



Original Article

# Atrial Fibrillation and Acute Ischemic Stroke: Evaluation of the Contemporary 2018 National Inpatient Sample Database

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## ABSTRACT

**Background:** Atrial fibrillation (AF) in acute ischemic stroke (AIS) is considered a binary entity regardless of AF type. We aim to investigate in-hospital morbidity and mortality among patients with non-paroxysmal AF-related AIS.

**Methods:** Patients hospitalized for AIS with associated paroxysmal or persistent AF were identified from the 2018 national inpatient sample database. We compared in-hospital mortality, stroke-related morbidity, hospital cost, length of stay, and discharge disposition in patients hospitalized with paroxysmal or persistent AF.

**Results:** A total of 26,470 patients were hospitalized for AIS with paroxysmal or persistent AF. Patient with AIS with persistent AF had a longer hospital length of stay (paroxysmal AF, mean [M] 5.7 days,

## RÉSUMÉ

**Contexte :** La fibrillation auriculaire (FA) dans l'accident vasculaire cérébral (AVC) ischémique aigu est considérée comme une entité binaire, quel que soit le type de FA. Nous voulons étudier la morbidité et la mortalité chez les patients hospitalisés pour un AVC ischémique aigu lié à une FA non paroxystique.

**Méthodologie :** Des patients hospitalisés pour un AVC ischémique aigu accompagné d'une FA paroxystique ou persistante ont été répertoriés à partir d'une base de données d'échantillons de patients hospitalisés à l'échelle du pays en 2018. Nous avons comparé la mortalité à l'hôpital, la morbidité liée à l'AVC, le coût de l'hospitalisation, la durée du séjour et les dispositions du congé chez les patients hospitalisés pour une FA paroxystique ou persistante.

Atrial fibrillation (AF) is a prominent source of morbidity and mortality in the world.<sup>1-4</sup> AF's onset and progression herald a worsening prognosis in heart failure,<sup>5</sup> ischemic heart disease,<sup>6,7</sup> and lung disease.<sup>8</sup> AF is classified based on temporal patterns, ranging from paroxysmal episodes, sudden onset, and self-termination within 7 days, to persistent AF, which signifies a larger burden of time in AF.<sup>9-12</sup> The pattern of AF provides indirect evidence about the burden of AF in patients with acute ischemic stroke (AIS).

The risk of thromboembolism from AF in AIS does not account for the burden or pattern of AF.<sup>13</sup> Major stroke events lead to a significantly disabling quality of life.<sup>14</sup> AIS prevention in AF is centred around anticoagulation, without active discussion regarding reduction of AF burden to reduce AIS-related events in addition to thromboprophylaxis. Further evidence is required to determine the impact of AF pattern on acute AIS-related morbidity and mortality; determining the direction of the impact of AF pattern on AIS morbidity and mortality may assist in this regard.<sup>15</sup> Therefore, we aimed to evaluate a set of real-world contemporary national inpatient sample (NIS) data from 2018 to study the effect of persistent vs paroxysmal AF pattern on acute AIS hospitalizations and their related morbidity, length of stay, hospital costs, and mortality.

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**Ethics Statement:** The analysis has adhered to the HCUP agency guidelines for methodological research (<https://www.hcup-us.ahrq.gov/db/nation/nis/nischecklist.jsp>). The research has adhered to the relevant ethical guidelines. The study was deemed exempt from IRB approval at Tulane University because it utilized deidentified data. All data and materials are publicly available at the HCUP agency website.

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See page 518 for disclosure information.

## Methods

### Study data

We used in-hospital discharge data available from the NIS 2018, from the Healthcare Cost and Utilization Project

standard deviation [SD]  $\pm 6.8$  days; persistent AF, M 7.4 days, SD  $\pm 11.9$  days,  $P < 0.001$ ) and in-hospital costs (paroxysmal AF, M \$15,449, SD  $\pm$ \$18,320; persistent AF, M \$19,834 SD  $\pm$ \$23,312,  $P < 0.001$ ). Patients with AIS with permanent AF had higher in-hospital mortality (paroxysmal AF, 4.6%, vs permanent AF, 6.2%,  $P < 0.001$ ). Indirect markers of stroke-related disability, like intracranial hemorrhage (odds ratio [OR]: 1.9, 95% confidence interval (CI): 1.6-2.2), need for gastrostomy (OR: 2.1, 95% CI: 1.8-2.4), and tracheostomy (OR: 3.1, 95% CI: 2.1-4.4) were more associated with AIS from persistent AF.

