. The annual incidence of ischemic stroke in patients with flutter was 1.38% (95% confidence interval [CI] 1.22%-1.57%) compared with 2.02% (95% CI 1.99%-2.05%) in patients with fibrillation. After adjustment for demographics and stroke risk factors, flutter was associated with a lower risk of stroke compared with fibrillation (hazard ratio .69; 95% CI .60-.79, $P < .05$). Within 1 year, 65.7% (95% CI 64.9%-66.4%) of patients with flutter converted to fibrillation but remained at a lower risk of ischemic stroke (hazard ratio .85; 95% CI .78-.92). *Conclusions:* Patients with atrial flutter faced a lower risk of ischemic stroke than patients with atrial fibrillation. **Key Words:** Stroke—atrial flutter—atrial fibrillation—arrhythmia.
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Atrial dysrhythmias are associated with an increased risk of ischemic stroke. Atrial fibrillation is a common cause of ischemic stroke and is the most common cause of cardioembolic stroke.[1-3] Patients with atrial fibrillation face a heightened stroke risk, and half of all ischemic strokes in high-income countries are attributed to atrial fibrillation.[4] A related and less prevalent atrial dysrhythmia, atrial flutter, is also associated with an increased risk of ischemic stroke.[5,6] The magnitude of stroke risk in patients with atrial flutter as compared with fibrillation remains unclear.

Stroke prevention guidelines recommend anticoagulation for patients with either atrial fibrillation or flutter.[7,8] Previous studies have shown an increased risk of stroke in patients with atrial flutter as compared with the general population.[3,4] However, a head-to-head comparison of stroke

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risk in patients with fibrillation and patients with flutter has not been performed. Given the uncertainty and potential clinical implications, we used inpatient and outpatient Medicare claims data to compare the rate of stroke in patients with atrial flutter and patients with atrial fibrillation.

Methods

Design

We performed a retrospective cohort study using administrative claims data from 2008 to 2014 on a 5% sample of Medicare beneficiaries. The Centers for Medicare and Medicaid provides these deidentified data for research purposes.[9] In the dataset, beneficiaries are given an anonymous identification number that allows for longitudinal tracking across all care settings while enrolled in Medicare. Administrative claims data such as these are useful for population-based epidemiological studies of stroke risk factors, especially risk factors that are relatively rare within the population, such as atrial flutter.[10,11] The Weill Cornell Medical Center Institutional Review Board approved our analysis.

Patient Population

We limited our cohort to patients 66 years of age or older to allow 1 year for patients to enter care as Medicare beneficiaries and for providers to document preexisting comorbidities. We only included beneficiaries with continuous coverage in traditional fee-for-service Medicare (both Parts A and B) for at least 1 year (or until death, if applicable).[12] Our sample included patients with a diagnosis of either atrial fibrillation or atrial flutter. Atrial flutter was defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* code 427.32, and atrial fibrillation was defined by *ICD-9-CM* diagnosis code 427.31. These *ICD-9-CM* codes have been previously validated to have a positive predictive value ranging from 70% to 96% when compared to expert medical record review for the ascertainment of atrial fibrillation or flutter.[13] Patients with a documented stroke before or at the same time as their first diagnosis of atrial fibrillation or flutter were excluded. In a sensitivity analysis, we limited our cohort to patients with atrial fibrillation and atrial flutter diagnosed specifically by a cardiologist.

Measurements

Our primary outcome of interest was ischemic stroke, identified using a previously validated *ICD-9-CM* diagnosis code algorithm with a sensitivity of 86%, specificity of 95%, and positive predictive value of 90%.[14] A diagnosis of ischemic stroke under this algorithm required an inpatient claim for *ICD-9-CM* codes 433.x1, 434, or 436 in any hospital discharge diagnosis position in the absence of a concomitant code for rehabilitation (V57) or traumatic brain injury (800 to 804, 850 to 854).[14]

Additional covariates included were demographics and traditional vascular risk factors. Patients' age, sex, and self-reported race were all determined from the Medicare denominator file. We used *ICD-9-CM* codes from all visits preceding the index diagnosis of atrial fibrillation or flutter to ascertain the following vascular risk factors: hypertension, diabetes mellitus, coronary artery disease, peripheral vascular disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, valvular heart disease, alcohol abuse, and tobacco use.[15] We used comorbidity data to calculate patients' CHA_2DS_2-VASc scores and Charlson comorbidities.[16,17] The Charlson Comorbidity Index reflects a comprehensive set of baseline comorbidities and predicts overall mortality.[17] Additionally, *ICD-9-CM* codes were used to identify patients with prior bleeding.[18] To account for possible differences in anticoagulation use, we performed separate analyses in which we additionally adjusted our models for the remaining comorbidities in the Charlson Comorbidity Index and prior bleeding as these factors may influence physicians' decisions regarding anticoagulation.

Statistical Analysis

Baseline characteristics were compared using the χ^2 test and the *t* test, when appropriate. We used descriptive statistics with binomial exact confidence intervals (CIs) to calculate crude rates of ischemic stroke. Survival statistics were used to determine the annual incidence of ischemic stroke and Kaplan–Meier curves were used to present cumulative rates. Because we were interested in understanding the risk of stroke while patients have atrial flutter and not atrial fibrillation, we censored patients with atrial flutter upon diagnosis of atrial fibrillation. However, because flutter and fibrillation frequently co-occur,[19] we performed a secondary analysis in which we did not censor patients with flutter upon diagnosis of fibrillation. This "intention-to-treat" analysis took into account the fact that the natural history of flutter often involves the development of fibrillation.

We also tested the hypothesis that the CHA_2DS_2-VASc score would be associated with the time to conversion from flutter to fibrillation. In a post hoc analysis, we modeled the CHA_2DS_2-VASc scores as a step function instead of a linear function. In all analyses, patients were censored at the time of first ischemic stroke, death, termination of Medicare coverage, or December 31, 2015. We used Cox proportional hazards models to compare the risk of stroke between flutter and fibrillation while adjusting for demographics and stroke risk factors. In an alternative model, we simply adjusted for CHA_2DS_2-VASc scores. All statistical analyses were performed using Stata/MP (Version 14, StataCorp LLC, College Station,

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