Neurology Asia 2022; 27(4) : 845 – 849

The effect of rivaroxaban vs aspirin on stroke recurrence among patients with history of cryptogenic stroke and left atrial cardiomyopathy: An analytical cross-sectional study

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Abstract

Background: Stroke is defined as a lack of blood flow in the brain that can cause neurological deficits. Approximately 25% of all ischemic stroke patients are classified as cryptogenic strokes, most of which are caused by an embolic mechanism. Anticoagulant treatment with rivaroxaban may result in a lower risk of recurrent stroke than aspirin in patients with history of cryptogenic stroke and left atrial cardiomyopathy. *Methods:* In this cross-sectional study, we compared the efficacy and safety of rivaroxaban with aspirin for the prevention of recurrent stroke in patients with history of cryptogenic stroke and left atrial cardiomyopathy. *Results:* The results showed that assuming the other variables such as age, sex, hypertension, and diabetes be constant, stroke recurrence odds ratio in the Aspirin therapy was 11 times more than rivaroxaban therapy (OR=11.35, CI 95%: 1.39-113.08, P-value=0.038). *Conclusion:* Rivaroxaban was superior to aspirin with regard to the prevention of recurrent stroke among patients with history of cryptogenic stroke and left atrial cardiomyopathy.

Keywords: Rivaroxaban, aspirin, cryptogenic stroke, atrial cardiomyopathy

INTRODUCTION

Stroke is defined as a lack of blood flow in the brain that can cause neurological deficits. It is the second leading cause of death, the third leading cause of death and disability combined in the world, and from 1990 to 2019 the burden increased substantially in populations residing in lower income and lower–middle income countries. There were large geographical differences in age-standardized stroke incidence, mortality, prevalence and DALYs (disability-adjusted life-years lost) rates, with the highest rates in lower–middle income countries, particularly in Eastern Europe, Asia, and Sub-Saharan Africa.[1] Although the point estimates of incident and prevalent strokes are higher in females than in males, there are no noticeable sex differences in the number of stroke-related deaths.[2] The lifetime risk of stroke is now about one in four people. The major leading risk factors for stroke are high systolic blood pressure (SBP), high body mass index (BMI), high fasting plasma glucose (FPG), ambient particulate matter (PM2.5) pollution, and smoking. Globally, metabolic, behavioral, dietary, and environmental risks combined account for 87.0% of the global stroke burden.[3]

In Iran, the stroke incident cases increased from 48,274 in 1990 to 102,778 in 2019, revealing a 2.1-fold increase, whereas the age-standardized incidence rate (ASIR) of stroke decreased in both gender from 166.6 in 1990 to 138.8 per 100,000 populations in 2019. The number of stroke deaths increased from 21,698 in 1990 to 40,912 in 2019. Moreover, age-standardized death rate (ASDR) of stroke decreased 45.1%.[4]

Approximately 25% of all ischemic stroke patients are classified as cryptogenic strokes, most of which are caused by an embolic mechanism. Cryptogenic strokes have usually meant a non-lacunar infarction without proximal arterial stenosis or cardioembolic sources; however, there is neither a widely accepted definition nor a

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Date of Submission: 5 September 2022; Date of Acceptance: 20 September 2022

https://doi.org/10.54029/2022fma

required universally agreed diagnostic assessment. This has inhibited clinical research into optimal preventive therapy for cryptogenic strokes.[5]

Recently, atrial cardiomyopathy (AC) is recognized as a significant contributor to atrial hypo contractility and a substrate for atrial fibrillation (AF) in susceptible populations. AC is becoming a new potential target for both drug and catheter-based treatments. Despite the significant differences in structure, function, and molecular/cellular content between atria and ventricles, there is comparatively much less known about atrial cardiomyopathy than is known about ventricular heart failure and cardiomyopathy.[6]

Despite the efforts of researchers and pharmaceutical companies, the risk of stroke recurrence remains high. Aspirin is a commonly used antiplatelet agent for secondary stroke prevention, but its benefit must be weighed against its bleeding risks, particularly in the aging population. It has been proved that aspirin is safe and beneficial in preventing stroke recurrence, but aspirin can only reduce recurrent vascular events by 20%.[7]

We hypothesized that rivaroxaban would be more effective and safer than aspirin in preventing stroke recurrence in patients with left atrial cardiomyopathy and cryptogenic stroke. This cross-sectional study sought to determine if patients with history of cryptogenic stroke, left atrial cardiomyopathy, and moderate or severe left atrial volume index (LAVI) were more likely to benefit from empirical treatment with rivaroxaban when compared with aspirin.