**Conclusions:** Persistent AF is associated with poor in-hospital stroke-related outcome, possibly due to a worse thrombo-embolic phenomenon. AF pattern may be a harbinger of worse stroke-related morbidity.

(HCUP), Agency for Healthcare Research and Quality. The NIS is an extensive, publicly available, all-payer administrative claims database, with information from a 20% sample of over 1000 hospitals in 47 states, representing 97% of the US population.<sup>16</sup> The NIS is designed to produce US national estimates of inpatient utilization, access, charges, quality, and outcomes, using the International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS) along with patient demographics, discharge status, length of stay, severity, and comorbidity measures.<sup>17</sup> National estimates of the entire US hospitalized population are calculated using the standardized HCUP sampling and weighting method.<sup>18</sup> All data and materials are publicly available at the HCUP agency website.<sup>19</sup>

### Study population

Discharges with a principal admission diagnosis of AIS (ICD-10-CM/PCS code I63) were identified. A principal diagnosis is the diagnosis for admission. The study population was further subdivided into those with paroxysmal AF and those with persistent AF, identified by the presence of listed ICD-10-CM/PCS codes in the secondary diagnosis fields. We also evaluated morbidity and mortality from permanent AF. Comorbidities were obtained using the Clinical Classifications Software Refined for ICD-10-CM diagnoses,<sup>20</sup> which aggregates more than 70,000 ICD-10-CM diagnosis codes into over 530 clinically meaningful categories. Using the logic put forward by the Agency for Healthcare Research and Quality, we identified coexisting medical conditions that were not related to the principal reason for admission and were likely to be conditions that originated before admission. The following comorbid conditions were included in the analysis: hypertension, diabetes mellitus, dyslipidemia, smoking history, coronary artery disease, peripheral arterial disease, obstructive sleep apnea, heart failure, prior cardiac surgery, presence of pacemaker/defibrillator, cognitive decline/dementia, prior stroke, alcohol history, rheumatic valve disease, chronic

**Résultats :** Au total, 26 470 patients ont été hospitalisés pour un AVC ischémique aigu accompagné d'une FA paroxystique ou persistante. Le séjour à l'hôpital était plus long pour les patients atteints d'un AVC ischémique aigu accompagné d'une FA persistante (FA paroxystique, moyenne [M] de 5,7 jours, écart-type [ET]  $\pm 6,8$  jours; FA persistante, M de 7,4 jours, ET  $\pm 11,9$  jours,  $p < 0,001$ ) et les coûts d'hospitalisation ont été plus élevés dans ce groupe de patients (FA paroxystique, M de 15 449 \$, ET  $\pm 18 320$  \$; FA persistante, M de 19 834 \$, ET  $\pm 23 312$  \$,  $p < 0,001$ ). La mortalité à l'hôpital était plus élevée chez les patients atteints d'un AVC ischémique aigu accompagné d'une FA permanente (FA paroxystique, 4,6 % vs FA permanente, 6,2 %,  $p < 0,001$ ). Des marqueurs indirects d'incapacité liée à l'AVC, comme une hémorragie intracrânienne (rapport des cotes [RC] : 1,9, intervalle de confiance [IC] à 95 % : 1,6-2,2), la nécessité d'une gastrostomie (RC : 2,1, IC à 95 % : 1,8-2,4) ou d'une trachéostomie (RC : 3,1, IC à 95 % : 2,1-4,4) ont été davantage associés à l'AVC ischémique aigu découlant d'une FA persistante.

