Original Article

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A Real-world Experience of the Safety and Efficacy of Non-vitamin K Oral Anticoagulants Versus Warfarin in Patients with Non-valvular Atrial Fibrillation—A Single-centre Retrospective Cohort Study in Singapore

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Abstract

Introduction: Non-vitamin K oral anticoagulants (NOACs) were shown to have better outcomes than warfarin for non-valvular atrial fibrillation (NVAF). Given limited local real-world data, this study aims to evaluate the safety and efficacy of NOACs versus warfarin for NVAF in Singapore.

Methods: This single-centre retrospective cohort study included 439 patients ≥ 21 years old that were newly prescribed with oral anticoagulants (OACs) for NVAF in 2015. Follow-ups for patients upon OAC initiation lasted either for 2 years or until the occurrence of bleeding or thromboembolism event or death (whichever was earlier). Primary endpoints included major bleeding and stroke, while secondary endpoints included overall bleeding and thromboembolic events. Time-to-events was evaluated via Kaplan-Meier survival analysis. Data on time in therapeutic range (TTR) and compliance were analysed.

Results: Patients were assigned to 4 groups: warfarin (157, 35.8%), rivaroxaban (154, 35.1%), apixaban (98, 22.3%) and dabigatran (30, 6.8%). With a mean age of 70.8 (±10.8) years old, the population were predominantly males (56.5%) and comprised Chinese (73.8%), Malays (18.7%) and others (7.5%). The rates of stroke per year were 0.7%, 1.7%, 2.2% and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively (P=0.411), whereas those of major bleeding were 2.7%, 1.4%, 2.2% and 0% (P=0.560). As compared to warfarin, no significant differences were observed for risks of stroke and of major bleeding for rivaroxaban (adjusted hazard ratio (HR) 4.19, 95% confidence interval (CI) 0.68–26.05, P=0.124 and adjusted HR 0.43, 95% CI 0.12–1.59, P=0.207) and apixaban (adjusted HR 5.33, 95% CI 0.85–33.34, P=0.074 and adjusted HR 1.54, 95% CI 0.39–6.15, P=0.538). Mean TTR was 68.8% (±24.3%) for warfarin. Compliance rates for rivaroxaban, apixaban, and dabigatran were 56.6%, 59.2%, and 44.8%, respectively (P=0.177).

Conclusion: NOACs were associated with similar stroke and major bleeding rates as warfarin for NVAF.

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Keywords: Anticoagulant, Asian, atrial fibrillation, compliance, haemorrhage, thrombosis

Introduction

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia associated with significant morbidity and mortality. According to the Framingham Heart Study, patients with AF are susceptible to increased risks of stroke and death by up to 5-fold and 2-fold, respectively.[1,2] Furthermore, the lifetime risk of AF has been found to be approximately 25% for those ≥ 40 years old regardless of gender, while its prevalence increases exponentially with age.[3,4] In Singapore, the overall prevalence of AF has been estimated to be 1.5% for individuals ≥ 55 years old and nearly quadrupled to 5.8% for those ≥ 80 years old.[5,6] Consequently, complications from AF, such as stroke or thromboembolism, impose

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a substantial burden to the economy and public health sector due to the need for medications, hospitalisations and long-term care.[7] Therefore, initiation of anticoagulation is essential for patients with AF in view of the significant health and economic burden, especially for a society with an ageing population like Singapore.

Warfarin has been used traditionally as an OAC for thromboprophylaxis and stroke prevention in NVAF. However, the presence of numerous drug and food interactions warrants the need for routine blood tests to determine the International Normalised Ratio (INR) for dose titrations, which can be cumbersome for patients. Moreover, its narrow therapeutic index makes it challenging for maintenance, while INR fluctuations above or below the stipulated range may compromise its safety or efficacy, leading to bleeding or thromboembolism, respectively.[8-10] In recent years, the introduction of NOACs for use in NVAF has served to mitigate the problems associated with warfarin. Major randomised clinical trials, which included Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY), demonstrated favourable safety and efficacy outcomes when apixaban, rivaroxaban and dabigatran were compared against warfarin, respectively.[11-18] However, head-to-head trials comparing the safety and efficacy outcomes between NOACs and warfarin were not extensive. Furthermore, limited real-world data is available for the local population in Singapore. This study aims to evaluate the safety and efficacy outcomes between NOACs and warfarin for patients with NVAF in Singapore.

