The Thromboembolism and Bleeding Event in Patients Receiving Warfarin, Dabigatran, or Rivaroxaban in Nonvalvular Atrial Fibrillation

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Received 30-07-2021  Accepted 07-08-2021  Available online 31-12-2021

ABSTRACT

Increasing in trend of Dabigatran and Rivaroxaban usage every year in Hospital Sultanah Nur Zahirah (HSNZ) has raised concerns regarding their effectiveness and safety compared to Warfarin. Therefore, we investigated the prevalence of thromboembolism (stroke or systemic embolism) and bleeding events in patients receiving Warfarin, Dabigatran or Rivaroxaban in our setting. This retrospective cohort study involved patients with nonvalvular atrial fibrillation who were started on Warfarin, Dabigatran or Rivaroxaban from January 1, 2014 to December 31, 2018. To fulfil inclusion criteria, patients must be on treatment for at least one year and for Warfarin group, at least 65% of Time in Therapeutic Range (TTR) should be achieved. Data were collected from Warfarin registration book, drug usage record card and Hospital Information System. 142 patients (Warfarin, n=98; Dabigatran, n=30; Rivaroxaban, n=14) with mean age of 68±8.7 years old were included in the study. Majority of them were male, Malay and non-smoker with 57.0%, 97.2% and 95.8% respectively. Upon study enrolment, all patients were at moderate risk of stroke (median CHA2DS2-VASc score=3) and low risk of bleeding (median HAS-BLED score=2). One Ischemic stroke was identified in each group of Rivaroxaban 15 mg and Dabigatran 150 mg. Four bleeding events occurred in all groups except for Dabigatran group that were hematuria, gum bleeding and upper gastrointestinal bleeding. Thromboembolism and bleeding events still occur in all groups. However, the prevalence is small in our setting with the percentage of 1.4% and 2.8% respectively. The events mostly attributed by the predisposed risk factors.

Keywords: Bleeding event, dabigatran, nonvalvular atrial fibrillation, prevalence, rivaroxaban, thromboembolism, warfarin.

Introduction

Atrial fibrillation (AF) is characterized by uncoordinated atrial activation with consequence deterioration of mechanical function (January et al., 2014) that associated with 3-5-fold increased risk of stroke (Xiaoxi et al., 2019). Guidelines for the
management of AF recommend anticoagulation for stroke prevention in patients with moderate to high stroke risk (January et al., 2014).

Warfarin has been the standard anticoagulation therapy, but it has narrow therapeutic window and requires dietary control (Gage et al., 2008). Non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced with an improved efficacy/safety ratio, a predictable anticoagulant effect without need for routine coagulation monitoring and fewer food and drug interactions compared to Warfarin. European guidelines have expressed a preference for NOACs over Warfarin in stroke prevention for AF patients, especially if newly initiated, based on the overall clinical benefit of NOACs (Madan et al., 2014).

As compared to Warfarin, RE-LY trial showed that Dabigatran 110 mg was associated with similar rates of stroke and systemic embolism as well as lower rates of major hemorrhage. In contrast, Dabigatran 150 mg was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage (Connolly et al., 2009). Meanwhile, in ROCKET trial, Rivaroxaban was non-inferior to Warfarin to the event of thromboembolism. In term of bleeding, there was no significant difference between-group in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the Rivaroxaban group (Patel et al., 2011). A study found that gastrointestinal bleeding was significantly more common in patient on Warfarin than on NOACs (Cangemi et al., 2017). In contrast, the rate of gastrointestinal bleeding was higher for patient with Dabigatran and Rivaroxaban compared to Warfarin (Linda & Wrick, 2018).

Due to the increasing trend of NOACs usage every year in HSNZ, concerns were raised regarding their effectiveness and safety compared to Warfarin. Therefore, we investigated the prevalence of thromboembolism (stroke or systemic embolism) and bleeding events in patients receiving Warfarin, Dabigatran or Rivaroxaban in our setting.

**Research Method**

A retrospective cohort study was conducted involving all adult patients who diagnosed as nonvalvular AF that newly started on Warfarin, Dabigatran or Rivaroxaban from 1st January 2014 to 31st December 2018. As presented in Figure 1, list of patients on Warfarin were traced from Warfarin registration book while for NOACs from drug usage record card and Hospital Information System (HIS). To be enrolled in the study, patients were required to receive continuous treatment of anticoagulants at HSNZ for at least one year from initiation date. For Warfarin group, patients must achieve at least 65% time in therapeutic range (TTR) throughout the one-year treatment that was calculated using Rosendaal’s method. Patients were excluded if they had history of deep vein thrombosis or pulmonary embolism, underwent
hip/knee replacement surgery within six weeks, kidney transplant, cancer, on dialysis and end stage renal failure. Then, data on prevalence of thromboembolism and bleeding events were retrieved from HIS.

