

# A single institution's experience with using dabigatran, rivaroxaban and warfarin for prevention of thromboembolism in atrial fibrillation

Proceedings of Singapore Healthcare  
2018, Vol. 27(1) 20–25  
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DOI: 10.1177/2010105817719913  
journals.sagepub.com/home/psh  


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## Abstract

**Background:** Although non-vitamin K antagonist oral anticoagulants (NOACs) are approved for stroke prevention in atrial fibrillation (AF) patients, their use in the local clinical setting has not been well studied. This study aims to evaluate the clinical outcomes of dabigatran, rivaroxaban and warfarin in a tertiary hospital in Singapore.

**Methods:** This is a retrospective cohort study with one-year follow-up. A total of 383 patients recruited between June 2011 and December 2014 were studied. Incidents of stroke, systemic embolism and clinically relevant bleeding events were compared between dabigatran, rivaroxaban and warfarin.

**Results:** Stroke rates were 5.47% per year with warfarin, 7.27% per year with dabigatran (HR=1.32; 95% CI 0.48–3.64;  $p=0.591$ ) and 2.76% per year with rivaroxaban (HR=0.49; 95% CI 0.14–1.69;  $p=0.261$ ). The warfarin group had significantly higher incidence of minor bleeding (62.4% vs 3.64% for dabigatran vs 13.79% for rivaroxaban;  $p<0.001$ ), major bleeding (3.91% for warfarin, 0.91% for dabigatran, 0% for rivaroxaban;  $p=0.028$ ) and other adverse events (51.18% for warfarin, 3.64% for dabigatran, 8.28% for rivaroxaban;  $p<0.001$ ). Incidence of dyspepsia was higher in both NOAC groups compared to warfarin (0% for warfarin, 7.27% for dabigatran, 5.52% for rivaroxaban;  $p=0.003$ ).

**Conclusion:** Stroke and venous thromboembolism rates after one year were comparable among dabigatran, rivaroxaban and warfarin. Warfarin was associated with more bleeding and adverse events while both NOACs were associated with higher rates of dyspepsia. Further study is needed to assess the clinical benefit of NOACs in the Singaporean population.

## Keywords

Warfarin, atrial fibrillation, bleeding, stroke, non-vitamin K antagonist oral anticoagulant

## Introduction

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, affecting about one in four, and it is associated with a three to fivefold increased risk of stroke.<sup>1,2</sup> This risk can be reduced with the use of anticoagulation.<sup>3</sup> Traditionally, warfarin, a vitamin K antagonist, is the drug of choice for oral anticoagulation.<sup>4</sup> However, its popularity is limited by its numerous interactions with drugs, herbs and foods, as well as the need for routine anticoagulation monitoring.<sup>5</sup>

Non-vitamin K oral anticoagulants (NOACs) were developed in an attempt to overcome the disadvantages of warfarin. Unlike warfarin, they have a more predictable dose response and do not require routine monitoring. Currently available NOACs fall into two classes: direct thrombin inhibitors (e.g. dabigatran) and factor Xa inhibitors (e.g. rivaroxaban, apixaban).<sup>4,6</sup> They have demonstrated better, or at least

equivalent, efficacy compared to warfarin in major landmark trials without compromising on safety.<sup>7,8</sup>

At present, there is a lack of post-marketing data on the use of dabigatran and rivaroxaban in Singapore. Thus, our study aimed to compare the clinical outcomes of dabigatran, rivaroxaban and warfarin in a tertiary hospital in Singapore.

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## Methods

### Study design

A one-year retrospective cohort study was conducted at Tan Tock Seng Hospital (TTSH). Recruited patients were followed up for a year from the date of initiation of oral anticoagulant.

### Study population

Patients who fulfilled the following criteria were recruited: (1) have their oral anticoagulation initiated at TTSH; (2) initiated on warfarin from June 2011 to July 2012 for AF; (3) started on dabigatran (between March 2011 and July 2012) or rivaroxaban (between June 2012 and December 2013) for AF; and (4) are intended for long-term anticoagulation. Patients whose anticoagulation therapy was neither started nor followed through at TTSH, intended for short-term use (less than one year) or used to treat venous thromboembolism (VTE) were excluded.

