Original research article

A Retrospective Study: Incidence of Acute Ischemic Stroke in Hospitalized Patients with Atrial Fibrillation WHO had Anticoagulation Interruptions

Dr. Manish Kumar[1], Dr. Archana Verma[2]

[1]MD (Med); DTM&H (UK); FICP, consultant Physician and cardiologist, ARC Hospital, Bhagalpur, Bihar, India

[2]Assistant Professor, Department of Radiodiagnosis, Katihar Medical College and Hospital, Katihar, Bihar, India.

Corresponding Author: Dr. Archana Verma

Abstract

Aim: To determine the Incidence of Acute Ischemic Stroke in Hospitalized PatientsWith Atrial Fibrillation Who Had Anticoagulation Interruption.

Methods: A retrospective study was conducted in the Department of Consultant Physician and Cardiologist, ARC Hospital, Bhagalpur, Bihar, India for 1 year. We included patients 18 years or older who were admitted to the hospital witha primary or secondary diagnosis of AF who had anticoagulation interruption without heparin bridge vs. non-interrupted group.

Results: A total of 450 patients were included in the study. In this cohort, mean age was 71.1 ± 10.21 years and 50.89% were female. A total of 50 patients out of 450 (11.11%) had anticoagulationinterruption in more than 48 h (median interruption of 67 h). Compared to non-interruption group, patients with anticoagulation interruption were older (mean age 75.45 ± 10.52 vs. 71.06 ± 10.88 years, P = 0.001), had slightly higher CHADS$_2$VASc score (3.88 vs. 3.52, P = 0.01), more likely to have heart failureand less likely to have HTN. Only 10 patients out of 450 (2.22%) had acute ischemicstroke during their hospital stay: 2 patient (4%) in the anticoagulation interruption group, and 8 patients (2%) in the non-interruption group. There was no statistically significant difference in incidence of ischemic stroke between the two groups (1.31% vs. 0.27%, P = 0.21). Short-term interruption of anticoagulation was not associated with a significant increased risk of in-hospital ischemic stroke. CHA$_2$DS$_2$VASc score was an independent strong predictor of in-hospital stroke (odds ratio (OR): 7.67, 95% confidence interval (CI): 2.89 - 18.03) In terms of secondary outcomes in anticoagulation interruption versus non-interruption groups, results were as follows: mortality (0 vs. 0.68%, P = 1), bleeding (4% vs. 1%,P = 0.03), number of readmissions within 90 days (48% vs. 37%, P = 0.03) and average LOS (7.74 vs. 2.75 days, P < 0.0001).

Conclusion: The 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$_2$DS$_2$VASc score.

Keywords: ischemic stroke, anticoagulation, AF

Introduction

Atrial fibrillation (AF) increases the risk of a cerebrovascular event (CVE) up to 5 times.[1] Patients with AF and history of stroke are at higher risk of death, heart failure, and long-term disability. Catheter ablation is the standard procedure for treating patients with AF, and recent studies have suggested that it may further reduce the risk of thromboembolism.[2-4] For

antithrombotic therapy after catheter ablation for AF, current guidelines recommend continued oral anticoagulation (OAC) therapy based on the CHA_2DS_2-VASc score risk profile for all patients.[5] However, in clinical practice, OAC therapy has been discontinued for many patients with a low-risk profile for thromboembolism. Very few studies have described outcomes in high-risk patients with apparently successful AF ablation following discontinuation of OAC therapy. Furthermore, these studies did not provide details of the type of stroke experienced (ie, whether past CVEs were cardiogenic embolisms). We hypothesized that different subtypes of ischemic stroke may present different risk factors, clinical features, and prognosis; therefore, the best post-procedural antithrombotic management for AF ablation may differ in patients with prior cardio embolic (CE) stroke and prior non-CE (ie, non-AF related) stroke. Although risk of ischemic stroke among patients with AF during sepsis exceeds the risks of both the general population with AF and patients with sepsis who do not experienceAF,[6] little evidence exists to support the use of anticoagulation for prophylaxis of arterial thromboembolism for patients with AF during sepsis.[7,8] Management decisions regarding the use of anticoagulation for prophylaxis of arterial thromboembolism during sepsis are complicated by changes to the coagulation cascade and acute organ dysfunction that may increase risks of bleeding and thrombosis.[9]

Materials and Methods
A retrospective study was conducted in the Department of Consultant Physician and Cardiologist, ARC Hospital, Bhagalpur, Bihar, India for 1 year. after taking the approval of the protocol review committee and institutional ethics committee. Patients with a primary or secondary diagnosis of AF were included in this study. 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.