Baseline characteristics of patients were analyzed using descriptive statistics. Categorical data are reported as proportions while continuous data were reported as medians with interquartile ranges (IQRs).

**Results and Discussion**

**Baseline Characteristics**

The baseline characteristics of patients are presented in Table 1. A total of 142 patients were enrolled (Warfarin, n=98; Dabigatran, n=30; Rivaroxaban, n=14) with mean age of 68.4±8.70 years.

Majority of the patients were male, Malay and non-smoker with 57%, 97.2% and 95.8%, respectively. Out of 142 patients, 71.1% had underlying hypertension, 35.2% had diabetes mellitus and 29.6% had history of stroke. Most of the patients had concomitant use of antiplatelet with the percentage of about 55% which may possess risk of bleeding. About 16% of patients received proton pump inhibitor. Prior to initiation of anticoagulants, risk of stroke and risk of bleeding were determined by using CHA2DS2-VASc and HAS-BLED score respectively. As shown in Table 2, majority of the patients in each group had moderate risk of stroke with the median score of 3 and low risk of bleeding with the median score of 2.

![Figure 1. Flow of the study.](image-url)
Table 1. Baseline characteristics of patients

|                  | Warfarin (n = 98) | Rivaroxaban (n=14) | Dabigatran (n=30) | Total (N=142) |
|------------------|-------------------|---------------------|-------------------|--------------|
| **Age, mean (SD), year** | 68.8 (7.85)       | 64.7 (12.80)        | 68.7 (9.34)       | 68.4 (8.70)  |
| **Age group, n (%), year** |                   |                     |                   |              |
| 18-64            | 30 (30.6)         | 4 (28.6)            | 5 (16.7)          | 39 (27.5)    |
| 65-74            | 42 (42.9)         | 8 (57.1)            | 15 (50.0)         | 65 (45.8)    |
| ≥75              | 26 (26.5)         | 2 (14.3)            | 10 (33.3)         | 38 (26.7)    |
| **Sex, n (%)**   |                   |                     |                   |              |
| Male             | 52 (53.0)         | 10 (71.4)           | 19 (63.3)         | 81 (57.0)    |
| Female           | 46 (47.0)         | 4 (28.6)            | 11 (36.7)         | 61 (43.0)    |
| **Race, n (%)**  |                   |                     |                   |              |
| Malay            | 94 (95.9)         | 14 (100.0)          | 30 (100.0)        | 138 (97.2)   |
| Chinese          | 4 (4.1)           | 0 (0.0)             | 0 (100.0)         | 4 (2.8)      |
| **Smoking, n (%)** |                   |                     |                   |              |
| No               | 94 (95.9)         | 13 (92.9)           | 29 (96.7)         | 136 (95.8)   |
| Yes              | 4 (4.1)           | 1 (7.1)             | 1 (3.3)           | 6 (4.2)      |
| **Hypertension, n (%)** |                   |                     |                   |              |
| No               | 28 (28.6)         | 7 (50.0)            | 6 (20.0)          | 41 (28.9)    |
| Yes              | 70 (71.4)         | 7 (50.0)            | 24 (80.0)         | 101 (71.1)   |
| **Diabetes Mellitus, n (%)** |                   |                     |                   |              |
| No               | 64 (65.3)         | 9 (64.3)            | 19 (63.3)         | 92 (64.8)    |
| Yes              | 34 (34.7)         | 5 (35.7)            | 11 (36.7)         | 50 (35.2)    |
| **Stroke, n (%)** |                   |                     |                   |              |
| No               | 70 (71.4)         | 10 (71.4)           | 20 (66.7)         | 100 (70.4)   |
| Yes              | 28 (28.6)         | 4 (28.6)            | 10 (33.7)         | 42 (29.6)    |
| **Antiplatelet, n (%)** |                   |                     |                   |              |
| No               | 43 (43.9)         | 3 (21.4)            | 18 (60.0)         | 64(45.1)     |
| Yes              | 55 (56.1)         | 11 (78.6)           | 12 (40.0)         | 78(54.9)     |
| **Proton Pump Inhibitor, n (%)** |                   |                     |                   |              |
| No               | 82 (83.7)         | 12 (85.7)           | 27 (90.0)         | 121(84.5)    |
| Yes              | 16 (16.3)         | 2 (14.3)            | 3 (10.0)          | 21(15.5)     |