The list of eligible patients on dabigatran and rivaroxaban was generated using the pharmacy dispensing system iPharm, while patients who were newly prescribed with warfarin for AF were identified using TTSH Anticoagulation Clinic's database. The patient list was then reviewed to exclude patients who failed to fulfill the inclusion criteria.

### Data source

Data were retrieved from case notes and computerized patient support systems (CPSS).

### Study drugs

The anticoagulant formulations available at TTSH are dabigatran 75, 110 and 150mg capsules, rivaroxaban 10, 15 and 20mg tablets, and warfarin 1, 3 and 5mg tablets.

### Outcomes

The primary outcome was incidence of stroke (ischaemic and haemorrhagic) or systemic embolic events. Secondary outcomes included clinically relevant bleeding events as well as other adverse events. Major bleeding events were defined using International Society on Thrombosis and Haemostasis (ISTH) criteria [i.e. fatal bleeding; bleeding in a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome); drop in haemoglobin concentration of more than or equal to 2.0g/dL; or transfusion of >2U of whole blood or packed red blood cells].<sup>12</sup> Minor bleeding events were defined as any bleeding event that did not meet the criteria for major bleeding.

### Statistical analysis

Descriptive statistics were used to summarize the patient demographics. Continuous variables were presented as mean (standard deviation) and categorical variables were summarized using frequency (percentages). Chi-square and

ANOVA tests were used to compare baseline characteristics as well as rates of stroke, venous thromboembolism and adverse events among the three treatment groups. A statistically significant difference was defined as  $p$ -value <0.05. Hazard ratios, confidence intervals and  $p$  values were calculated using Cox regression.

All analyses were based on the intention-to-treat principle, and conducted using Stata v13.1 (Stata Corp, College Station, Texas, USA).

## Results

### Patient characteristics

A total of 137 warfarin, 168 dabigatran and 279 rivaroxaban patients were identified. After applying the exclusion criteria, 128 warfarin, 110 dabigatran patients and 145 rivaroxaban patients were eligible. Baseline demographics are summarized in Table 1.

### Primary outcome

No systemic embolic event occurred in all treatment groups. Stroke occurred in seven patients receiving warfarin, eight patients receiving dabigatran, and four patients receiving rivaroxaban. Stroke rates were 5.47 per 100 patient years with warfarin, 7.27 per 100 patient years with dabigatran (HR=1.32; 95% CI = 0.48–3.64;  $p$ -value=0.591) and 2.76 per 100 patient years with rivaroxaban (HR=0.49; 95% CI = 0.14–1.69;  $p$ -value=0.261) (Table 2).

### Secondary outcomes

For safety outcomes, warfarin appeared to be associated with significantly higher rates of minor bleeding events ( $p$ <0.001), major bleeding events ( $p$ =0.028) and other adverse events ( $p$ <0.001) as compared to both NOACs. However, dyspepsia rates were significantly higher ( $p$ <0.001) for both NOACs compared with warfarin (Table 3).

### Comparison of dabigatran and rivaroxaban

The incidence of stroke and VTE was not significantly different between the dabigatran and rivaroxaban groups. Secondary outcomes like bleeding, death and other adverse events also did not differ significantly between the two groups (Table 4).

## Discussion

To our knowledge, this is the first local study to examine the clinical outcomes of dabigatran and rivaroxaban compared to warfarin in AF patients within TTSH. Incidence of stroke, systemic embolism, bleeding and other adverse events were compared.

Some differences in prescribing of oral anticoagulants were observed in this study. Firstly, although there was no significant difference in the baseline stroke risk (as determined by the CHA<sub>2</sub>DS<sub>2</sub>-VASc scores), we observed that a higher proportion of patients on NOACs had previously

