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,

Table 1. *Characteristics of patients with atrial fibrillation and patients with atrial flutter*

Characteristic*	Atrial flutter (N = 14,953)	Atrial fibrillation (N = 318,138)
Age, mean (SD), years	76.9 (7.7)	78.4 (8.0)
Female	5957 (39.8)	164,856 (51.8)
Race		
White	13,243 (88.6)	290,426 (91.3)
Black	1134 (7.6)	15,580 (4.9)
Other	576 (3.9)	12,132 (3.8)
Hypertension	6409 (42.9)	158,582 (49.9)
Coronary heart disease	4432 (29.6)	92,038 (28.9)
Congestive heart failure	2488 (16.6)	62,867 (19.8)
Diabetes	2130 (14.2)	54,472 (17.1)
Valvular heart disease	1831 (12.3)	41,562 (13.1)
Chronic obstructive pulmonary disease	1432 (9.6)	35,406 (11.1)
Chronic kidney disease	974 (6.5)	22,120 (7.0)
Peripheral vascular disease	709 (4.7)	16,378 (5.2)
Tobacco use	436 (2.9)	9332 (2.9)
Alcohol abuse	380 (2.5)	7240 (2.3)
CHA_2DS_2-VASc score	3.0 (1.2)	3.3 (1.3)

Abbreviations: SD, standard deviation.
$P < .005$ for all comparisons.
*Data are represented as number (%) unless otherwise specified.

TX). The threshold of statistical significance was set at $\alpha = .05$.

Results

Patient Characteristics

We identified 14,953 patients with atrial flutter and 318,138 with atrial fibrillation. The mean age of patients with flutter was 76.9 years (±7.7 years) and that of patients with fibrillation was 78.4 years (±8.0 years). Patients with flutter were less often female (39.8% versus 51.8%); were less likely to suffer from hypertension, diabetes, and congestive heart failure; and had lower mean CHA_2DS_2-VASc scores (3.0 ± 1.2 versus 3.3 ± 1.3). The prevalence of other vascular risk factors was similar between patients with flutter and fibrillation (Table 1).

During a mean follow-up period of 2.8 (±2.3) years, 18,900 patients were hospitalized for ischemic stroke. Ischemic strokes occurred in 236 patients with atrial flutter and in 18,664 patients with atrial fibrillation. In the primary analysis, in which patients with flutter were censored upon the diagnosis of fibrillation, the annual incidence of ischemic stroke in patients with flutter was 1.38% (95% CI 1.22%-1.57%) versus 2.02% (95% CI 1.99%-2.05%) in patients with fibrillation (Fig 1). After adjustment for demographics and vascular risk factors, atrial flutter was associated with a lower risk of ischemic stroke than fibrillation (hazard ratio [HR] .69; 95% CI .61-.79) (Table 2). In a sensitivity analysis limited to cases of atrial flutter and fibrillation diagnosed by cardiologists only, flutter was associated with a significantly lower risk of stroke than fibrillation, although this association was somewhat attenuated (HR .84; 95% CI .75-.94). In an alternative model adjusted for the CHA_2DS_2-VASc score, atrial flutter was similarly associated with a lower risk of ischemic stroke (HR .69; 95% CI .60-.78). Our results were unchanged when we adjusted for the remaining comorbidities in the Charlson Comorbidity Index and bleeding history (Table 2).

By 1 year after their initial diagnosis of atrial flutter, 65.67% (95% CI 64.91%-66.43%) had received a diagnosis of atrial fibrillation. We found a significant but weak association between the CHA_2DS_2-VASc score and the time from flutter diagnosis until conversion to fibrillation (HR per 1-point increase, 1.02; 95% CI 1.005-1.03). In a post hoc analysis in which we modeled the CHA_2DS_2-VASc scores as a step function instead of a linear function, it appeared that there was an increased risk of conversion from flutter to fibrillation in those with CHA_2DS_2-VASc scores of 5 or higher compared with those with scores lower than 5 (HR 1.10; 95% CI 1.05-1.15).

In a secondary analysis in which patients with atrial flutter were not censored upon diagnosis of atrial fibrillation, the annual incidence of stroke in patients with flutter was 1.57% (95% CI 1.46%-1.70%) compared with the 2.02% (95% CI 1.99%-2.05%) incidence in atrial fibrillation. In this analysis, atrial flutter remained associated with a lower adjusted risk of stroke, although the difference was attenuated (HR .84; 95% CI .41-.92) (Table 2).

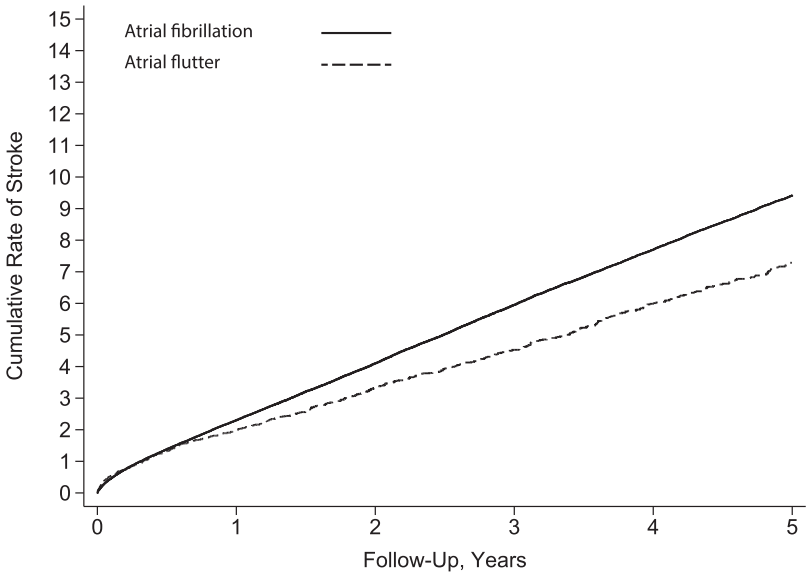

Figure 1. *Cumulative rates of ischemic stroke in patients with atrial flutter versus atrial fibrillation.*

Discussion

In a nationally representative sample of Medicare beneficiaries, we found a lower risk of ischemic stroke in patients with atrial flutter as compared with patients with atrial fibrillation. The risk of risk associated with flutter remained significantly lower regardless of whether we censored patients at the time of fibrillation and in analyses limited to diagnoses made by cardiologists only.