**Thromboembolic Events**

One incident of ischemic stroke was observed in patient receiving Rivaroxaban 15 mg and Dabigatran 150 mg respectively (Table 3). Those on Rivaroxaban 15 mg is an elderly with underlying heart disease and has several concomitant risk factors of stroke which are uncontrolled hypertension (BP: 199/111 mmHg), uncontrolled diabetes mellitus (CBG: 13.2mmol/L), as well as hyperlipidemia (LDL: 3.1mmol/L). According to Amelia K et al., (2017), risk factors for stroke can be categorized as modifiable and non-modifiable. Age, sex, and race/ethnicity are non-modifiable risk factors for stroke while hypertension, smoking, diet, and physical inactivity are among some of the more commonly reported modifiable risk factors.

Patient who was on Dabigatran 150 mg had hyperthyroidism which predisposed him to thromboembolic event. The overactive thyroid was associated with a 44% increased risk for ischemic stroke which is stroke cause by blocked arteries (Sheu (2010)).
Table 2. CHA\textsubscript{2}DS\textsubscript{2}-VASc and HAS-BLED score

|                | Warfarin (n=98) | Rivaroxaban (n=14) | Dabigatran (n=30) |
|----------------|-----------------|---------------------|-------------------|
| CHA\textsubscript{2}DS\textsubscript{2}-VASc score |                 |                     |                   |
| Median (IQR)   | 3 (2-3)         | 3 (2-4)             | 3 (2-5)           |
| Low risk: 0-1, n (%) | 9 (9.2)        | 0 (0.0)             | 4 (13.2)          |
| Moderate risk: 2-3, n (%) | 66 (67.3)   | 9 (64.3)            | 13 (43.4)         |
| High risk: ≥ 4, n (%) | 23 (23.5)    | 5 (35.7)            | 13 (43.4)         |
| HAS-BLED score |                 |                     |                   |
| Median (IQR)   | 2 (1-3)         | 2 (1-3)             | 2 (2-3)           |
| Low risk: 0-2, n (%) | 59 (60.2)   | 8 (57.1)            | 17 (56.7)         |
| High risk: ≥ 3, n (%) | 39 (39.8)   | 6 (42.9)            | 13 (43.3)         |

CHA2DS2-VASc=congestive heart failure, 1 point; hypertension, 1 point; ≥75 years old, 2 points; diabetes mellitus, 1 point; previous stroke, transient ischemic attack or thromboembolism, 2 points; vascular disease, 1 point; 65 to 74 years old, 1 point; female sex, 1 point.

HAS-BLED=hypertension, 1 point; >65 years old, 1 point; stroke history, 1 point; bleeding history or predisposition, 1 point; liable international normalized ratio, not assessed; ethanol or drug abuse, 1 point; drug predisposing to bleeding, 1 point.

Table 3. Prevalence of thromboembolic event

|                | Warfarin (n=98) | Dabigatran 110 mg (n=12) | Dabigatran 150 mg (n=18) | Rivaroxaban 15 mg (n=5) | Rivaroxaban 20 mg (n=9) |
|----------------|-----------------|---------------------------|--------------------------|-------------------------|-------------------------|
| Prevalence of thromboembolism, n (%) |               |                           |                          |                         |                         |
| No             | 98 (100.0)      | 12 (100.0)                | 17 (94.4)                | 4 (80.0)                | 9 (100.0)               |
| Yes            | 0 (0.0)         | 0 (0.0)                   | 1 (5.6)                  | 1 (20.0)                | 0 (0.0)                 |

Table 4. Prevalence of bleeding event

|                | Warfarin (n=98) | Dabigatran 110 mg (n=12) | Dabigatran 150 mg (n=18) | Rivaroxaban 15 mg (n=5) | Rivaroxaban 20 mg (n=9) |
|----------------|-----------------|---------------------------|--------------------------|-------------------------|-------------------------|
| Prevalence of bleeding, n (%) |               |                           |                          |                         |                         |
| No             | 96 (98.0)       | 12 (100.0)                | 16 (100.0)               | 4 (80.0)                | 8 (88.9)                |
| Yes            | 2 (2.0)         | 0 (0.0)                   | 0 (0.0)                  | 1 (20.0)                | 1 (11.1)                |

Bleeding Events

An event of gum bleeding and hematuria were found in Warfarin group. Meanwhile, gum bleeding and upper gastrointestinal bleeding (UGIB) was observed in Rivaroxaban 15 mg and Rivaroxaban 20 mg group respectively (Table 4).