**Table 1.** Baseline demographics of patients.

Variable	Treatment drug			p-value
	Warfarin (n=128)	Dabigatran (n=110)	Rivaroxaban (n=145)	
<b>Gender</b>				
Male	69 (53.91%)	61 (55.45%)	74 (51.03%)	0.77
<b>Race</b>				0.148
Chinese	110 (85.94%)	96 (87.27%)	121 (83.45%)	
Malay	13 (10.16%)	5 (4.55%)	14 (9.66%)	
Indian	3 (2.34%)	1 (0.91%)	5 (3.45%)	
Others	2 (1.56%)	8 (7.27%)	5 (3.45%)	
<b>Age, mean (years) (SD)</b>	69.75 (10.39)	70.88 (9.47)	72.19 (9.66)	0.124
<b>Diabetes mellitus</b>	53 (41.41%)	44 (40.00%)	53 (36.55%)	0.698
<b>Hypertension</b>	104 (81.25%)	100 (90.91%)	110 (75.86%)	0.008
<b>CHF or LV dysfunction</b>	36 (28.13%)	19 (17.27%)	31 (21.38%)	0.125
<b>Previous stroke or TIA</b>	67 (52.34%)	50 (45.45%)	65 (44.83%)	0.367
<b>Previous systemic embolic event</b>	0 (0%)	9 (8.18%)	9 (6.21%)	0.001
<b>Known vascular disease</b>	9 (7.03%)	6 (5.45%)	10 (6.9%)	0.864
<b>History of MI</b>	20 (15.63%)	17 (15.45%)	19 (13.1%)	0.806
<b>Mean CHADS<sub>2</sub> score (SD)</b>	2.95 (1.32)	2.75 (1.21)	2.71 (1.56)	0.346
<b>Mean CHA<sub>2</sub>DS<sub>2</sub>VASc score (SD)</b>	4.30 (1.78)	4.20 (1.57)	4.06 (1.95)	0.5522
<b>Mean CrCl (SD)</b>	65.87 (29.97)	72.24 (25.24)	58.89 (24.82)	<0.001
<b>CrCl Range</b>				0.021
>50ml/min	87 (67.97%)	86 (78.18%)	82 (56.55%)	
30–50ml/min	34 (26.56%)	21 (19.09%)	54 (37.24%)	
15–29ml/min	6 (4.69%)	3 (2.73%)	7 (4.83%)	
<15ml/min	1 (0.78%)	0 (0%)	0 (0%)	
Missing	0 (0%)	0 (0%)	2 (1.38%)	
<b>Hepatic impairment</b>	0 (0%)	1 (0.91%)	4 (2.76%)	0.133
<b>Bleed history</b>	52 (40.63%)	22 (20%)	46 (31.72%)	0.003
<b>Previous antiplatelet use</b>	92 (71.88%)	48 (43.64%)	90 (62.07%)	<0.001
<b>On concurrent antiplatelet</b>	34 (26.56%)	14 (12.73%)	27 (18.62%)	0.026
<b>Mean HASBLED score (SD)</b>	2.73 (1.28)	2.48 (1.04)	2.57 (1.25)	0.2659

CHF: congestive heart failure; CHADS<sub>2</sub>: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischaemic attack; CHA<sub>2</sub>DS<sub>2</sub>VASc: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischaemic attack/thromboembolism, age 65–74, vascular disease; CrCl: creatinine clearance; LV: left ventricular dysfunction; SD: standard deviation; TIA: transient ischaemic attack.

**Table 2.** Cox regression model comparing stroke rates of NOACs vs warfarin.

Outcome	Warfarin			Dabigatran			Hazard Ratio (95% CI)	p-value	Rivaroxaban			Hazard Ratio (95% CI)	p-value
	No. of patients	No. of events	Event rate/100 patient years	No. of patients	No. of events	Event rate/100 patient years			No. of patients	No. of events	Event rate/100 patient years		
Stroke after 1 year	128	7	5.47	110	8	7.27	1.32 (0.48–3.64)	0.591	145	4	2.76	0.49 (0.14–1.69)	0.261

The median follow-up time was 365 days.

Hazard ratios are for the dabigatran and rivaroxaban group as compared with the warfarin group.

experienced a systemic embolic event. This could be due to the high proportion of such patients in the clinical trial,<sup>8</sup> which increased physicians' confidence in prescribing NOACs for these patients. Since this study also included patients who were not anticoagulant-naïve, we speculate that some patients may have been switched from warfarin to a NOAC after they experienced a systemic embolic event while on warfarin.

