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Original Article

Cardiol Res. 2021;12(4):225-230

Incidence of Acute Ischemic Stroke in Hospitalized Patients With Atrial Fibrillation Who Had Anticoagulation Interruption: A Retrospective Study

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Abstract

Background: Atrial fibrillation (AF) is one of the leading causes of acute ischemic stroke requiring anticoagulation. Many patients experience treatment interruption in the hospital setting. The aim of this study was to evaluate the effect of anticoagulation interruption on short-term risk of ischemic stroke in hospitalized patients with AF.

Methods: We performed a retrospective medical record review using the Hospital Corporation of America (HCA) database. We included patients admitted to our institution between December 2015 and December 2018 who had a prior history of AF. Patients were excluded if they had ischemic stroke, hemorrhagic stroke, history venous thromboembolism or mechanical valve on admission. We compared the incidence of ischemic stroke in patients in whom anticoagulation was interrupted for more than 48 h to those who continued anticoagulation.

Results: A total of 2,277 patients with history of AF were included in the study. In this cohort, 79 patients (3.47%) had anticoagulation interruption of more than 48 h during their hospital stay. There was no difference in incidence of stroke between the interruption and no interruption groups (1.27% (n = 1) vs. 0.23% (n = 5), P = 0.19). Interruption of anticoagulation did not associate with a significant increase in the risk of in-hospital ischemic stroke. CHA_2DS_2VASc score was a strong predictor of in-hospital stroke risk regardless of anticoagulation interruption (odds ratio: 7.199, 95% confidence interval: 2.920 - 17.751).

Conclusion: In this study, the in-hospital incidence of ischemic stroke in patients with AF did not significantly increase by short-term anticoagulation interruption.

Keywords: Atrial fibrillation; Ischemic stroke; CHA_2DS_2VASc score; Anticoagulation; Anticoagulation interruption; AF and stroke; In-hospital stroke

Manuscript submitted May 14, 2021, accepted June 11, 2021
Published online July 9, 2021

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doi: https://doi.org/10.14740/cr1263

Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia and carries with it an increased risk of thromboembolism. Therefore, anticoagulation therapy is indicated in certain patients with AF [1, 2]. Risk factors that increase the likelihood of stroke or systemic thromboembolism have been incorporated into a scoring system (CHA_2DS_2VASc score) which was developed to predict 1-year risk of stroke [3-6]. These risk factors include congestive heart failure (CHF), hypertension (HTN), age, diabetes, history of stroke or transient ischemic attack (TIA), vascular disease and gender. A CHA_2DS_2VASc score of ≥ 2 warrants the use of anticoagulation therapy due to higher risks of stroke.

Anticoagulation interruption is frequently indicated in hospitalized patients, most commonly due to procedures or bleeding. Multiple factors are considered prior to making the decision to interrupt anticoagulation to balance bleeding risk versus risk of stroke. However, anticoagulation management varies widely due to lack of adequate data. The American College of Cardiology (ACC) published the 2017 expert consensus decision pathway for peri-procedural management of anticoagulation [7-9]. However, this approach is taken from studies done in mostly intermediate risk patients undergoing elective outpatient procedures and the management of high-risk patients remains controversial. The aim of this study was to evaluate the effect of anticoagulation interruption on short-term risk of stroke in patients with AF who are hospitalized.