**Conclusions :** La FA persistante est associée à une issue défavorable liée à l'AVC chez les patients hospitalisés, possiblement en raison d'un phénomène thrombo-embolique aggravé. La forme de la FA peut être annonciatrice d'une plus grande morbidité liée à l'AVC.

obstructive lung disease, obesity, iron/nutritional deficiency anemia, cirrhosis, and severe chronic kidney disease (CKD) (stage 4, 5, end-stage renal disease [ESRD]) (Supplemental Table S1). The CHA<sub>2</sub>DS<sub>2</sub>-VASc (Congestive Heart Failure, Hypertension, Age [ $\geq 75$  Years] [doubled], Diabetes Mellitus, Stroke [doubled], Vascular Disease, Age [65-74] Years, Sex Category [Female]) score was extrapolated from the above variables.

### Study endpoints

The primary endpoint of the study was in-hospital mortality, stroke-related morbidity (intracerebral hemorrhage, sepsis), and indirect measure of functional outcome (discharge to facility [non-home discharges], in-hospital tracheostomy, and percutaneous gastrostomy tube placement). Secondary endpoints were cost of hospitalization, length of stay, and All Patient Refined Diagnosis Related Groups (APR-DRGs) payment-related severity of illness class. Admissions with a higher class (eg, major or extreme) are more likely to consume more significant healthcare resources in hospitals than patients with a lower class in the same DRG.

### Statistical analysis

The analysis was done according to the Methodological Standards in Research Using the NIS.<sup>21</sup> The data are presented using survey-specific discharge weights in the NIS to provide the national estimates. Descriptive statistics are presented as frequencies, with percentages for categorical variables. Mean with standard deviation are reported for continuous measures. Baseline characteristics were compared using the  $\chi^2$  test for categorical variables, and the Student *t* test for continuous variables. A multivariate survey-specific logistic regression model was created to determine the odds of AF pattern with the risk of death, brain hemorrhage, sepsis, tracheostomy, gastrostomy, and non-home discharges. The model was adjusted for the following covariates: age, sex, race, insurance, hospital region, hypertension, diabetes mellitus,

**Table 1. Baseline characteristics**

Characteristic	Paroxysmal AF	Persistent AF	P
Total number of hospital admissions	24,240	2230	
Age, y			< 0.001
< 65	15.1	13.0	
65–75	23.6	20.6	
> 75	61.3	66.4	
Female	52.6	52.7	0.9
Race			0.06
White	77.2	74.1	
Black	10.5	11.1	
Hispanic	6.6	9.3	
Others	5.7	5.5	
Comorbidities			
Hypertension	89.5	86.8	0.001
Diabetes	37.8	33.4	0.001
Dyslipidemia	63.9	55.6	< 0.001
Smoker	10.3	8.7	0.02
Coronary artery disease	39.5	38.1	0.2
Peripheral arterial disease	10.9	8.5	0.001
Obstructive sleep apnea	8.9	9.6	0.3
Heart failure	29.7	40.6	< 0.001
Prior cardiac surgery	13.1	10.1	< 0.001
Pacemaker/defibrillator	9.8	8.7	0.1
Dementia	19.2	18.8	0.7
Prior stroke	17.7	14.3	< 0.001
Alcohol use	2.7	2.7	0.9
Rheumatic valvular disease	5.7	8.3	< 0.001
Chronic obstructive lung disease	16.2	13.9	0.005
Obesity	14.3	12.6	0.02
Iron/nutritional deficiency anemia	4.8	2.5	< 0.001
Cirrhosis	1.6	3.8	< 0.001
CKD (stage 4, 5; ESRD)	5.6	3.6	< 0.001
Primary payer			0.3
Medicare	81.2	80.5	
Private	11.8	11.9	
Medicaid/self-pay/other	7.0	7.6	
Hospital characteristics			
Teaching hospital	69.7	74.0	< 0.001
Rural location	8.5	6.7	< 0.001
Bed size: large	49.8	55.4	< 0.001
Stroke-related procedures			
Tissue plasminogen activator	6.4	7.3	0.1
Thrombectomy use	3.4	5	< 0.001

AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Values are percentage (%) of the total number in the groups, unless otherwise indicated.

dyslipidemia, smoking history, coronary artery disease, peripheral arterial disease, obstructive sleep apnea, heart failure, prior cardiac surgery, presence of pacemaker/defibrillator, cognitive decline/dementia, prior stroke, alcohol history, rheumatic valve disease, chronic obstructive lung disease, obesity, iron/nutritional deficiency anemia, cirrhosis, and CKD (stage 4, 5 ESRD). A type I error (*P* value) of < 0.01 was considered statistically significant. All statistical analyses were performed with SPSS software, version 27 (IBM Corp., Armonk, NY).