Methods

In this single-centre retrospective cohort study, patients aged ≥ 21 years old with NVAF and newly initiated with OACs between 1 January 2015 and 31 December 2015 were identified from electronic medical records. Firstly, the pharmacy system was used to generate a list of patients on warfarin, rivaroxaban, apixaban or dabigatran, regardless of indication and time of initiation. Secondly, patients newly started on these OACs in 2015 were then identified. Lastly, the indication for NVAF was determined from consultation notes by cardiovascular medicine or pharmacy anticoagulation clinic, Hospital Inpatient Discharge Summary, and patients' problem lists through Sunrise Care Manager. Those receiving anticoagulation for other indications (e.g. deep vein thrombosis or pulmonary embolism) and diagnosed with valvular AF (presence of rheumatic mitral stenosis, mechanical or bio-prosthetic heart valve or mitral valve repair) were excluded from the study.[9] Follow-ups for patients upon OAC initiation lasted either for 2 years or until the occurrence of bleeding, thromboembolism event or death (whichever was earlier). For scenarios involving a switch or discontinuation of OACs during the study period, the allocation of patients was such that they would be categorised as belonging to the treatment groups based on the first OAC prescribed. Ethics approval was obtained from SingHealth Centralised Institutional Review Board.

Data on patient baseline demographics and clinical characteristics required for the computation of CHA_2DS_2-VASc and HAS-BLED scores were collected. Information on other relevant factors potentially affecting the outcomes of this study were also gathered, such as compliance, concomitant medications (e.g. antiplatelets), comorbidities (e.g. hypertension, heart failure or diabetes), and smoking or alcoholic status. Creatinine clearance (CrCl) was calculated through Cockcroft-Gault equation to evaluate the dose appropriateness of NOACs in accordance to the American Heart Association/American College of Cardiology/Heart Rhythm Society 2014 Guidelines.[9] Patients on rivaroxaban received a 20mg once-daily regimen if CrCl > 50ml/min (dose adjusted to 15mg once daily if CrCl was 15–50ml/min). Patients on apixaban received a 5mg twice-daily regimen if CrCl > 25ml/min (dose adjusted to 2.5mg twice daily if any 2 of the following factors were present: age ≥ 80 years old, weight ≤ 60kg, and serum creatinine > 1.5mg/dl). Patients on dabigatran received a 150mg twice-daily regimen if CrCl > 30ml/min (dose adjusted to 110mg twice daily if high bleeding risk was present).[9]

Primary safety and efficacy endpoints included major bleeding and stroke, respectively. According to criteria stipulated by the International Society on Thrombosis and Haemostasis, major bleeding is defined as symptomatic bleeding that occurs at a critical site (e.g. intracranial, intraspinal, intraocular, intra-articular, intramuscular with compartment syndrome, retroperitoneal or pericardial), results in a decrease in haemoglobin by ≥ 2g/dl, necessitates transfusion of ≥ 2 units of packed red cells, or causes death.[19] An expert consensus document collaboratively drafted by the American Heart Association and American Stroke Association defines stroke as an episode of acute neurological dysfunction that is secondary to ischaemia or haemorrhage and lasts for ≥ 24 hours or until death.[20]

Secondary safety and efficacy endpoints included overall bleeding and thromboembolic events. This

study defines overall bleeding as a composite of major bleeding and clinically relevant non-major bleeding. The International Society on Thrombosis and Haemostasis defines clinically relevant non-major bleeding as any acute overt bleeding which does not fulfil the criteria for major bleeding but necessitates hospitalisation, medical intervention by healthcare professionals, and an increased level of care.[21] This study defines thromboembolic events as a composite of stroke, transient ischaemic attack, and systemic embolism. A transient ischaemic attack refers to a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia without acute infarction.[20,22] Systemic embolism refers to an acute vascular occlusion of an extremity or organ, with evidence via imaging, surgery or autopsy.[13] The number of events occurring for each endpoint and follow-up duration were recorded for all treatment groups. Subsequently, the crude incidence (per 100 person-years) was calculated through the following formula:

$$\frac{\text{no. of events}}{\frac{\text{mean follow-up days}}{365} \times \text{no. of patients}} \text{ x } 100\%$$

The event rates per 100 person-years were presented as proportions of patients per year.