Materials and Methods

A retrospective medical record review of patients admitted with a primary or secondary diagnosis of AF was conducted. Data were pulled from the Hospital Corporation of America

(HCA) database for patients admitted to our institution from December 2015 through December 2018 using Teradata SQL. Analyses were done using SAS 9.4 software. We included patients 18 years or older who were admitted to the hospital with a primary or secondary diagnosis of AF who had anticoagulation interruption without heparin bridge vs. non-interrupted group. We excluded patients who had acute ischemic cerebrovascular accident (CVA), hemorrhagic CVA, mechanical heart valves, previous or current deep vein thrombosis or pulmonary embolism on admission. This study was exempted from IRB, and it was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Definitions

Anticoagulation was defined as the use of warfarin, dabigatran, rivaroxaban, apixaban or edoxaban. We defined anticoagulation interruption as a time frame of more than 48 h off anticoagulation. Primary outcome was the in-hospital incidence of stroke. Secondary outcomes included major bleeding, mortality, readmission rate within 90 days and the average length of hospital stay (LOS). Bleeding was defined according to the ICD 10 codes as follows: acute or chronic gastric ulcer with hemorrhage and/or perforation, acute or chronic duodenal ulcer with hemorrhage and/or perforation, acute or chronic peptic ulcer with hemorrhage and/or perforation, acute or chronic gastrojejunal ulcer with hemorrhage and/or perforation, gastrointestinal hemorrhage, acute bleeding from esophageal varices, epistaxis, hematemesis, melena, acute or chronic gastritis with bleeding, alcoholic gastritis with bleeding, acute or chronic atrophic gastritis with bleeding, acute or chronic duodenitis with bleeding, angiodysplasia with bleeding, hemorrhage of anus or rectum, intracranial hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, extradural hemorrhage and epidural hemorrhage. CHA_2DS_2VASc score was calculated using the description by Lip et al and included age, gender, history of CHF, history of HTN, history of CVA/TIA/thromboembolism, history of vascular disease (prior myocardial infarction (MI), peripheral artery disease (PAD), aortic plaque) and history of diabetes [10-12].

Statistical analysis

Baseline characteristics and outcomes were summarized by frequency tabulation and means with standard deviations as appropriate to compare patients with anticoagulation interruption vs. no interruption. T-tests were used to test for differences in-group means. Chi-square and Fisher's exact tests were used to test for differences in categorical variables (Fisher's exact tests used when one group in the comparison has less than five observations). Data were pulled from the HCA database using Teradata SQL. All analyses were done using SAS 9.4 software.

To further evaluate the effect of anticoagulation interruption on the incidence of ischemic stroke, it was adjusted to $CHADS_2VASc$ score in a logistic regression model.

Results

A total of 2,277 patients were included in the study. In this cohort, mean age was 72.9 ± 11 years and 50.6% were female. A total of 79 patients out of 2,277 (3.47%) had anticoagulation interruption in more than 48 h (median interruption of 67 h). Compared to non-interruption group, patients with anticoagulation interruption were older (mean age 76.35 ± 9.45 vs. 72.76 ± 11.14 years, P = 0.001), had slightly higher $CHADS_2VASc$ score (3.78 vs. 3.42, P = 0.01), more likely to have heart failure and less likely to have HTN. Other characteristics and differences between anticoagulation interruption and non-interruption groups are summarized in Table 1.

Only six patients out of 2,277 (0.26%) had acute ischemic stroke during their hospital stay: one patient (1.27%) in the anticoagulation interruption group, and five patients (0.23%) in the non-interruption group. There was no statistically significant difference in incidence of ischemic stroke between the two groups (1.27% vs. 0.23%, P = 0.19) (Table 2).

Short-term interruption of anticoagulation was not associated with a significant increased risk of in-hospital ischemic stroke. CHA_2DS_2VASc score was an independent strong predictor of in-hospital stroke (odds ratio (OR): 7.199, 95% confidence interval (CI): 2.920 - 17.751) (Table 3). The risk of ischemic stroke increased significantly in the moderate and high risk CHA_2DS_2VASc categories (score ≥ 5), only one patient developed stroke in the anticoagulation interruption group and had a $CHADS_2VASc$ score ≥ 7. None of the patients in the low risk group CHA_2DS_2VASc < 5 had a stroke (Table 4). Details of the six patients who developed a stroke in the hospital are summarized in Table 5.