Secondly, although there was no significant difference in baseline bleeding risk (as determined by the HASBLED

score), we observed that there was a significantly higher proportion of warfarin patients who either had a history of bleed or were on concurrent antiplatelets. This could be due to the fact that combination antithrombotic therapy (e.g. oral anti-coagulant with either one or two antiplatelet agents) is commonly indicated for patients with AF with acute coronary syndrome and/or percutaneous coronary intervention and due to limited evidence available for NOACs, warfarin is currently the preferred anticoagulant of choice in such cases.<sup>18,19</sup>

**Table 3.** Rates of bleeding and other adverse events.

Adverse event	Treatment drug			p-value
	Warfarin (n=128)	Dabigatran (n=110)	Rivaroxaban (n=145)	
<b>Minor bleed</b>	77 (61.60%)	4 (3.64%)	14 (9.66%)	<0.001
<b>GI bleeding</b>	3 (2.34%)	2 (1.82%)	4 (2.76%)	0.886
<b>Intracranial bleeding</b>	1 (0.78%)	0 (0%)	2 (1.38%)	0.465
<b>Drop in Hb <math>\geq</math>2g/dL</b>	3 (2.36%)	3 (2.73%)	4 (2.76%)	1
<b>Major bleed</b>	5 (3.91%)	1 (0.91%)	0 (0.00%)	0.028
<b>Dyspepsia</b>	0 (0.00%)	8 (7.27%)	8 (5.52%)	0.003
<b>Other adverse events</b>	65 (51.18%)	4 (3.64%)	11 (7.59%)	<0.001
<b>Death</b>	0 (0.00%)	1 (0.91%)	7 (4.83%)	0.012
<b>Treatment-related death</b>	0 (0.00%)	1 (0.91%)	1 (0.69%)	0.7463

**Table 4.** Rates of stroke, bleeding and other adverse events for dabigatran and rivaroxaban.

Event	Dabigatran (n=110)	Rivaroxaban (n=145)	p-value
<b>Stroke</b>	8 (7.27%)	4 (2.76%)	0.134
<b>Minor bleed</b>	4 (3.64%)	14 (9.66%)	0.084
<b>Major bleed</b>	1 (0.91%)	0 (0.00%)	0.431
<b>Dyspepsia</b>	8 (7.27%)	8 (5.52%)	0.567
<b>Other adverse events</b>	4 (3.64%)	11 (7.59%)	0.192
<b>Death</b>	1 (0.91%)	7 (4.83%)	0.143

We noticed that the stroke rates reported in this study appeared to be much higher than those reported in clinical trials such as the RE-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)] trial for dabigatran and ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial for rivaroxaban; even the ROCKET-AF trial, which recruited patients with a higher baseline stroke risk (mean CHADS<sub>2</sub> score of 3.48 $\pm$ 0.94 for the rivaroxaban group vs 3.46 $\pm$ 0.95 for the warfarin group), showed overall lower stroke rates.<sup>7,8</sup> This discrepancy could be attributed to differences in design (retrospective cohort study versus randomized controlled trial), sample sizes, recruitment criteria and follow-up duration.

In this study, there was no significant difference in stroke rates between dabigatran, rivaroxaban and warfarin. These results are largely consistent with that from RE-LY and ROCKET-AF, which showed that both dabigatran dosed at 110mg twice daily and rivaroxaban had comparable stroke risk to warfarin.<sup>7,8</sup> Although the RE-LY trial showed that dabigatran dosed at 150mg twice daily was superior to warfarin in terms of stroke prevention, this difference was not detected in our study.<sup>7</sup> A possible reason could be that this study did not distinguish between patients on different doses of dabigatran as the sample size was too small. Nonetheless, several other observational studies have reported similar effectiveness between various doses of dabigatran and warfarin in the “real-world” clinical setting, suggesting that dabigatran 150mg’s superior effect may be diminished in clinical practice.<sup>20,21,22</sup>

Warfarin was associated with significantly higher rates of bleeding and adverse events compared to dabigatran and rivaroxaban. This was partly similar to the results of the RE-LY study, where warfarin had higher major and minor bleed

rates than dabigatran dosed at 110mg twice daily, and higher minor bleed rates than dabigatran dosed at 150mg twice daily.<sup>7</sup> One reason for the higher rates of bleeding and adverse events for warfarin in this study could be different monitoring frequency of patients in different treatment groups. In this study, pharmacists from the TTSH Anticoagulation Clinic team followed up with warfarin patients regularly at intervals ranging from two weeks to three months depending on the stability of their International Normalised Ratio (INR). At the follow-up sessions, patients were asked to report bleeding and adverse events that occurred during the treatment period. Patients on NOACs, on the other hand, were not followed up as frequently as those on warfarin. The longer follow-up duration, which ranged from three to six months, for these patients could have resulted in reporting bias.