## Results

### Baseline characteristics

The total sample size was 5294, reflecting a national estimate of 26,470 admissions for AIS with associated AF.

Paroxysmal AF was more common in older patients (age 76.4 ± 10.9 years) than persistent AF (age 77.6 ± 10.7 years; *P* < 0.001). AF pattern was equivalent in both sexes (*P* = 0.9). Paroxysmal AF patients had a higher prevalence of comorbidities, such as diabetes (*P* = 0.001), dyslipidemia (*P* < 0.001), and CKD (*P* < 0.001; [Table 1](#)). Heart failure was more common in persistent AF (*P* < 0.001). No difference in tissue plasminogen activator (tPA) use was seen between the 2 groups (*P* = 0.1). Use of thrombectomy was more prevalent in the persistent AF group (*P* < 0.001). CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were evenly distributed among the 2 admitted groups (paroxysmal AF, mean [M] 4.3, standard deviation [SD] 1.5; persistent AF, M 4.4, SD 1.6, *P* = 0.1; [Fig. 1](#)). Baseline characteristics of permanent AF are listed in [Supplemental Table S2](#).

### Morbidity and functional outcome in persistent vs paroxysmal AF

Evaluation of APR-DRG severity-of-illness classification during AIS hospitalizations and AF pattern established major/extreme loss of function to be significantly more prevalent in the AIS with persistent AF group (paroxysmal AF, 62.3%; persistent AF, 76.9%; *P* < 0.001).

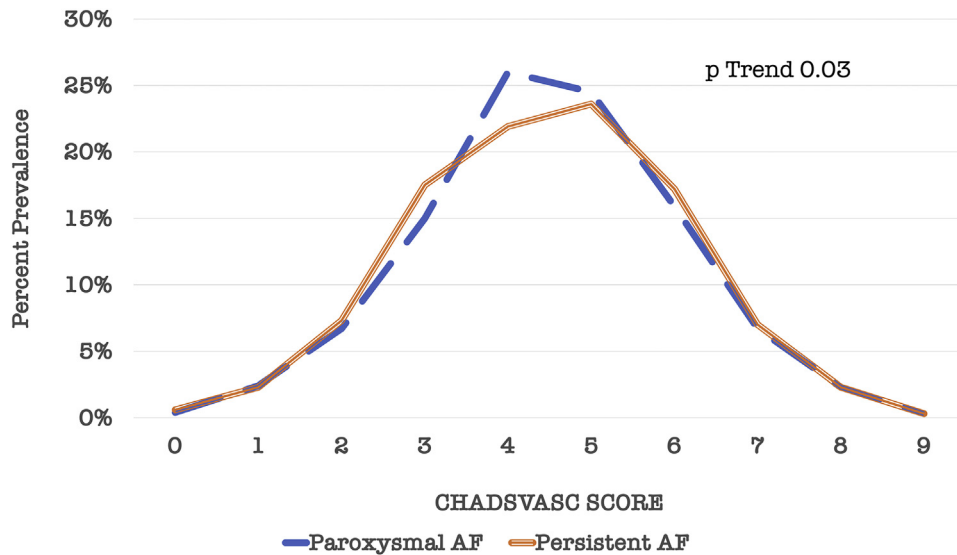
Risk-adjusted multivariate regression analysis was performed to evaluate morbidity, functional outcome, and mortality of AIS and AF patterns with paroxysmal AF as a reference group ([Fig. 2](#)). Stroke-related morbidity and functional outcome was worse in the persistent AF group, with a significant risk of intracranial hemorrhage (odds ratio [OR]: 1.9, 95% confidence interval [CI]: 1.6-2.2), percutaneous gastrostomy placement (OR: 2.1, 95% CI: 1.8-2.4), tracheostomy procedures (OR: 3.1, 95% CI: 2.1-4.4), sepsis (OR: 1.5, 95% CI: 1.2-1.9), and non-home discharge to a facility (OR: 1.2, 95% CI: 1.1-1.4). There was a nonsignificant trend toward increased mortality in the persistent AF group (OR: 1.1, 95% CI: 0.9-1.3).