The TTR was calculated through the Rosendaal method to assess the quality of anticoagulation for patients on warfarin. It measures the duration of time in which the INR values are within the desired therapeutic range.[23] In this study, the target INR range for NVAF could either be between 2.0 and 3.0 according to international guidelines or be decided by the clinician.[9,10] A deviation of 0.2 from the target INR range was allowed and considered therapeutic. INR values during the first 7 days of warfarin initiation and periods of instability (e.g. hospitalisation) were excluded from TTR calculation.

Given that therapeutic drug monitoring for NOACs (anti-Xa and anti-IIa levels) are not routinely available, compliance is important in determining the quality of anticoagulation. The medication possession ratio (MPR) was used to evaluate the compliance of NOAC users. It is defined as:

$$\frac{\text{total number of days of medications dispensed}}{\text{last Rx date} - \text{first Rx date} + \text{no. of days of medications dispensed from last Rx}}$$

for a given period of time. A minimum of 2 prescription refills is required for MPR calculation.[24-26] Compliance to NOACs is achieved when MPR $\geq$ 0.8. Medication prescribing and collection data were obtained electronically from Sunrise Care Manager and Pharmacy Management System, whereas those from non-governmental institutions (e.g. private clinics and hospitals or overseas refills) could not be tracked and were excluded.

For categorical variables, Pearson's chi-square test and Fisher's Exact test were used to evaluate the differences in baseline demographics and clinical characteristics (e.g. gender, ethnicity and comorbidities) between the treatment groups. For numerical variables, one-way ANOVA and Kruskal-Wallis test were used for comparing parametric (e.g. age and follow-up days) and non-parametric data distribution (e.g. CHA_2DS_2-VASc and HAS-BLED scores), respectively. Logistic regression was used to test for differences in the incidence between the treatment groups for each endpoint with the warfarin group as reference. Odds ratios (OR) with 95% confidence intervals (CI) were obtained. Kaplan-Meier survival analysis and log-rank test were done to evaluate the differences in the time-to-event between the treatment groups for each endpoint with the warfarin group as reference. Cox regression analysis was performed for the bleeding and thrombosis outcomes whereby the individual factors of the HAS-BLED and CHA_2DS_2-VASc scores were specified as covariates to control for confounding. Adjusted hazard ratios (HR) with 95% CIs were reported. Survival curves were plotted for visual comparisons. Post-hoc comparisons were conducted using warfarin group as reference, when overall comparison showed significant differences between the treatment groups. A P value of <0.05 is considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences Software for Windows, Version 19.0 (IBM Corp, Armonk, US).

Results

A total of 564 patients newly prescribed with OACs between 1 January 2015 and 31 December 2015 were assessed for suitability for inclusion in this study. Upon selection, 439 patients taking the OACs for NVAF were included and then assigned to 4 groups: warfarin (157, 35.8%), rivaroxaban (154, 35.1%), apixaban (98, 22.3%) and dabigatran (30, 6.8%) (Fig. 1). With a mean age of 70.8 (±10.8) years old, the population were predominantly males (56.5%) and comprised Chinese (73.8%), Malays (18.7%), and others (7.5%). Median CHA_2DS_2-VASc scores were similar between the treatment groups (P=0.156). The initiation of OACs was warranted and appropriate as per guideline recommendations since the majority (85.2%) of the patients had CHA_2DS_2-VASc scores of $\geq$ 2.[9,10] The rivaroxaban and dabigatran groups had significantly lower median HAS-BLED scores than the warfarin group. The rates of switching from one

OAC to another were as follows: those initially on warfarin (13%), rivaroxaban (21%), apixaban (13%) and dabigatran (37%). The follow-up duration for all patients was 684.1 (±157.0) days and there was no loss to follow-up (Table 1). Other baseline characteristics are also listed in Table 1.

