

Rivaroxaban-associated intracranial hemorrhage in Saudi atrial fibrillation patients

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Abstract

Atrial fibrillation is the most common cardiac arrhythmia. Anticoagulation therapy effectively reduces systemic embolization in patients with non-valvular atrial fibrillation, but intracranial hemorrhage (ICH) is a major possible complication. This study assessed the real-time rate of rivaroxaban-associated ICH in Saudi patients.

We retrospectively reviewed patients with ICH during rivaroxaban therapy, assessing clinical features and outcomes.

Four cases out of 690 patients were identified in total, indicating an incidence of ICH during rivaroxaban therapy of 0.58%. Hematoma expansion developed in 1 case. Three out of four patients were discharged after ICH, and 1 patient died.

The incidence of rivaroxaban-related ICH was similar to that previously reported, and the risk of hematoma expansion was low. Further studies are required to validate our results.

Abbreviations: CHA2DS2-VASc = congestive heart failure, hypertension, age > 75 years, history of diabetes or prior stroke, age > 65 years, female sex, and vascular disease, DOAC = direct oral anticoagulant, HAS-BLED = hypertension, abnormal renal, and liver function, stroke, bleeding tendency, labile INR in patients taking warfarin, elderly age, and the use of concomitant drugs, ICH = intracranial hemorrhage, INR = international normalized ratio, SDH = subdural hematoma.

Keywords: anticoagulation therapy, atrial fibrillation, hemorrhage, intracranial, rivaroxaban

1. Introduction

Atrial fibrillation is the most common cardiac arrhythmia, with a 2010 systemic review having estimated that around 33.5 million individuals are living with this condition worldwide.^[1] Patients with atrial fibrillation are at risk of systemic embolization, and ischemic stroke is the most common related embolic phenomena. The risk of stroke in patients with non-valvular atrial fibrillation can be assessed by the congestive heart failure, hypertension age > 75 years score history of diabetes or prior stroke, age > 65 years, female sex, and vascular disease (CHA2DS2-VASc) (1 point each for CHA2DS2-VASc). The mean rate of stroke is 1.3%, 2.2%, and 3.2% per year for CHA2DS2-VASc of 1, 2, and 3, respectively.^[2,3] Compared with antiplatelet therapy, anticoagulant therapy effectively reduces the risk of systemic embolization in patients

with non-valvular atrial fibrillation.^[4] Although warfarin therapy has proven effective in reducing the risk of stroke, this medication has significant problems. An effective dose requires frequent blood monitoring and has significant interactions with food and other medications. Because of these problems, direct oral anticoagulant (DOAC) therapy was introduced. DOACs produce their anticoagulant effect either by direct thrombin inhibition or direct factor Xa inhibition. Dabigatran (direct thrombin inhibitor) was approved in the United States for use in 2010, with other DOACs approved shortly after.

Rivaroxaban is a DOAC that acts by directly inhibiting factor Xa. A randomized double blind trial comparing rivaroxaban with warfarin in preventing ischemic stroke showed that the rivaroxaban reduces stroke rates in patients with non-valvular atrial fibrillation with the same efficacy as warfarin (2.1% per year for the rivaroxaban group and 2.4% per year for the warfarin group, with a hazard ratio of 0.88; 95% CI, 0.74 to 1.03; $P < .001$ for noninferiority; $P = .12$ for superiority).^[5] Conveniently, rivaroxaban does not need blood monitoring and does not have major interactions with food or other medications. However, it is not approved yet for treatment of valvular atrial fibrillation. The dose needs to be adjusted in patients with mild to moderate renal impairment,^[6] and it is not recommended for use in patients with severe renal impairment or end stage renal disease.

At present, there are only observational studies comparing the effect of rivaroxaban with other DOACs. The risk of stroke or systemic embolization was similar between rivaroxaban and dabigatran (HR 1.00; 95% CI, 0.75-1.32), as well as rivaroxaban and apixaban (HR 1.05; 95% CI, 0.64-1.72).^[7,8]

Bleeding is the most common complication of anticoagulant therapy, and intracranial hemorrhage (ICH) is one potential devastating outcome. Although major bleeding was not significantly different between rivaroxaban and warfarin, patients administered the former tend to develop ICH less often compared with patients administered warfarin (0.8% versus 1.2%).^[5]

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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To date, there are no studies that assess the risk of ICH in Saudi patients receiving rivaroxaban or other DOACs. This study aims to assess the incidence of rivaroxaban-associated ICH in Saudi patients at tertiary care center, clinical characteristics and their outcomes.