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). 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 450 patients were included in the study. In this cohort, mean age was 71.1 ± 10.21 years and 50.89% were female. A total of 50 patients out of 450 (11.11%) 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 75.45 ± 10.52 vs. 71.06 ± 10.88 years, P = 0.001), had slightly higher $CHADS_2VASc$ score (3.88 vs. 3.52, 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 10 patients out of 450 (2.22%) had acute ischemic stroke during their hospital stay: 2 patient (4%) in the anticoagulation interruption group, and 8 patients (2%) in the non-

interruption group. There was no statistically significant difference in incidence of ischemic stroke between thetwo groups (1.31% vs. 0.27%, P = 0.21) (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): 7.67, 95% confidence interval (CI): 2.89 - 18.03) (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 andhad a $CHADS_2VASc$ score ≥ 7. None of the patients in the lowrisk group $CHA_2DS_2VASc < 5$ had a stroke (Table 4).

In terms of secondary outcomes in anticoagulation interruption versus non-interruption groups, results were as follows: mortality (0 vs. 0.68%, P = 1), bleeding (4% vs. 1%, P = 0.03), number of readmissions within 90 days (48% vs. 37%, P = 0.03) and average LOS (7.74 vs. 2.75 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.

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

Parameter	Anticoagulant interruption 48 h+ N=50	No anticoagulation interruption=400	P –value
Age (mean ± SD)	75.45 ± 10.52	71.06 ± 10.88	0.001
Male, n (%)	21 (42)	200 (50)	0.11
CHA_2DS_2VASc (mean ± SD)	3.88 ± 1.13	3.52 ± 1.23	0.01
Ischemic CVA, n (%)	2 (4)	8 (2)	0.25
CHF, n (%)	28 (56)	120 (30)	< 0.001
HTN, n (%)	20 (40)	272 (68)	0.001
Age ≥ 75 years, n (%)	32 (64)	188(47)	0.014
Age 65 - 74 years, n (%)	18 (36)	212 (53)	0.21
Diabetes, n (%)	13 (26)	120 (30)	0.57
Vascular disease, n (%)	23 (46)	176 (44)	0.61
Bleeding, n (%)	2 (4)	4 (1)	0.03
Mortality, n (%)	0 (0)	2 (0.5)	1.00
Readmission within 90 days, n (%)	24 (48)	148 (37)	0.03
Average LOS (mean ± SD)	7.74 ± 4.78	2.75 ± 2.39	< 0.0001

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

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)	75.45 ± 10.52 (N = 10)	71.06 ± 10.88 (N = 440)	0.19
Male, n (%)	3 (30)	212 (48.18)	0.61
Female, n (%)	7 (7)	228 (51.82)	0.61
CHA_2DS_2VASc (mean ± SD)	6.70 ± 0.87	3.52 ± 1.63	0.07

CHF, n (%)	2 (20)	140 (31.82)	0.62
HTN, n (%)	8 (80)	249 (56.59)	0.24
Age ≥ 75 years, n (%)	6 (60)	208(47.27)	0.45
Age 65 - 74 years, n (%)	4 (40)	145 (32.95)	1.11
Diabetes, n (%)	3 (30)	139 (31.59)	0.63
Vascular disease, n (%)	3 (30)	177 (40.23)	0.64
Anticoagulation interrupted, n (%)	2 (20)	18 (4.09)	0.17
No anticoagulation interruption, n (%)	8 (80)	422 (95.91)	0.17
Bleeding, n (%)	0 (0)	5 (1.14)	1.2
Mortality, n (%)	0 (0)	3 (0.68)	1.2
Readmission within 90 days, n (%)	6 (60)	148(33.64)	0.62
Average LOS (mean ± SD)	6.90 ± 11.23	2.91 ± 2.24	0.43

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

Table 3. CHA$_2$DS$_2$VASc 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)	4.51	0.49	45.12
CHA$_2$DS$_2$VASc	7.67	2.89	18.03

Patients with higher CHA$_2$DS$_2$VASc scores are more likely than those with lower CHA$_2$DS$_2$VASc scores to have an in-hospital CVA. CHA$_2$DS$_2$VASc: 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$_2$DS$_2$VASc Risk Categories

CHA2DS2VASc 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 = 354)	0/27 (0%)	0/327 (0%)	1.11
Intermediate risk (score of 5 - 6) (N = 70)	0/22 (0%)	1/48 (2.08%)	1.11
High risk (score ≥ 7) (N = 26)	1/1 (100%)	2/25 (8%)	0.14

There is not a significant difference in the number of people that had a stroke between interruption and non-interruption groups, within each CHA$_2$DS-$_2$VASc risk category. Majority of the patients who suffered stroke were in the intermediate and high-risk categories. CVA: cerebrovascular accident; AC: anticoagulation

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 ($CHA_2DS_2VASc \geq 7$) groups.