METHODS

This was a cross-sectional study conducted at a neurology clinic in Isfahan city, Iran, from March 2020 to March 2022. A total of 73 patients with history of cryptogenic stroke, left atrial cardiomyopathy, and moderate or severe LAVI were selected from the neurovascular unit database admitted during this period. The study was approved by ethics committee medical university of Isfahan (IR.MUI.MED.REC.1400.347).

From the medical records, clinical covariates were extracted. Hypertension was defined as high systolic (>140 mm Hg) or diastolic (>90 mm Hg) blood pressure at discharge, preexisting diagnosis of hypertension or on medication. Diabetes mellitus was defined as an admitting HbA1C greater than 6.5%, preexisting diagnosis of diabetes or on medication. Non-contrast head CT or brain MRI was reviewed for each patient to confirm presence of an acute or subacute cryptogenic stroke and left atrial cardiomyopathy.

The inclusion criteria included history of prior cryptogenic stroke, cardiac ejection fraction>30, absence of atrial fibrillation (AF), absence of stenosis>50% of the cervical and intracerebral arteries, absence of prosthetic cardiac valves, absence of moderate to severe stenosis of cardiac valves, prior monitoring of cardiac rhythm for at least 24 hours. On the other hand, patients entered the study if they had at least two of the following atrial cardiomyopathy criteria: LAVI ≥35, episodes of high atrial rates known as frequent premature atrial contraction, CHADS2-VASc (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)) score above≥4, and spontaneous echocontrast in left atrium in transesophageal echocardiography (smoke like echo phenomenon with a swirling pattern of blood flow). The exclusion criteria included atrial fibrillation, stenosis of more than 50% of the cervical and intracerebral arteries, and functional patent foramen ovale (PFO). Patients met inclusion criteria and at least two of atrial cardiomyopathy criteria were extracted from the neurovascular unit database. Some patients took rivaroxaban and others aspirin for secondary prevention according to discretion of neurologist (level C evidence). We divided all patients into two groups according to using rivaroxaban or aspirin and then monitored the recurrence of stroke as the outcome in two groups during the following two years. Admission transthoracic echocardiograms were reviewed for all patients and the left atrial volume index (LAVI) ≥ 35 mL/m2 was extracted from reports.

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM corporation, Armonk, New York, USA). Initially, we compared baseline characteristics across two groups. Descriptive statistics are presented as mean ± SD for continuous variables and as percentages for categorical variables. For continuous variables, groups were compared using the one-way analysis of variance if group variances were homogeneous or Welch analysis of variance in presence of heterogeneity. For unequally distributed variables, we used the nonparametric Kruskal-Wallis test and for categorical variables, the chi square or Fisher exact test were performed to compare the groups. Logistic regression analysis was performed to compare recurrent stroke among two groups, after controlling for hypertension and diabetes

Table 1: Comparing baseline characteristics of the cryptogenic stroke

Variables	Rivaroxaban (n=33)	Aspirin (n=40)	Total	P-value [b]
Age, y, mean ±SD	62.21± 10.51	59.40± 10.28	60.67 ±10.41	0.254
Gender, Male, n (%)	19(57.6)	25(62.5)	44 (60.3)	0.669
Diabetes Mellitus, n (%)	7(21.2)	11(27.5)	18(24.7)	0.535
Hypertension, n (%)	8(24.2)	14(35.0)	22(30.1)	0.319

as confounding variables. A p-value< 0.05 was considered statistically significant.

RESULTS

Our sample included 73 patients, median age 62 years (range 35–85), the mean age was 60.67± 10.41 years and 60.3% was male. The distribution of age, hypertension, and diabetes were similar across two groups. Furthermore, we examined the risk factors associated with atrial cardiomyopathy in groups. Table 1 presented baseline characteristics of cryptogenic stroke.

The mean (SD) CHA2DS2-VASc score was 4.55(0.746) and there was no statistically significant difference between two groups (p-value=0.219). Since the beginning of this study, frequent premature atrial contraction (FPAC) in rivaroxaban and aspirin groups was the same (93% and 90% respectively), and there was no statistically significant difference between two groups (P-value=0.541). Nevertheless, atrial fibrillation (AF) had developed in 12% of the rivaroxaban group and 15.5% of the aspirin group during the study period; likewise, 18.2% in the rivaroxaban group and 25.0% in the aspirin group had developed transient atrial fibrillation (TAF). The atrial arrhythmia was not reported in 6 patients. There was no statistically significant difference between rivaroxaban and aspirin treatment groups in terms of left atrial volume index, CHADS2-VASc score and episodes of high atrial rates (frequent premature atrial contraction) (Table 2).