2. Method

This is a retrospective cohort study. Ethical approval was obtained from the Institutional Review Board of King Abdullah Medical City, a tertiary care center in the Makkah region of Saudi Arabia, where the study was carried out. Patients on rivaroxaban at King Abdullah Medical City from 2014 to 2019 were identified from the pharmacy database, and cases of ICH were detected after reviewing the radiological database for all patients on rivaroxaban. We excluded patients with ICH secondary to trauma or other bleeding disorders. From charts and brain images, the following data were obtained: age, gender (male or female), presence of comorbidities (e.g., hypertension, diabetes mellitus, or cardiac disease), taking antiplatelet medication (aspirin, aspirin with clopidogrel, or clopidogrel), smoking status, type of ICH (subdural hematoma [SDH], epidural, subarachnoid hemorrhage, intracerebral hemorrhage, or intraventricular hemorrhage), bleeding from other areas (gastrointestinal, respiratory, skin, or genitourinary), clinical presentation, blood pressure measurement at presentation, HAS BLED score, hematological parameters (international normalized ratio [INR], platelets, and partial thromboplastin time), and outcome (hematoma expansion, surgical intervention, or death).

3. Results

3.1. Patient characteristics:

Out of 690 patients on rivaroxaban, a total of 5 had ICH. One patient had hemorrhagic transformation so he was excluded from analysis. The incidence of spontaneous ICH in our study population 0.58%. Table 1 shows patients' demographic data. All 4 ICH patients had atrial fibrillation. Cardiac failure was the most common cardiac comorbidity. All patients used antiplatelet therapy with rivaroxaban, and the hypertension, abnormal renal, and liver function, stroke, bleeding tendency, labile INR in patients taking warfarin, elderly age, and the use of concomitant drugs (HAS-BLED) score exceeded 3 in 2 of the 4 patients. All of our patients had a mean systolic blood pressure of 125 +/- 10 in the month before ICH, and none underwent an MRI study to assess micro-bleed before starting rivaroxaban

3.2. Clinical characteristics:

Table 2 shows patients' clinical characteristics. Intracerebral hemorrhage was the most common type of ICH. Only 1 patient had a SDH, and none had epidural, subarachnoid, or intraventricular hemorrhages. Blood pressure varied between patients. None of our patients had significant bleeding from other sites, except 1 patient with mild gum bleeding. Clinically, all patients presented with altered mental state and with associated clinical weakness depending on the site of involvement.

3.3. Outcome:

Hematoma expansion, defined as a 33% increase in hematoma volume,^[6] occurred in 1 patient with SDH. One case required

Table 1

Patients' demographic data and baseline clinical features.

Variables	Results
Age (median)	(53-72) 62.6
Gender	
Male	2
Female	2
Hypertension	
Yes	3
No	1
Diabetes Mellitus	
Yes	2
NO	2
Cardiac disease	
Heart failure	3
Aortic stenosis	1
No	0
HAS-BLED Score	
< 3	2
3	2
Antiplatelet	
No antiplatelet	0
Single antiplatelet	3
Double antiplatelet	1
Smoking	
Yes	2
No	2

HAS-BLED = hypertension, abnormal renal, and liver function, stroke, bleeding tendency.

Table 2

Characteristics of ICH.

Variables	Results
Type of ICH	
Subdural Hematoma	1
Intracerebral	3
Subarachnoid/ Epidural and intraventricular hemorrhage	0
Other bleeding	
GIT	0
Respiratory	0
Skin	1 (gum bleeding)
Genitourinary	0
Clinical presentation	
Headache	1
Weakness	3
Ataxia	0
Altered level of consciousness	4
BP at presentation	
<140/90	0
140/90–160/90	3
>160/90	1
Hematological parameters	
Platelet	All more than 150,000
INR	All are less than 1.4
PTT	All less than 44 sec

aPTT = partial thromboplastin time, ICH = intracranial haemorrhage, INR = international normalized ratio.

surgical intervention, and 1 patient died during the acute stage of ICH. All other patients were discharged from the hospital.