We recognize, however, that the minor bleeding rates for the warfarin arm in this study could have been falsely elevated. This is because unlike other studies, our study did not limit the definition of “minor bleed” only to bleeding events that were clinically relevant.<sup>7,8,23,24</sup> As such, some nuisance bleeding events could have been included into the analysis even though they were not clinically significant. Nonetheless, our findings are consistent with that from other studies which showed lower bleed rates with NOACs when compared to warfarin.<sup>22,24,26</sup> A large prospective observational study involving 6784 patients from 311 centres across Europe, Israel and Canada also demonstrated that rates of major bleeding were low (2.1 events/100 patient years, compared to 3.6 events/100 patient years in ROCKET-AF) in patients on rivaroxaban in clinical practice.<sup>25</sup>

In this study, both NOACs were associated with significantly higher rates of dyspepsia compared to warfarin. This was observed in RE-LY, where dabigatran dosed at both 110mg twice a day and 150mg twice a day was associated

with significantly higher rates of dyspepsia compared to warfarin.<sup>7</sup> Some studies have also cited dyspepsia as a common reason for treatment discontinuation.<sup>27,28,30</sup> It has been postulated that this gastrointestinal side effect is caused by tartaric acid, present in the core of dabigatran capsules, which is used to create an acidic environment for drug absorption.<sup>29</sup> In contrast, dyspepsia is not a commonly reported symptom for rivaroxaban in literature.<sup>31</sup> It was also not evaluated in the ROCKET-AF study.<sup>8</sup> As we did not collect information on factors that may predispose patients to dyspepsia, such as any history of dyspepsia, concomitant use of medications that may contribute to dyspepsia (e.g. non-steroidal anti-inflammatory medications, antibiotics, steroids), or any concomitant use of gastric protectants (e.g. proton pump inhibitors, H2 receptor antagonists), it is not known if the higher rates of dyspepsia observed with rivaroxaban in this study were due to these factors. More information would be needed before any conclusion can be made.

Although the death rate in the rivaroxaban group was significantly higher than the other groups (4.83% vs 0.91% for dabigatran and 0% for warfarin,  $p=0.012$ ), only one case appeared to be treatment-related because the subject had died of spontaneous intracerebral haemorrhage. Among the other death cases, three were due to infections, one was due to non-ischaemic cardiomyopathy while reasons for the other deaths were unspecified. The single case of death in the dabigatran group was due to non-ST-segment elevation myocardial infarction (NSTEMI), and it could have been treatment-related since dabigatran was found to be associated with increased risk of myocardial infarction when compared with warfarin in several randomized controlled trials.<sup>10,11</sup>

There were no significant differences in rates of stroke, VTE and adverse events between dabigatran and rivaroxaban. This suggests that the NOACs can be selected based on patient factors and preference.

## Study limitations and future directions

Apart from the aforementioned reasons, other limitations of this study include its small sample size and short follow-up duration. Due to its small sample size, propensity matching could not be done to adjust for baseline differences and this limited the validity of our data. In addition, adherence to study medications, as well as the time in therapeutic INR range (TTR) for patients on warfarin were not measured.

Future studies should aim to have a longer follow-up duration to assess the long-term clinical outcomes of NOACs, since these drugs are usually intended for long-term use. Other future directions to consider include evaluating the individual doses of NOACs (e.g. dabigatran 110mg twice daily vs 150mg twice daily dosing), as well as adherence to treatment drugs.

## Conclusion

In this study, stroke and venous thromboembolism rates appeared to be comparable among dabigatran, rivaroxaban and warfarin. Warfarin was associated with more bleeding

and adverse events while the NOACs were associated with higher rates of dyspepsia. However, due to the observational nature and small sample size of this study, more studies with larger sample sizes are required to affirm the real-world benefit of NOACs, and to provide guidance for the choice of anticoagulation in AF patients.

## Acknowledgements

The authors thank medical statistician Sun Bing for her help in statistical analysis.

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

## Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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