European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 08, Issue 04, 2021

Original research article

A Retrospective Evaluation of the Incidence of Acute Ischemic Stroke in Hospitalized Patients with Atrial Fibrillation Who Had Anticoagulation Interruption

Dr. Rana Randhir Kumar Singh[1], Dr.Madan Pal Singh[2], Dr. J.K.L Das[3]

[1]Associate Professor, Department of Geriatrics medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

[2]Professor, Department of General Medicine, Patna Medical College and Hospital, Patna, Bihar, India.

[3]Professor, Department of Geriatrics medicine, Patna Medical College and Hospital, Patna, Bihar, India.

Corresponding Author: Dr. Madan Pal Singh

Abstract

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

Methods: A retrospective study was conducted in the Department of Geriatrics- Medicine , Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India for 1 year. The patients of 60 years and above age group were included in the present study 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.

Results: the mean age was 72.1 ± 11.21 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 76.45 ± 11.52 vs. 72.06 ± 11.88 years, P = 0.001), had slightly higher $CHADS_2VASc$ score (3.98 vs. 3.62, P = 0.01), more likely to have heart failure and less likely to have HTN. 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 the two groups (1.31% vs. 0.27%, P = 0.27). 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): 7.77, 95% con- fidence interval (CI): 2.99 - 19.03) 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 = 0.04), number of readmissions within 90 days (48% vs. 37%, P = 0.04) 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_2DS_2VASc score.

Keywords: AF, ischemic stroke, anticoagulation

Introduction

The prevalence of atrial fibrillation (AF) ranges from 0.5 to 1%. 70% of afflicted persons are between the ages 65 and 85 with a median age of diagnosis of 75 years.[1-4] Discrepancies may be seen with gender, race, and the presence or absence of cardiovascular disease. There is an increased prevalence of AF in age-adjusted male population as compared to women. However, nearly 60% of AF patients over the age of 75 years are women. Caucasians have a higher prevalence of AF at 2.2 compared to 1.5% in African Americans over the age of 50 years.[1] Lastly, patients with known clinical cardiovascular disease have been shown to have AF rates as high as 9.1% in both men and women compared to 4.6% in comparable groups with subclinical disease and 1.6% in patients without cardiovascular disease.[2] Rates of hospitalizations have also increased 2–3 fold.[5] There is a well-established relationship between AF and chronic heart failure (CHF). A Framingham study showed AF accounts for 14% of deaths in the first few months of CHF diagnosis.[6] In some CHF clinical trials, the prevalence of AF was 4% in functional class I patients, 10%–27% in those with functional class II–III, and 50% in those with functional class IV. This shows the strong correlation between worsening cardiac function, age, and AF.[7] Net effects include an increase in cost to the health care system due to the annual cost of AF-related expenses, which are estimated to be nearly 16 billion dollars in the United States alone.[8]

Materials and methods

A retrospective study was conducted in the Department of Geriatrics- medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, 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

All the data were entered and analysed using SPSS version 25.0

Results

A total of 450 patients were included in the study. In this cohort, mean age was 72.1 ± 11.21 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 65 h). Compared to non-interruption group, patients with anticoagulation interruption were older (mean age 76.45 ± 11.52 vs. 72.06 ± 11.88 years, P = 0.001), had slightly higher $CHADS_2VASc$ score (3.98 vs. 3.62, 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 the two groups (1.31% vs. 0.27%, P = 0.27) (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): 7.77, 95% confidence interval (CI): 2.99 - 19.03) (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 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).

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 = 0.04), number of readmissions within 90 days (48% vs. 37%, P = 0.04) and average LOS (7.84 vs. 2.85 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)	76.45 ± 11.52	72.06 ± 11.88	0.001
Male, n (%)	21 (42)	200 (50)	0.15
CHA2DS2VASc (mean ± SD)	3.98 ± 1.13	3.62 ± 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)	7.84 ± 4.78	2.85 ± 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)	76.45 ± 10.52 (N = 10)	72.06 ± 10.88 (N = 440)	0.21
Male, n (%)	3 (30)	212 (48.18)	0.67
Female, n (%)	7 (7)	228 (51.82)	0.67
CHA2DS2VASc (mean ± SD)	6.70 ± 0.87	3.52 ± 1.63	0.06
CHF, n (%)	2 (20)	140 (31.82)	0.67
HTN, n (%)	8 (80)	249 (56.59)	0.29
Age ≥ 75 years, n (%)	6 (60)	208(47.27)	0.41
Age 65 - 74 years, n (%)	4 (40)	145 (32.95)	1.21
Diabetes, n (%)	3 (30)	139 (31.59)	0.65

Vascular disease, n (%)	3 (30)	177 (40.23)	0.69
Anticoagulation interrupted, n (%)	2 (20)	18 (4.09)	0.19
No anticoagulation interruption, n (%)	8 (80)	422 (95.91)	0.19
Bleeding, n (%)	0 (0)	5 (1.14)	1.5
Mortality, n (%)	0 (0)	3 (0.68)	1.5
Readmission within 90 days, n (%)	6 (60)	148(33.64)	0.55
Average LOS (mean ± SD)	6.90 ± 11.23	2.91 ± 2.24	0.38

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)	4.51	0.49	46.12
CHA_2DS_2VASc	7.77	2.99	19.03

Patients with higher CHA2DS2VASc scores are more likely than those with lower CHA2DS2VASc scores to have an in-hospital CVA. CHA2DS2VASc: 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_2 DS_2 VASc 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_2DS- 2VASc risk category. Majority of the patients who suffered stroke were in the intermediate and high-risk categories. CVA: cerebrovascular accident; AC: anticoagulation

Discussion

Regardless of the strategy of symptom control, every patient needs to be evaluated for thromboembolic risk. An appropriate strategy must also be identified at the time of diagnosis and re-evaluated with each clinical encounter. Maintenance of anticoagulation in the immediate setting is critical to prevent systemic thromboembolism including stroke following

pharmacologic or electrical cardioversion, which occurs within the first 3 days of restoration of sinus rhythm.

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 (CHA2DS2VASc ≥ 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[9-12] ; 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.[13,14] Our results are in line with current guidelines. In the 2017 ACC guidelines[15-17] , 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.[17-18] 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

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. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA.* 2001;285:2370–5.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469–73.
3. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (The cardiovascular health study) *Am J Cardiol.* 1994;74:236–41.
4. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation.* 1997;96:2455–61.
5. Stewart S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospital activity, morbidity and case fatality related to atrial fibrillation in Scotland, 1986-1996. *Eur Heart J.* 2001;22:693–701.
6. Deedwania PC, Lardizabal JA. Atrial fibrillation in heart failure: A comprehensive review. *Am J Med.* 2010;123:198–204.
7. De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L, et al. Atrial fibrillation in heart failure patients: Prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. *Eur J Heart Fail.* 2007;9:502–9.
8. Le Heuzey JY, Paziaud O, Piot O, Said MA, Copie X, Lavergne T, et al. Cost of care distribution in atrial fibrillation patients: The COCAF study. *Am Heart J.* 2004;147:121–6
9. 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.
10. 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. Thromb Haemost. 2015;113(3):625-632.
11. 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.
12. 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 Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-e184S.
13. 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.
14. 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.
15. 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.

16. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collabora- tion with EACTS. Eur Heart J. 2016;37(38):2893-2962.
17. 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 Am Coll Cardiol. 2017;69(7):871-898
18. 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.

Received: 07-05-2021 // Revised: 20-05-2021 // Accepted: 23-06-2021