For the primary outcomes, the crude incidences per year for stroke and major bleeding were 1.3% (95% CI 0.8–2.4) and 1.9% (95% CI 1.2–3.1), respectively. The rates of stroke per year were 0.7%, 1.7%, 2.2%, and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively, with no statistically-significant differences between the groups (*P*=0.411). The rates of major bleeding per year were 2.7%, 1.4%, 2.2% and 0% for the respective groups, likewise with no statistically-significant differences between them (*P*=0.560) (Table 2).

Time-to-event analyses have revealed no significant difference in the risks of stroke for the rivaroxaban (adjusted HR 4.19, 95% CI 0.68–26.05, *P*=0.124) and apixaban groups (adjusted HR 5.33, 95% CI 0.85–33.34, *P*=0.074) as compared to the warfarin group. There was also no significant difference in the risks of major bleeding for the rivaroxaban (adjusted HR 0.43, 95% CI 0.12–1.59, *P*=0.207) and apixaban groups (adjusted HR 1.54, 95% CI 0.39–6.15, *P*=0.538) as compared to the warfarin group. For the dabigatran group, no stroke or major bleeding was observed, hence the associated HR with the 95% CI could not be determined (Fig. 2).

For the secondary outcomes, the crude incidences per year for thromboembolic events and overall bleeding were 1.0% (95% CI 2.1–4.4) and 5.7% (95% CI 4.4–7.4), respectively. The rates of thromboembolic events per year were 1.0%, 3.4%, 6.6% and 0% for warfarin, rivaroxaban, apixaban and dabigatran, respectively, with statistically-significant differences between the groups (*P*=0.003). The rates of overall bleeding per year were 4.7%, 5.5%, 8.3% and 4.0% for the respective groups, with no statistically-significant differences between them (*P*=0.406) (Table 2).

Time-to-event analyses have shown that the rivaroxaban (adjusted HR 4.42, 95% CI 1.18–16.62, *P*=0.028) and apixaban groups (adjusted HR 7.10, 95% CI 1.97–25.63, *P*=0.003) had significantly higher risk of thromboembolic events than the warfarin group. For the dabigatran group, no thromboembolic events were observed, hence the associated HR with the 95% CI could not be determined. As compared to the warfarin group, there was no significant difference in the risks of overall bleeding for the rivaroxaban (adjusted HR 1.19, 95% CI 0.51–2.74, *P*=0.688), apixaban (adjusted HR 2.41, 95% CI 0.96–6.02, *P*=0.061) and dabigatran groups (adjusted HR 0.95, 95% CI 0.20–4.45, *P*=0.945) (Fig. 2).

The mean TTR for the warfarin group was 68.8% (±24.3%). The percentages of patients with MPR ≥ 0.8 were 56.6%, 59.2% and 44.8% for the rivaroxaban, apixaban and dabigatran groups, respectively, by which they were considered to have been compliant with the medications. The compliance rates were found to be similar among the NOAC groups (*P*=0.177).