Table 2. *Hazard ratios for ischemic stroke in atrial flutter as compared with atrial fibrillation*

Model	Hazard ratio (95% CI)
Primary analysis: *Patients with atrial flutter censored upon the diagnosis of fibrillation*	
Adjusted for demographics and vascular risk factors	.69 (.61-.79)
Adjusted for CHA_2DS_2-VASc score	.69 (.60-.78)
Adjusted for demographics, vascular risk factors, remaining Charlson comorbidities*, and prior bleeding	.70 (.61-.79)
Secondary analysis: *Patients with atrial flutter not censored upon the diagnosis of fibrillation*	
Adjusted for demographics and vascular risk factors	.84 (.41-.92)
Adjusted for CHA_2DS_2-VASc score	.84 (.77-.90)
Adjusted for demographics, vascular risk factors, remaining Charlson comorbidities*, and prior bleeding	.85 (.79-.92)

Abbreviations: CI, confidence interval.
*Charlson Comorbidity Index quantifies patients' overall morbidity and mortality.

There are few comparative data on the risks of ischemic stroke in atrial flutter versus atrial fibrillation. In a large observational study by Biblo et al, the risk of stroke in patients with atrial flutter appeared lower than the risk in patients with fibrillation, but the 2 conditions were not directly compared, and the study was limited by its exclusive use of inpatient claims data, which likely captured nongeneralizable cases of flutter and fibrillation.[20] Other studies have reported that atrial flutter is associated with an increased risk of stroke and that this risk may be equivalent to the stroke risk in patients with atrial fibrillation, but these studies included relatively few cases of atrial flutter and thus may have lacked sufficient power to conclusively compare stroke risk in these closely related dysrhythmias.[21-24] In contrast to the prevailing clinical understanding, our results suggest that the risk of stroke associated with atrial flutter is not equivalent to the risk associated with atrial fibrillation.

Our findings are in parallel with studies of the burden of atrial fibrillation and stroke risk. Although it was long taught that the risk of stroke was similar regardless of the burden of atrial fibrillation, recent studies have indicated that the risk of stroke is higher in permanent rather than paroxysmal atrial fibrillation.[25] In this context, our study adds further evidence that specific features of atrial dysrhythmias may reflect different degrees of associated stroke risk. From a mechanistic point of view, it remains unclear to what degree atrial flutter and fibrillation cause varying rates of thromboembolism and to what degree these different dysrhythmias reflect varying degrees of severity of atrial cardiomyopathy, which in turn causes thromboembolism.[26,27]

Regardless of any differences in pathophysiology and thromboembolic risk between these 2 conditions, we found that most patients with atrial flutter were soon diagnosed with atrial fibrillation, which is consistent with

previous reports.[22,24] When accounting for this high rate of conversion, we found that the risk of stroke in flutter became more similar, although still not equivalent, to stroke risk in fibrillation. In the absence of clear predictors of conversion from flutter to fibrillation, our findings generally support current guidelines that recommend anticoagulation for patients with atrial flutter if it is accompanied by other stroke risk factors.[7,8] If the temporal evolution of these dysrhythmias could be robustly predicted, then more personalized use of anticoagulation may be possible. Our results indicate that the CHA_2DS_2-VASc score is not strongly associated with this temporal evolution from flutter to fibrillation.

Our results should be considered in light of multiple limitations. First, our reliance on administrative claims data may have led to misclassification of both predictors and outcomes. To minimize such misclassification, we used outcome codes that have been previously validated.[13,14] Whereas diagnosis codes 427.3x allow reliable ascertainment of atrial fibrillation and/or flutter as an overall group of related dysrhythmias,[13] the specificity of codes 427.31 and 427.32 for the individual conditions is uncertain. Bias may be possible if clinicians systematically classified ambiguous dysrhythmias in lower risk patients as atrial flutter and those in higher risk patients as atrial fibrillation, but this seems unlikely given the prevailing clinical teaching that these 2 conditions have similar stroke risk. Furthermore, we found a lower risk of stroke in flutter versus fibrillation even in sensitivity analyses that required diagnosis of atrial fibrillation or atrial flutter specifically by a cardiologist, which would be expected to increase the accuracy of these diagnoses. Second, we lacked data on anticoagulant medication use, but it is unlikely that our results were explained by a higher rate of anticoagulant therapy in atrial flutter versus fibrillation given current guidelines and the prevailing understanding of stroke risk in these 2 conditions.[7,8] Third, the patients in our cohort were at least 66 years old, so our findings may not be generalized to younger patients.

Conclusions

Among a nationally representative cohort of elderly Americans, patients with atrial flutter faced a lower risk of ischemic stroke than patients with atrial fibrillation. Strategies to identify patients with isolated atrial flutter may allow for more personalized anticoagulation recommendations, although it must be kept in mind that most cases of atrial flutter soon evolve into atrial fibrillation.

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