The comparison of stroke recurrence and cardiomyopathy showed that there was a statistically significant difference in rivaroxaban and aspirin groups. The odds ratio (OR) of stroke recurrence and atrial cardiomyopathy depicted that stroke recurrence in aspirin group was more than 6 times versus rivaroxaban (OR=6.78, CI 95%: 0.789-58.33, P-value=0.048). The results showed that eight cases of stroke recurrence occurred in the aspirin group, on the contrary, only one case was observed in the rivaroxaban group (crude Risk Ratio=6.6, 95% CI:0.869-50.11). We used the logistic regression model to explain the relationship between stroke recurrence and treatments among the two groups. The results showed that assuming the other variables such as age, sex, hypertension, and diabetes be constant, stroke recurrence odds ratio in the aspirin therapy was 11 times more than Rivaroxaban therapy (OR=11.35, CI 95%: 1.39-113.08, P-value=0.038). Results identified patients with history of cryptogenic stroke and left atrial cardiomyopathy more likely to benefit from rivaroxaban therapy over aspirin for reducing recurrent stroke (Table 3).

DISCUSSION

The efficacy of rivaroxaban versus aspirin in recurrence of cryptogenic stroke and left atrial cardiomyopathy has not yet been shown to predict clinical efficacy. It is estimated that 11% of individuals will have a recurrence within a year of their first stroke and 26% within 5 years.[7]

Table 2: characteristics of the left atrial cardiomyopathy among treatment groups

Variables		Rivaroxaban	Aspirin	P-value [a]
CHADS2-VASc score		4.67±0.854	4.45±0.639	0.219
Left atrial volume index		40.61±3.316	40.40±3.136	0.786
Arrhythmia*	Frequent premature atrial contraction	31(93.9)	36(90.0)	0.541
	Absent	2(6.1)	4(10.0)	0.541
* At commence of the study				

Table 3: The relationship between stroke recurrence and rivaroxaban vs aspirin therapy

Groups Study	Stroke Re.[a]	Odds Ratio	Std. Err.	P-value	95% Conf. Interval	
Aspirin (n=40)	8(20.0)[b]	11.35	13.31	0.038	1.13	113.08
Rivaroxaban (n=33)	1(3.0)					

[a] Re: recurrence, [b] n(%)

Aspirin is a commonly used antiplatelet agent for secondary stroke prevention, but its benefit must be weighed against its bleeding risks, particularly in the aging population. It has been demonstrated that aspirin is safe and beneficial in preventing stroke recurrence, but it can only reduce recurrent vascular events by 20%.[8]

This study depicted anticoagulant therapy by rivaroxaban comparing to aspirin reduced the occurrence of stroke in these patients (OR=0.088, P-value=0.038, 95% CI: 0.0088-0.8779). We found that rivaroxaban versus aspirin did reduce the risk of recurrent stroke in patient with the atrial cardiomyopathy, a condition which is very capable to develop AF, a serious arrhythmia that increases with age and contributes to extraordinarily high health care utilization and costs. Nonetheless, recent studies, such as Saadatnia *et al*. showed a correlation between atrial pathology markers and ischemic stroke, and suggested that the tissue substrate, rather than the arrhythmic state, could be the most important trigger of stroke risk.[9]

Our results are not in line with Hart *et al*. They compared a daily dose of 15 mg of rivaroxaban to 100 mg of aspirin for stroke prevention after embolic stroke of undetermined source (ESUS). They concluded rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding.[10] But our results are consistent with Jeff *et al*. study. They demonstrated rivaroxaban was associated with a reduced risk of recurrent stroke among patients with ESUS and moderate or severe left atrial enlargement.[11] In addition, consistent with our results, Alexander *et al*. found that rivaroxaban was superior to aspirin in reducing the risk of recurrent stroke or systemic embolism.[12]

Study limitations included retrospective design in a single center study and small sample size.

In conclusion, rivaroxaban was superior to aspirin with regard to the prevention of recurrent stroke among patients with history of cryptogenic stroke and left atrial cardiomyopathy. This cross-sectional study may not only have informative therapeutic implications for primary and secondary stroke prevention, but also help to spur a conceptual reorientation that will open up many fruitful avenues of future research on reducing the burden of atrial cardiomyopathy and stroke.

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