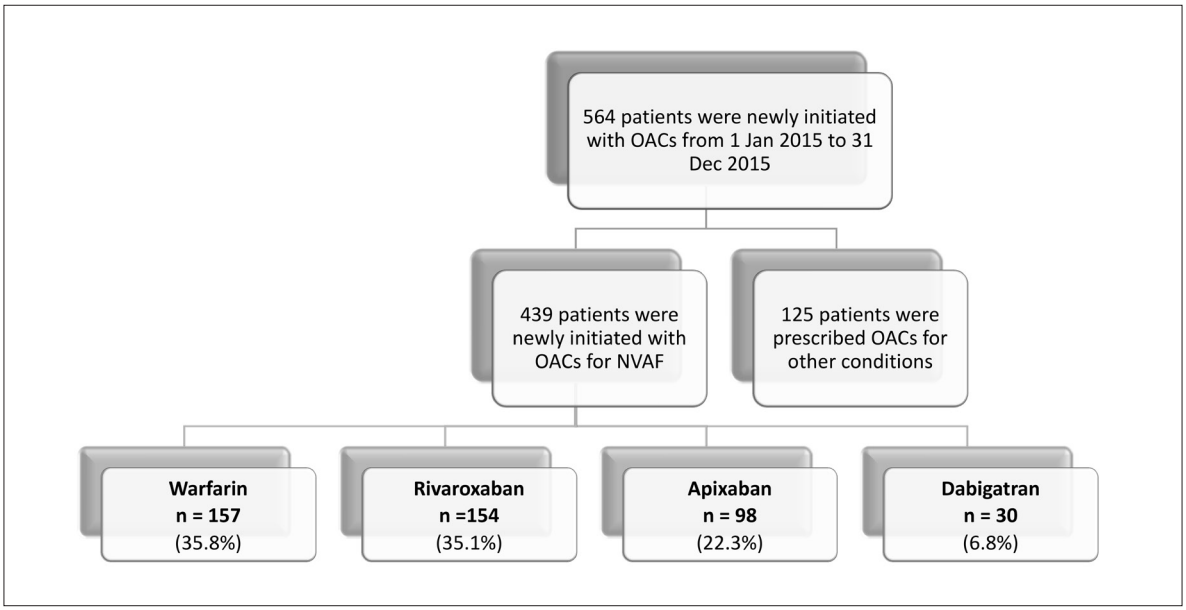


Fig. 1. Flowchart of study enrolment process
NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant

Table 1. Baseline characteristics of patients in the respective treatment groups

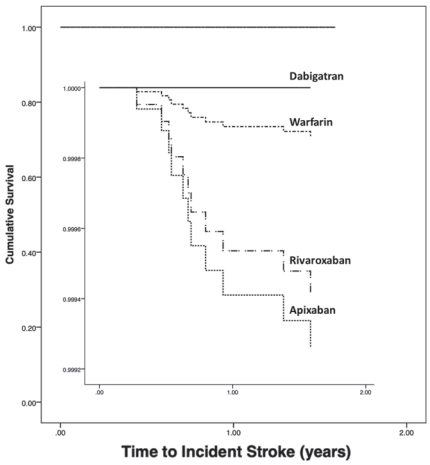
	Overall	Warfarin	Rivaroxaban	Apixaban	Dabigatran	*P* value
n (%)	439 (100)	157 (35.8)	154 (35.1)	98 (22.3)	30 (6.8)	-
Female, n (%)	191 (43.5)	66 (42.0)	66 (42.9)	46 (46.9)	13 (43.3)	0.889
Race, n (%)						
Chinese	324 (73.8)	110 (70.5)	116 (75.3)	73 (74.5)	25 (83.3)	
Malay	82 (18.7)	35 (22.3)	28 (18.2)	15 (15.3)	4 (13.3)	0.648
Others	33 (7.5)	12 (7.6)	10 (6.5)	10 (10.2)	1 (3.3)	
Mean age, years (SD)	70.8 (10.8)	70.4 (10.4)	70.5 (11.1)	72.9 (10.6)	67.4 (11.4)	0.069
CHA_2DS_2-VASc scores						
Median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (1.0–4.0)	0.156
0, n (%)	22 (5.0)	2 (1.3)	8 (5.2)	6 (6.1)	6 (20.0)	-
1, n (%)	43 (9.8)	20 (12.7)	10 (6.5)	10 (10.2)	3 (10.0)	-
≥2, n (%)	374 (85.2)	135 (86.0)	136 (88.3)	82 (83.7)	21 (70.0)	-
HAS-BLED scores						
Median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)*	1.0 (1.0–2.0)	1.0 (1.0–1.0)*	<0.001
0, n (%)	77 (17.5)	19 (12.1)	37 (24.0)	15 (15.3)	6 (20.0)	-
1-2, n (%)	320 (72.9)	113 (72.0)	108 (70.1)	75 (76.5)	24 (80.0)	-
≥3, n (%)	42 (9.6)	25 (15.9)	9 (5.9)	8 (8.2)	0 (0.0)	-
History of thrombosis and bleeding, n (%)						
Previous thromboembolic events	72 (16.4)	31 (19.7)	16 (10.4)*	20 (20.4)	5 (16.7)	0.051
Previous overall bleeding	15 (3.4)	8 (5.1)	0 (0)	6 (6.1)	1 (3.3)	0.157
Comorbidities, n (%)						
Hypertension	338 (77.0)	125 (79.6)	128 (83.1)	65 (66.3)*	20 (66.7)	0.007
Heart failure	120 (27.3)	57 (36.3)	33 (21.4)*	26 (25.5)	4 (13.3)*	0.007
Diabetes	169 (38.5)	63 (40.1)	63 (40.9)	35 (35.7)	8 (26.7)	0.449
Ischemic heart disease	154 (35.1)	58 (37.7)	51 (33.1)	38 (24.7)	7 (4.5)	0.406
Concomitant antiplatelets, n (%)						
SAPT	146 (33.3)	65 (41.4)	50 (32.5)	22 (22.4)*	9 (30)	0.018
DAPT	26 (5.9)	13 (8.3)	9 (5.8)	2 (2.0)	2 (6.7)	0.288
Mean CrCl, ml/min (SD)	60.3 (27.9)	58.6 (29.9)	60.5 (25.5)	58.7 (28.6)	70.9 (28.4)	0.166
Mean follow-up duration, days (SD)	684.1 (157.0)	691.7 (145.3)	690.5 (141.4)	684.5 (160.5)	609.8 (246.0)	0.137

CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥ 75 years old, diabetes mellitus, stroke/transient ischaemic attack, vascular disease, age 65–74 years old, sex category (female); CrCl: creatinine clearance; DAPT: dual anti-platelet therapy; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile International Normalised Ratio, elderly age > 65 years old; IQR: interquartile range; SAPT: single anti-platelet therapy; SD: standard deviation

*P<0.05 when compared to warfarin group (reference group)

Primary Endpoints

A) Stroke

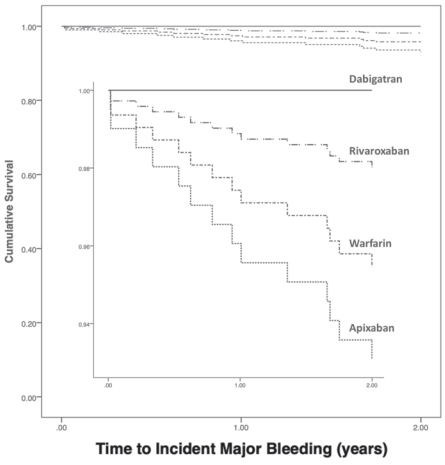


	Adjusted HR (95% CI)	*P* value
Rivaroxaban	4.19 (0.68–26.05)	0.124
Apixaban	5.33 (0.85–33.34)	0.074
Dabigatran	0.00 (-)	0.982

Number at risk:

Time (Years)	0	1	2
Warfarin	155	155	155
Rivaroxaban	151	149	149
Apixaban	94	94	94
Dabigatran	30	30	30

B) Major Bleeding

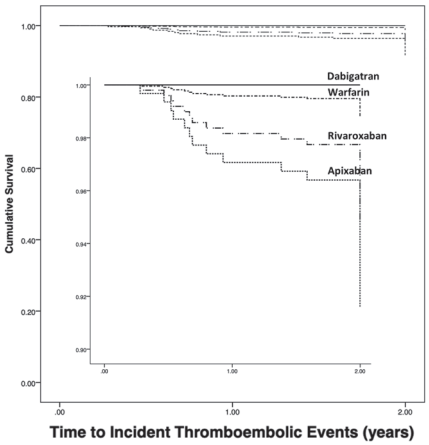


	Adjusted HR (95% CI)	*P* value
Rivaroxaban	0.43 (0.12–1.59)	0.207
Apixaban	1.54 (0.39–6.15)	0.538
Dabigatran	0.00 (-)	0.984

Number at risk:

Time (Years)	0	1	2
Warfarin	155	155	147
Rivaroxaban	151	149	145
Apixaban	94	94	90
Dabigatran	30	30	30