In terms of secondary outcomes in anticoagulation interruption versus non-interruption groups, results were as follows: mortality (0 vs. 0.23%, P = 1), bleeding (3.8% vs. 0.91%, P = 0.04), number of readmissions within 90 days (48.1% vs. 36.3%, P = 0.04) and average LOS (7.54 vs. 2.5 days, P < 0.0001). There was a statistically significant difference between two groups in terms of bleeding, readmissions and average LOS. There was no difference in in-hospital mortality between the two groups.

Discussion

In this study, the in-hospital incidence of ischemic stroke in patients with AF did not significantly increase with short-term anticoagulation interruption. CHA_2DS_2VASc score was a strong predictor of the risk of in-hospital stroke regardless of anticoagulation interruption. The risk of ischemic stroke was significantly increased in the moderate (CHA_2DS_2VASc score 5 - 6) and high-risk (CHA_2DS_2VASc ≥ 7) groups.

The results of the study are important in two ways. First, previous studies have quantified 30-day and 1-year risk for ischemic stroke [13-16]; however, our study quantifies the short-term in-hospital risk of ischemic stroke in AF patients who are admitted to the hospital. This gives physicians more solid data to weigh risk versus benefit of interrupting anticoagulation in hospitalized patients with high bleeding risk. The CHA_2DS-

Table 1. Patient Characteristics of Anticoagulation Interruption Versus No Interruption Groups

Variables	Anticoagulant interruption 48 h+ (N = 79)	No anticoagulation interruption (N = 2,198)	P-value
Age (mean ± SD)	76.35 ± 9.45	72.76 ± 11.14	0.001
Male, n (%)	32 (40.51)	1,091 (49.64)	0.14
CHA_2DS_2VASc (mean ± SD)	3.78 ± 1.23	3.42 ± 1.33	0.01
Ischemic CVA, n (%)	1 (1.27)	5 (0.23)	0.19
CHF, n (%)	43 (54.43)	666 (30.30)	< 0.001
HTN, n (%)	31 (39.24)	1,247 (56.73)	0.002
Age ≥ 75 years, n (%)	49 (62.03)	1,039 (47.27)	0.011
Age 65 - 74 years, n (%)	21 (26.58)	731 (33.26)	0.23
Diabetes, n (%)	20 (25.32)	629 (28.62)	0.61
Vascular disease, n (%)	37 (46.84)	972 (44.22)	0.65
Bleeding, n (%)	3 (3.80)	20 (0.91)	0.04
Mortality, n (%)	0 (0)	5 (0.23)	1.00
Readmission within 90 days, n (%)	38 (48.10)	799 (36.35)	0.04
Average LOS (mean ± SD)	7.54 ± 4.58	2.55 ± 2.19	< 0.0001

SD: standard deviation; CVA: cerebrovascular accident; CHF: congestive heart failure; HTN: hypertension; LOS: length of hospital stay.

$_2$VASc score was formulated to predict the 1-year risk of ischemic stroke and has not been validated to predict short-term outcomes. Our study supports the common practice of using CHA_2DS_2VASC score as a predictor of short-term ischemic stroke risk in hospitalized patients with AF.

Second, our study included hospitalized patients with AF who had anticoagulation interruption for any reason. Most studies on anticoagulation interruption included patients undergoing elective procedures. The BRIDGE trial which was the first prospective multicenter randomized controlled trial of patients with AF undergoing procedures showed no significant difference between treatments interrupted group compared to non-interrupted group with regards to stroke, systemic thromboembolism or TIA at 30 days. In our study

Table 2. Association of Selected Factors With Acute In-Hospital Ischemic Stroke in Hospitalized Patients With a History of AF