### In-hospital mortality, procedures, and costs in permanent, persistent vs paroxysmal

As can be seen from [Figure 3](#), the persistent AF group had a higher number of in-hospital procedures (paroxysmal AF: M 1.1, SD ±2.2; persistent AF: M 1.4, SD ±2.4, *P* < 0.001), a longer length of stay in days (paroxysmal AF: M 5.7, SD ±6.8; persistent AF: M 7.4, ±11.9, *P* < 0.001), and higher in-hospital costs in dollars (paroxysmal AF: M \$15,449, SD ±\$18,320; persistent AF: M \$19,834, SD ±\$23,312, *P* < 0.001). AIS with permanent AF had significantly higher in-hospital mortality (paroxysmal AF 4.6% vs permanent AF 6.2%, *P* < 0.001; [Supplemental Table S2](#)).

## Discussion

Our survey analysis of the inpatient hospitalization 2018 NIS data demonstrates a considerable difference in stroke and AF pattern of persistent, vs paroxysmal, AF. The paroxysmal AF phenotype was more prevalent in patients with vascular risk factors, such as diabetes, and a prior history of stroke and dyslipidemia. Persistent AF had a higher prevalence of comorbid heart failure. The overall CHA<sub>2</sub>DS<sub>2</sub>-VASc score was equivalent among both AF-related patterns with AIS. The

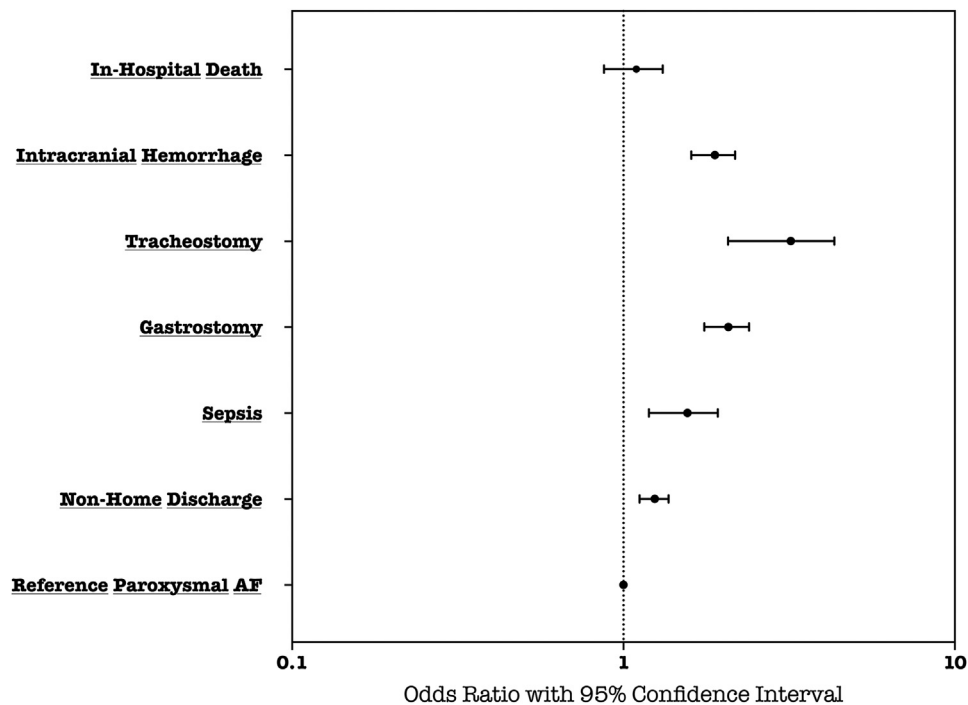


**Figure 1.** Prevalence of **C**ongestive Heart Failure, **H**ypertension, **A**ge ( $\geq 75$  Years) (doubled), **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge (65-74) Years, **S**ex Category (Female) (CHA<sub>2</sub>DS<sub>2</sub>-VASc) score in paroxysmal vs persistent atrial fibrillation (AF).