C) Thromboembolic Events

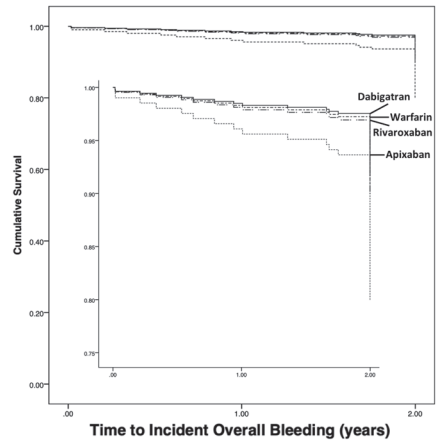


	Adjusted HR (95% CI)	*P* value
Rivaroxaban	4.42 (1.18–16.62)	0.028*
Apixaban	7.10 (1.97–25.63)	0.003*
Dabigatran	0.00 (-)	0.976

Number at risk:

Time (Years)	0	1	2
Warfarin	155	155	154
Rivaroxaban	151	149	144
Apixaban	94	94	86
Dabigatran	30	30	30

D) Overall Bleeding



	Adjusted HR (95% CI)	*P* value
Rivaroxaban	1.19 (0.51–2.74)	0.688
Apixaban	2.41 (0.96–6.02)	0.061
Dabigatran	0.95 (0.20–4.45)	0.945

Number at risk:

Time (Years)	0	1	2
Warfarin	155	155	141
Rivaroxaban	151	149	133
Apixaban	94	94	79
Dabigatran	30	30	28

Fig. 2. Cox-regression survival curves depicting time-to-event for each endpoint
CI: confidence interval; HR: hazard ratio
**P*<0.05 when compared to warfarin group (reference group)
Note: Cumulative survival of 1.0 represents no event and survival plots are presented up to 2 years. Initial number of patients at risk differed from the number of patients recruited into each study group because some patients died during the recruitment year (or less than 1 year)

Table 2. Incidence of bleeding and thrombosis event in the respective treatment groups

	Overall (n = 439)	Warfarin (n = 157)	Rivaroxaban (n = 154)	Apixaban (n = 98)	Dabigatran (n = 30)	*P* value
Stroke[a]						
Events, n (%)	11 (2.5)	2 (1.3)	5 (3.2)	4 (4.1)	0 (0.0)	0.411
Incidence rate[e]	1.3	0.7	1.7	2.2	0.0	-
Thromboembolic events[b]						
Events, n (%)	25 (5.7)	3 (1.9)	10 (6.5)	12 (12.2)	0 (0.0)	0.003
Incidence rate[e]	1.0	1.0	3.4	6.6*	0.0	-
Major bleeding[c]						
Events, n (%)	16 (3.6)	8 (5.1)	4 (2.6)	4 (4.1)	0 (0.0)	0.560
Incidence rate[e]	1.9	2.7	1.4	2.2	0.0	-
Overall bleeding[d]						
Events, n (%)	47 (10.7)	14 (8.9)	16 (10.4)	15 (15.3)	2 (6.7)	0.406
Incidence rate[e]	5.7	4.7	5.5	8.3	4.0	-

[a]Ischaemic stroke only
[b]Composite of stroke, transient ischaemic attack and systemic embolism
[c]Symptomatic bleeding that occurred at a critical site, resulted in a decrease in haemoglobin by ≥ 2g/dl, required transfusion of ≥ 2 units of packed red cells, or caused death
[d]Composite of major bleeding and clinically relevant non-major bleeding
[e]Per 100 person-years
*P<0.05 when compared to warfarin group (reference group)

Discussion

The rivaroxaban and apixaban groups demonstrated similar time-to-events for stroke, major bleeding and overall bleeding as compared to the warfarin group. However, the 2 groups had significantly shorter time to thromboembolic events as compared to the warfarin group. The dabigatran group demonstrated similar time to overall bleeding as compared to the warfarin group. No stroke, major bleeding and thromboembolic events occurred in the dabigatran group.