In Warfarin group, one event of bleeding episode occurred in patient receiving dual antiplatelet medications. These anti-thrombotic combination therapies likely have an additive blood thinning effect which predisposed patient to bleeding episode. Besides, concurrent use of antiplatelet in patient who also had worsening renal function may explain the incident of hematuria in one patient within Warfarin group.

In parallel to Warfarin group, concurrent use of double antiplatelet may be the precipitating factor for gum bleeding episode in Rivaroxaban 15 mg.
group. Meanwhile, those who experienced UGIB in Rivaroxaban 20 mg group also receiving concurrent antiplatelet and having deterioration in renal function during therapy. Patient also had advanced age in addition to these modifiable bleeding risk factors which may explain the occurrence of UGIB episode. A study done by CBecattini et al., (2018) summarized that variation in renal function over time is associated with the risk of major bleeding in AF patients treated with NOACs. Other study also mentioned that in patients with AF, all combinations of Warfarin, Aspirin, and Clopidogrel are associated with increased risk of nonfatal and fatal bleeding. Dual warfarin and Clopidogrel therapy and triple therapy carried a more than 3-fold higher risk than did Warfarin monotherapy (Morten L et al., 2010).

Conclusion

The prevalence of thromboembolism and bleeding events are small in our setting with the percentage of 1.4% and 2.8% respectively. One ischemic stroke case was found in each group of Rivaroxaban 15 mg and Dabigatran 150 mg meanwhile bleeding events were found in two patients within each group of Warfarin and Rivaroxaban. These events mostly attributed by the predisposed risk factors. More thorough and prospective cohort study should be performed to defy outliers.

Acknowledgment

We thank to the Director General of Health, Ministry of Health Malaysia and Head of Pharmacy Department, HSNZ for their support towards the success of this study.

Reference

January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; 2014. Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. doi: 10.1016/j.jacc.2014.03.022.

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellollio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy MD, 2019. Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation.

Gage BF, Eby C, Johnson JA, Deych E, Rieder MJ, Ridker PM, et al. 2008. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther.; 84:326–331. doi: 10.1038/.

Madan, S., Shah, S., Partovi, S., & Parikh, S. A. (2014). Use of novel oral anticoagulant agents in atrial fibrillation: current evidence and future perspective. Cardiovascular
diagnosis and therapy, 4(4), 314-23.

Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; 2019. Re-Ly Steering Committee and Investigators, Dabigatran versus warfarin in patients with atrial fibrillation; 361:1139–1151. N Engl J Med., doi: 10.1056/NEJMoa0905561.

Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; 2011. ROCKET AF Investigators. N Engl J Med, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. 365:883–891. doi: 10.1056/NEJMoa1009638.

David J cangemi, Timothy Krill, Rick WeideMAN, Daisha Cipher, Stuart J Spechler, Linda A Feagins,2017. A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin, 112(5):734-739. doi: 10.1038/ajg.2017.39.

Linda A. Feagins, Rick A. Weideman, 2018. Gi Bleeding Risk of DOACs Versus Warfarin: Is Newer Better?

Digestive Diseases and Sciences (2018) 63:1675–1677.

Amelia K. Boehme, Charles Esenwa and Mitchell S.V. Elkind, 2017. Stroke Risk Factors, Genetics, and Prevention https://doi.org/10.1161/CIRCRESAHA.

Sheu, J.J, 2010. Overactive Thyroid May Raise Early Stroke Risk, Stroke: Journal of the American Heart Association.

C Becattini, M Giustozzi, M G Ranalli, G Bogliari, F Cianella, M Verso, G Agnelli, M C Vedovati, 2018. Variation of renal function over time is associated with major bleeding in patients treated with direct oral anticoagulants for atrial fibrillation, DOI: 10.1111/jth.13985.

Morten L. Hansen, MD, PhD Rikke Sørensen, MD Mette T. Clausen, 2010. Risk of Bleeding with Single, Dual, or Triple Therapy with Warfarin, Aspirin, and Clopidogrel in Patients with Atrial Fibrillation, doi:10.1001/archinternmed.2010.27.