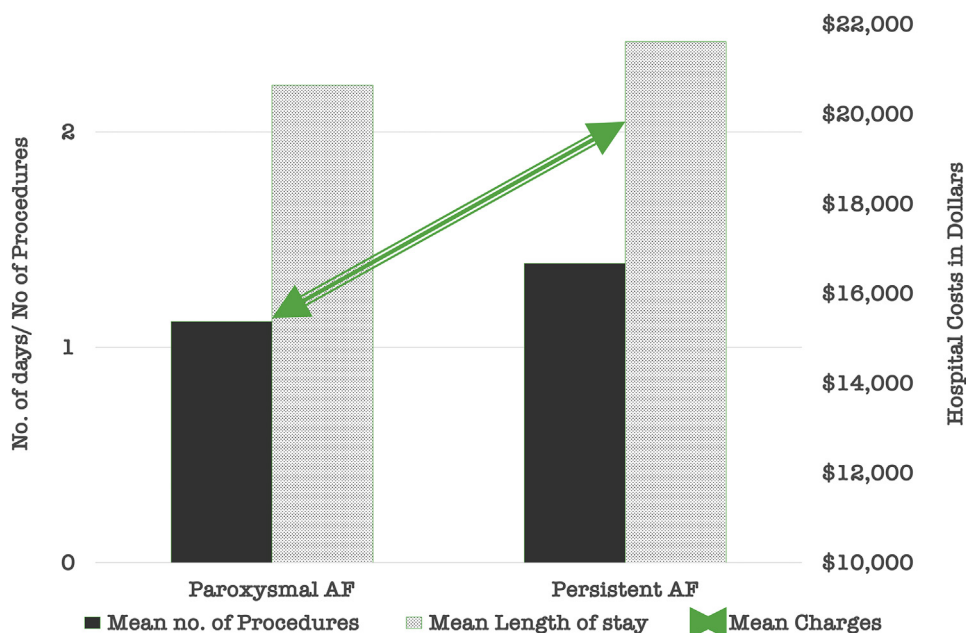
persistent AF group had prolonged in-hospital stay, high inpatient cost, a significantly greater number of tests and procedures, and worse APR-DRG-related severity of illness charted during their stay. On multivariate analysis, AIS stroke patients admitted with persistent AF had worse stroke-related morbidity and functional outcome. This finding was present

despite a similar rate of tissue plasminogen activator use in paroxysmal vs persistent AF patients.

AF increases the hospital cost of AIS substantially, which may reflect severity of stroke, or the added costs of diagnosis and treatment of previously undiagnosed AF. Wang et al. demonstrated that the presence of AF adds 26% to the



**Figure 2.** Risk-adjusted odds of morbidity and mortality in persistent atrial fibrillation (AF) with paroxysmal AF as a reference standard. Morbidity defined intracranial hemorrhage, sepsis, and functional class by need for tracheostomy, gastrostomy tube placement, and non-home discharges. The model is adjusted for: age, sex, race, insurance, hospital region, hypertension, diabetes mellitus, dyslipidemia, smoking history, coronary artery disease, peripheral arterial disease, obstructive sleep apnea, heart failure, prior cardiac surgery, presence of pacemaker/defibrillator, cognitive decline/dementia, prior stroke, alcohol history, rheumatic valve disease, chronic obstructive lung disease, obesity, iron/nutritional deficiency anemia, cirrhosis, and chronic kidney disease (stage 4, 5, end-stage renal disease).



**Figure 3.** Mean number (no.) of procedures, length of stay, and in-hospital costs among patients admitted to the hospital with acute ischemic stroke with different patterns of atrial fibrillation (AF).

inpatient cost of stroke.<sup>22</sup> We further found that length of stay, cost of hospitalization, and payer-related severity were higher in AIS in the presence of persistent, compared with paroxysmal, AF. This issue was not evaluated in previous trials and could account for the contrasting high cost of AIS with AF. This information may be valuable to guide decision-making for resource allocation, especially for those investigating strategies to mitigate cost in patients with stroke.<sup>23</sup>