Variables	Ischemic CVA	No ischemic CVA	P-value
Age (mean ± SD)	77.00 ± 6.57 (N = 6)	72.87 ± 11.12 (N = 2,271)	0.1853
Male, n (%)	2 (33.33)	1,121 (49.36)	0.6873
Female, n (%)	4 (66.66)	1,150 (50.64)	0.6873
CHA_2DS_2VASc (mean ± SD)	6.00 ± 0.894	3.4280 ± 1.32	0.0009
CHF, n (%)	1 (16.67)	708 (31.18)	0.6725
HTN, n (%)	5 (83.33)	1,273 (56.05)	0.2392
Age ≥ 75 years, n (%)	4 (66.67)	1,084 (47.73)	0.4342
Age 65 - 74 years, n (%)	2 (33.33)	750 (33.03)	1.0000
Diabetes, n (%)	2 (33.33)	647 (28.49)	0.6803
Vascular disease, n (%)	2 (33.33)	1,007 (44.34)	0.6991
Anticoagulation interrupted, n (%)	1 (16.67)	78 (3.43)	0.1911
No anticoagulation interruption, n (%)	5 (83.33)	2,193 (96.57)	0.1911
Bleeding, n (%)	0 (0)	23 (1.01)	1.000
Mortality, n (%)	0 (0)	5 (0.22)	1.000
Readmission within 90 days, n (%)	3 (50)	834 (36.72)	0.6754
Average LOS (mean ± SD)	6.50 ± 10.13	2.71 ± 2.44	0.4021

AF: atrial fibrillation; SD: standard deviation; CVA: cerebrovascular accident; CHF: congestive heart failure; HTN: hypertension; LOS: length of hospital stay.

Table 3. CHA_2DS_2VASc Significantly Associated With the Outcome Variable of In-Hospital CVA

Effect	Odds ratio	95% Confidence interval	
Any interruption 48+ h (1: presence vs. 0: no presence)	4.21	0.39	44.89
CHA_2DS_2VASc	7.20	2.92	17.75

Patients with higher CHA_2DS_2VASc scores are more likely than those with lower CHA_2DS_2VASc scores to have an in-hospital CVA. CHA_2DS_2VASc: congestive heart failure/left ventricular dysfunction, hypertension, age > 75 (two points), diabetes mellitus, history of stroke/TIA or thromboembolism (two points), vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque), age 65 - 74, sex category. CVA: cerebrovascular accident; TIA: transient ischemic attack.

Table 4. Incidence of Acute Ischemic CVA in Relation to CHA_2DS_2VASc Risk Categories

CHA_2DS_2VASc risk groups	Acute ischemic CVA in patients with AC interruption	Acute ischemic CVA in patients without AC interruption	P-value
Low risk (score of 0 - 4) (N = 1,818)	0/60 (0%)	0/1,758 (0%)	1.000
Intermediate risk (score of 5 - 6) (N = 446)	0/18 (0%)	4/428 (0.94%)	1.000
High risk (score ≥ 7) (N = 13)	1/1 (100%)	1/12 (8.33%)	0.1538

There is not a significant difference in the number of people that had a stroke between interruption and non-interruption groups, within each CHA_2DS_2VASc risk category. Majority of the patients who suffered stroke were in the intermediate and high-risk categories. CVA: cerebrovascular accident; AC: anticoagulation.

we included all patients who had their anticoagulation interrupted and not bridged with heparin regardless of the reason. We could not ascertain the specific reason for the interruption though due to limitation in the data extraction. The rate of ischemic events was similar to that seen in the BRIDGE trial which was 0.3-0.4% for arterial thrombotic events over 30 days [17, 18].