The results of the study are important in two ways. First, previous studies have quantified 30-day and 1-year risk for is-chemic stroke[10-13] ; 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-_2VASc score was formulated to predict the 1-year risk of is-chemic 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 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.[14,15] Our results are in line with current guidelines. In the 2017 ACC guidelines[16-18] , 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.[18-20] 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.

Conclusion

The present study concluded that 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.

Reference

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991; **22**: 983– 8.
2. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol*. 2011; **22**: 839– 45.
3. Takigawa M, Takahashi A, Kuwahara T, Takahashi Y, Okubo K, Nakashima E, et al. Late-phase thromboembolism after catheter ablation for paroxysmal atrial fibrillation. *Circ J*. 2014; **78**: 2394– 401.
4. Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J*. 2016; **37**: 2478– 87.
5. Calkins H, Hindricks G, Cappato R, Kim Y-H, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *J Arrhythm*. 2017; **33**: 369– 409
6. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA*.2011;306(20):2248-2254.
7. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. *Chest*. 2010; 137(2):263-272.
8. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.
9. Zeerleder S, Hack CE,WuilleminWA. Disseminated intravascular coagulation in sepsis.*Chest*. 2005;128(4):2864-2875.
10. Siegal D, Yudin J, Kaatz S, Douketis JD, Lim W, Spy- ropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Cir-culation. 2012;126(13):1630-1639.
11. Douketis JD, Healey JS, Brueckmann M, Eikelboom JW,Ezekowitz MD, Fraessdorf M, Noack H, et al. Periopera-tive bridging anticoagulation during dabigatran or warfa-rin interruption among patients who had an elective sur- gery or procedure. Substudy of the RE-LY trial. ThrombHaemost. 2015;113(3):625-632.
12. Cavallari I, Ruff CT, Nordio F, Deenadayalu N, Shi M, Lanz H, Rutman H, et al. Clinical events after interruption of anticoagulation in patients with atrial fibrilla-tion: An analysis from the ENGAGE AF-TIMI 48 trial. Int J Cardiol. 2018;257:102-107.
13. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J,Kovacs MJ, Svensson PJ, et al. Evidence-based manage- ment of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical PracticeGuidelines. Chest. 2012;141(2 Suppl):e152S-e184S.
14. Essebag V, Proietti R, Birnie DH, Wang J, Douketis J, Coutu B, Parkash R, et al. Short-term dabigatran inter- ruption before cardiac rhythm device implantation: multi-centre experience from the RE-LY trial. Europace.2017;19(10):1630-1636.
15. Kim TH, Kim JY, Mun HS, Lee HY, Roh YH, Uhm JS, Pak HN, et al. Heparin bridging in warfarin anticoagulation therapy initiation could increase bleeding in non-valvular atrial fibrillation patients: a multicenter propensity-matched analysis. J Thromb Haemost. 2015;13(2):182-190.
16. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Preven- tion of

Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.Chest. 2012;141(2 Suppl):e531S-e575S.

17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, et al. 2016 ESC Guidelines for themanagement of atrial fibrillation developed in collabora-tion with EACTS. Eur Heart J. 2016;37(38):2893-2962.

18. Doherty JU, Gluckman TJ, Hucker WJ, Januzzi JL, Jr., Ortel TL, Saxonhouse SJ, Spinler SA. 2017 ACC expert consensus decision pathway for periprocedural manage- ment of anticoagulation in patients with nonvalvular atri-al fibrillation: a report of the American college of cardiol-ogy clinical expert consensus document task force. J AmColl Cardiol. 2017;69(7):871-898

19. Steinberg BA, Peterson ED, Kim S, Thomas L, Gersh BJ,Fonarow GC, Kowey PR, et al. Use and outcomes asso- ciated with bridging during anticoagulation interruptions in patients with atrial fibrillation: findings from the Out- comes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation. 2015;131(5):488- 494.

20. Krishnamoorthy A, Ortel T. A bridge to nowhere? Ben- efits and risks for periprocedural anticoagulation in atrialfibrillation. Curr Cardiol Rep. 2016;18(10):101.