Stroke-related morbidity leads to significant loss of quality of life and hastens mortality.<sup>24</sup> Deguchi et al.<sup>25</sup>, in a retrospective analysis in Japan, reported that patients admitted with persistent AF and AIS had significantly worse National Institutes of Health Stroke Scale (NIHSS) scores compared to those with paroxysmal AF ( $P < 0.001$ ). At a 90-day follow-up, the persistent AF group also had poor neurologic recovery ( $P < 0.001$ ). Another study, by Inaba et al.<sup>26</sup> attributed this difference to a larger stroke burden in those with persistent AF. In their study, nonparoxysmal AF and stroke patients had a significantly larger infarct brain volume, as assessed by computed tomography or magnetic resonance imaging, compared with patients with paroxysmal AF and stroke (paroxysmal AF, median: 4.4 [interquartile range: 1.1-32] mL; persistent AF median: 64 [interquartile range: 6.9-170] mL;  $P < 0.0001$ ). We report a higher incidence of invasive procedures in AIS patients hospitalized with persistent AF, specifically, thrombectomy, gastrostomy, and tracheostomy. The use of gastrostomy and tracheostomy in AIS patients is an indicator of poor functional recovery.<sup>27</sup> Additionally, patients with AIS and persistent AF had a higher likelihood of being discharged to skilled nursing facilities, hinting at poor neurologic recovery despite an increase in interventions.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc score predicts the risk of AIS in patients with AF with accurate predictability.<sup>28</sup> However, the score has poor validity in predicting the severity of stroke.<sup>29,30</sup>

Persistent AF reflects a multifactorial pathognomonic process of atrial remodeling, coagulopathy, and impending cardiac dysfunction. It signifies a higher burden of AF in patients who are not monitored with devices.<sup>31</sup> The milieu may cause rapid progression and enlargement of thrombogenic foci in the cerebral circulation. This possibility is corroborated by our finding of worse morbidity and functional outcome in AIS patients admitted to the hospital with persistent AF. Catheter ablation reduces AF electrical burden and delays progression of AF pattern. The early rhythm control strategy for AF used in the Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial has demonstrated a reduction in future stroke incidence in addition to use of anticoagulation therapy.<sup>32</sup> Aggressive identification and multidisciplinary management of adverse AF patterns has the potential to reduce morbidity and mortality.

### Limitations

Our study has inherent limitations. First, the NIS is an administrative billing database with an inherent risk of mis-coding errors. The use of a contemporary 2018 database using the ICD-10-CM/PCS ameliorates this discrepancy, to a limit, given its very high sensitivity and positive predictive value in external validation studies.<sup>33,34</sup> Second, evaluation of the burden of AF was not possible, especially in patients with paroxysmal AF, given that some patients may have had silent AF episodes for a long duration. Also, we cannot account for the variability and consistency of coding for AF pattern at different centres. However, this issue does not impact our study finding of a poor morbidity outcome in nonparoxysmal AF patients. Third, improved AF detection techniques may have led to the inclusion of healthier subjects, but this would be limited to outpatients and less likely to impact AF detection in hospitalized patients with AIS.

Furthermore, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in our study was evenly distributed among the 3 groups. Fourth, there is a lack of clinical, laboratory, and imaging data to validate our findings. There is an absence of information on anticoagulation initiation, timing, and implantable AF monitoring devices. We have used surrogates of stroke severity used in multiple prior administrative database studies.<sup>35,36</sup> Fifth, we were unable to exclude other etiologies of AIS, such as large vessel atherosclerosis or small vessel lacunar strokes, which may have impacted our findings. Finally, the bias of unmeasured confounders may have affected the outcome of our study.

## Summary and Conclusions

AIS secondary to a nonparoxysmal AF pattern may contribute to increased length of stay, hospital costs, stroke severity, and mortality. Our study attempts to fill a knowledge gap by attributing the severity of AF burden to severity of stroke. Our findings may help determine a future research focus on the examination of the clinical and economic burden of AIS and allow us to determine the cost effectiveness of interventions for AF in AIS control and prevention.

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## Disclosures

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### Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjopen.ca/> and at <https://doi.org/10.1016/j.cjco.2022.01.010>.