Our results are in line with current guidelines. In the 2017 ACC guidelines [7-9], the ACC estimates the peri-procedural risk in AF patients at 0.35% for 30 days (based on BRIDGE and ORBIT AF studies) and recommends estimating an individual's daily risk of stroke or TIA by dividing the annual stroke risk by 365 days [9, 19, 20]. However, this approach is taken from studies done in mostly intermediate risk patients undergoing elective procedures. Our study adds to the current literature by providing the actual rate of stroke during hospitalization which is higher than what would be expected using the ACC method of estimation. Although the ACC recommends that patients at highest risk for thromboembolic events without excessive bleeding risk should consider bridging, it acknowledges that whether or not to bridge patients with AF and a high CHA_2DS_2VASc score remains unclear. However, based on available data, some physicians consider bridging anticoagulation for patients with a confirmed recent stroke. Our study results agree with the ACC guidelines. It shows that the risk of acute stroke in low risk patients ($CHA_2DS_2VASc < 5$) is negligible and this population can be safely taken off anticoagulation. And all stroke cases occurred in intermediate or high-risk group. The lack of statistically significant difference in the incidence of stroke between the two groups in intermediate and high-risk patients is likely due to small number of events.

Table 5. Details of the Six Patients Who Developed a Stroke in the Hospital

Patient	Primary final diagnosis	Secondary diagnoses	INR on admission	Anticoagulant prior to admission	Anticoagulation interruption > 48 h
1	Paroxysmal AF	Type 2 DM, HTN, HLD, obesity	0.96	Apixaban 5 mg twice daily	No
2	AFL	Type 2 DM, HTN, HLD, OSA, obesity	1.03	Warfarin 3 mg daily	No
3	Atherosclerotic heart disease	AF, HTN, HLD, dementia	4.47	Warfarin 4 mg daily	No
4	AFL	HTN, HLD, COPD, HFpEF, PVD, CKD, CAD, history of lung cancer	1.10	Rivaroxaban 10 mg daily	No
5	AF	AMS, HTN, HLD	0.97	Apixaban 2.5 mg twice daily	No
6	AFL	CAP, severe sepsis with septic shock, COPD, acute post-hemorrhagic anemia, AKI, HFpEF, NHL, obesity, hypothyroidism	1.47	None	Yes

AF: atrial fibrillation; AFL: atrial flutter; DM: diabetes mellitus; HTN: hypertension; HLD: hyperlipidemia; OSA: obstructive sleep apnea; COPD: chronic obstructive pulmonary disease; HFpEF: heart failure with preserved ejection fraction; PVD: peripheral vascular disease; CKD: chronic kidney disease; CAD: coronary artery disease; AMS: altered mental status; CAP: community-acquired pneumonia; NHL: non-Hodgkin's lymphoma.

Study limitations

The study should be interpreted in the light of following limitations. First, this is a single center retrospective study, and the risk of selection bias could not be eliminated. Second, the incidence of acute ischemic stroke during short period of time (hospitalization time) is very low, and that will probably decrease the power of the study and limit our ability to evaluate the impact of continued anticoagulation in high-risk group. Third, the reason for anticoagulation interruption could not be ascertained due to the administrative nature of the data. Lastly, patients on antiplatelet medications were not excluded in this study which may potentially affect the outcomes including but not limited stroke prevention or bleeding rates.

Conclusion

In hospitalized patients with AF the incidence of ischemic stroke during hospitalization is low and did not significantly increase with short-term interruption of anticoagulation. The incidence of ischemic stroke in hospitalized patients with AF is strongly correlated with CHA_2DS_2VASc score. Further investigations are needed to evaluate the impact of duration of anticoagulation interruption on stroke incidence in high-risk group.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

Access to data: Syed Hasan, Faluk and Abusaada had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They contributed equally to this work. Concept and design: Syed Hasan, Faluk, Abusaada, Albaeni, Abdelmaseih, Patel, and Chacko. Acquisition, analysis, or interpretation of data: Syed Hasan, Faluk, Finer, Patel and Abusaada. Drafting of the manuscript: Syed Hasan, Faluk, Abdelmaseih, Patel, and Thakker. Critical revision of the manuscript for important intellectual content: Syed Hasan, Faluk, Abdelmaseih, Abusaada, Albaeni and Chacko. Statistical analysis: Alexis Finer. Supervision: Abusaada and Albaeni.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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