4. Discussion

In this retrospective study, the incidence of ICH with rivaroxaban was 0.58%, comparable with the incidence rate in the

randomized double blind trial of comparing rivaroxaban with warfarin in preventing ischemic stroke trial of 0.8%,^[5] and significantly lower than the warfarin-related ICH risk of 1.2%.^[5] The lower risk of ICH with rivaroxaban compared with warfarin was assessed in a systematic review comparing the efficacy and safety of rivaroxaban with that of warfarin in patients with non-valvular atrial fibrillation. Rivaroxaban has a lower risk of ICH (RR 0.64, 95% CI [0.45–0.92]) but a higher risk of gastrointestinal hemorrhage (RR 1.3, 95% CI [1.19–1.42]).^[8]

Intracerebral hemorrhage was the most common type of ICH. Two cases had supratentorial intracerebral hemorrhages, and 1 had a cerebellar hemorrhage. Only 1 patient had spontaneous SDH. Different types of ICH in relation to rivaroxaban therapy have been reported in the literature including epidural hematoma and choroidal hemorrhage.^[9–11]

Heart failure was the most common cardiac condition found in our patient series. All of our patients had stable blood pressure before the development of ICH. All patients had been on antiplatelet therapy, and 2 were on double antiplatelet therapy. A sub-analysis of EXPAND study showed that the combination of rivaroxaban with antiplatelet increased the risk for major bleeding (1.6, 1.2–2.3, $P = .0030$).^[12–13] Further studies are required to confirm this results.

HAS-BLED is a scoring system used to estimate the risk of bleeding in patients with atrial fibrillation based on 7 risk factors: hypertension, abnormal renal and liver function, stroke, bleeding tendency, labile INR in patients taking warfarin, elderly age, and the use of concomitant drugs.^[14] HAS-BLED has been found to predict hemorrhage risk better compared with other scoring systems.^[15] Higher bleeding risk results in a score of 3 or more.^[14] In our patient series, two patients with ICH had a score of 3, while the other 2 patients with ICH scored less than 3. We did not check the HAS-BLED score for patients who did not bleed. In another comparison between warfarin-related and rivaroxaban-related ICH, all patients had high HAS-BLED scores, unlike our series.^[7] In another series, patients with DOAC-related ICH had a mean HAS-BLED score of 1.5+/-0.5 like our patients.^[16] In the same series, ICH occurred even in a setting of acceptable blood pressure control.^[16]

In our study, only 1 patient had hematoma expansion, which occurred within 48 hours of onset; the patient remained stable and did not require surgical intervention. All patients were treated similarly with ICU admission, frequent evaluation, and stopping anticoagulant and antiplatelet therapies. No patients had a reversal of anticoagulation. Only 1 patient required surgical intervention, after presenting late with intracerebral hemorrhage and herniation. Evacuation was done the same day but unfortunately the patient died in the course of that admission.

A study comparing rivaroxaban-related ICH with warfarin-related ICH showed that hematomas are smaller in size in the former group. The study also showed that patients with rivaroxaban-related ICH have higher bleeding tendency in comparison with the warfarin-related group. However, none of the patients have hematoma expansion. Patients with rivaroxaban-related ICH discharged with better modified Rankin Scale in comparison with the warfarin group. None died as a result of ICH in the rivaroxaban group versus an 18% fatality outcome in the warfarin-related ICH group.^[7] Further studies assessing ICH related to DOACs in comparison with warfarin showed similar results, including smaller hematoma, no hematoma expansion, and better outcome even in absence of reversal agents.^[16–21]

Reversal agents for DOACs were only developed recently. For patients with DOAC-related bleeding, it is recommended to stop the anticoagulant therapy and provide supportive care. In cases of serious life-threatening hemorrhage like ICH, it is recommended that anticoagulation be reversed.^[22,23] Andexanet alfa is a reversal agent approved by the FDA for reversing rivaroxaban-related life-threatening hemorrhage. It is a modified recombinant inactive form of human factor Xa. In cases of serious bleeding like gastrointestinal hemorrhage and ICH, it was found to be an effective method of reversing the effect of anti-factor Xa (namely rivaroxaban and apixaban). After a bolus of andexanet alfa, the effect of anti-factor Xa of rivaroxaban is reduced by 92% (95% CI, 88 to 94).^[23] Andexanet is not available at our institute, and so for all patients with DOAC-related bleeding, we stopped the anticoagulant and provided supportive care.

4.1. Limitations

The small number of cases is a major limitation of our study, and statistical analysis was difficult to perform as a result. We also did not compare our sample with patients with warfarin-related ICH.

5. Conclusion

The incidence of rivaroxaban-related ICH in our sample is 0.58% comparable to that previously reported. Hematoma expansion was uncommon. Further studies are required to assess whether a concomitant use of antiplatelet therapy with rivaroxaban increases the risk of bleeding

Author contributions

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References

- Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837–47.
- Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–429.
- Joundi RA, Cipriano LE, Sposato LA, et al. Ischemic stroke risk in patients with atrial fibrillation and CHA2DS2-VASc Score of 1: systematic review and meta-analysis. *Stroke* 2016;47:1364–7.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–91.
- Zbigniew K, Hubert S, Andrzej J, et al. Safety of new oral anticoagulants for patients with chronic kidney disease. *Curr Pharm Des* 2018;24:4505–10.
- Hagii J, Tomita H, Metoki N, et al. Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. *Stroke* 2014;45:2805–7.

- [8] Aronow WS, Shamliyan TA. Comparative effectiveness and safety of rivaroxaban in adults with nonvalvular atrial fibrillation. *Am J Ther* 2018;26:e679–703.
- [9] Ruschel LG, Rego FM, Milano JB, et al. Spontaneous intracranial epidural hematoma during rivaroxaban treatment. *Rev Assoc Med Bras (1992)* 2016;62:721–4.
- [10] Stollberger C, Bastovansky A, Finsterer J. Fatal intracerebral bleeding under rivaroxaban. *Int J Cardiol* 2015;201:110–2.
- [11] Atia R, Bonnel S, Vallos M, et al. Spontaneous choroidal hemorrhage associated with novel oral anticoagulants: A report of two cases and literature review. *J Fr Ophtalmol* 2018;41:767–72.
- [12] Shimokawa H, Yamashita T, Uchiyama S, et al. The EXPAND study: efficacy and safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation. *Int J Cardiol* 2018;258:126–32.
- [13] Sakuma I, Uchiyama S, Atarashi H, et al. Clinical risk factors of stroke and major bleeding in patients with non-valvular atrial fibrillation under rivaroxaban: the EXPAND Study sub-analysis. *Heart Vessels* 2019;34:1839–51.
- [14] Pisters R, Lane DA, Nieuwlaat R, et al. 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;138:1093–100.
- [15] Zhu W, He W, Guo L, et al. The HAS-BLED score for predicting major bleeding risk in anticoagulated patients with atrial fibrillation: a systematic review and meta-analysis. *Clin Cardiol* 2015;38:555–61.
- [16] Akiyama H, Uchino K, Hasegawa Y. Characteristics of symptomatic intracranial hemorrhage in patients receiving non-vitamin k antagonist oral anticoagulant therapy. *PLoS One* 2015;10:e0132900.
- [17] Sardar P, Chatterjee S, Wu WC, et al. New oral anticoagulants are not superior to warfarin in secondary prevention of stroke or transient ischemic attacks, but lower the risk of intracranial bleeding: insights from a meta-analysis and indirect treatment comparisons. *PLoS One* 2013;8:e77694.
- [18] Takahashi H, Jimbo Y, Takano H, et al. Intracerebral hematoma occurring during warfarin versus non-vitamin k antagonist oral anticoagulant therapy. *Am J Cardiol* 2016;118:222–5.
- [19] Adachi T, Hoshino H, Takagi M, et al. Volume and characteristics of intracerebral hemorrhage with direct oral anticoagulants in comparison with warfarin. *Cerebrovasc Dis Extra* 2017;7:62–71.
- [20] Woo HG, Chung I, Gwak DS, et al. Intracerebral hemorrhage associated with warfarin versus non-vitamin K antagonist oral anticoagulants in Asian patients. *J Clin Neurosci* 2019;61:160–5.
- [21] Kawabori M, Niiya Y, Iwasaki M, et al. Characteristics of symptomatic intracerebral hemorrhage in patient receiving direct oral anticoagulants: comparison with warfarin. *J Stroke Cerebrovasc Dis* 2018;27:1338–42.
- [22] Chaudhary R, Sharma T, Garg J, et al. Direct oral anticoagulants: a review on the current role and scope of reversal agents. *J Thromb Thrombolysis* 2019;49:271–86.
- [23] Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor xa inhibitors. *N Engl J Med* 2019;380:1326–35.