The outcomes on stroke and major bleeding for the rivaroxaban and apixaban groups were consistent with the literature, including studies involving patients of Asian origin.[16,27-30] The shorter time to thromboembolic events for these 2 groups might have been attributed to the relatively low compliance in this real-world study (the proportions of patients with MPR ≥ 0.8 were 56.6% and 59.2% for the rivaroxaban and apixaban group, respectively). The pharmacokinetic consideration is that the short half-life of NOACs will lead to an elevated risk of thrombosis when doses are missed, hence the importance of compliance. Studies involving populations in Taiwan and Singapore have found lower serum drug levels among Asians prescribed rivaroxaban than non-Asians.[31,32] This deviation from the expected levels in clinical studies might have led to the shorter time to thromboembolic events for the rivaroxaban group in this study. Most patients on rivaroxaban (82.6%) received an appropriate renally adjusted dose based on CrCl (excluding 6 patients with incomplete data). All patients on apixaban (100%) received an appropriate dose adjusted based on their age, weight and CrCl (excluding 5 patients with incomplete data).

It is difficult to elucidate the safety and efficacy for dabigatran because of the low incidence of outcomes. This is attributed to the small sample size, with one underlying reason being the clinicians' preference for rivaroxaban or apixaban given their less stringent criteria for renal dose adjustments. Another plausible reason is that the population in this study were generally more advanced in age with poorer renal function, for whom dabigatran would be inappropriate (since it is contraindicated in individuals with CrCl < 30ml/min who were excluded from the RE-LY trial).[13] Patients in the dabigatran group are mostly younger with mean age of 67.4 (±11.4) years old and better renal function as reflected by the mean CrCl of 70.9 (±28.4) ml/min. With the exception of 1 patient,

those on dabigatran received an appropriate renally adjusted dose based on CrCl. Future research with larger sample sizes is necessary to more accurately characterise the safety and efficacy of dabigatran for NVAF management in the real-world setting.

In this study, the warfarin group had a higher mean TTR of 68.8% (±24.3%) than those reported in major clinical trials (ranging from 55% to 65%).[11-13] This could be attributed to compliance reinforcement and regular INR monitoring by the pharmacist-led anticoagulation clinics. The high TTR might have contributed to the lower rate of stroke and thromboembolic events in the warfarin group as compared to the rivaroxaban and apixaban groups. Therefore, warfarin remains an option for NVAF management when TTR can be optimised.

The international consensus for defining compliance to medications is a compliance rate of at least 80%. The International Society for Pharmaceutical and Outcomes Research defines compliance as MPR $\geq$ 0.8.[25,33] The data on compliance herein revealed that an MPR $\geq$ 0.8 was noted for 56.6% of patients on rivaroxaban, 59.2% of those on apixaban, and 44.8% of those on dabigatran. The relatively low compliance rate might be a contributory factor to the higher rates of stroke and thromboembolic events in the rivaroxaban and apixaban groups as compared to the warfarin group. Hence, compliance to NOACs is important to achieve better outcomes. Numerous reasons have been found to underlie non-compliance such as polypharmacy, side effects of medications, costs, personal beliefs and forgetfulness.[34] For NOACs, compliance remains a problem in the real-world setting because they are more expensive than warfarin and less affordable for some patients.[26,35] In Singapore, NOACs are classified as 'non-standard' drugs that are not eligible for subsidies (unless the patients qualify for financial aid schemes such as Medication Assistance Fund).[36] Affordability is thus a vital aspect of compliance in the practical setting that needs to be addressed in order to optimise the usage of NOACs for NVAF management locally.

Medication-use strategies may be employed to enhance patients' compliance to NOACs. Firstly, in view of the rising trend of NOAC use for NVAF in Singapore, pharmacist-led anticoagulation clinics can be expanded to include NOAC monitoring, where compliance reinforcement, renal function tests, dosage adjustments, identification of drug interactions, and smooth transition between OACs can be performed.[37] According to Shore et al., compliance to dabigatran improved with the introduction of pharmacist-led clinics for monitoring.[38] Furthermore, medication therapy management and counselling sessions in the outpatient setting can be conducted for patients non-compliant to NOACs. Secondly, the involvement of medical social workers is also important to ensure that NOACs remain affordable to patients, such that compliance is not compromised. Thirdly, a team-based approach to include doctors, nurses, pharmacists, case managers and medical social workers is essential for the success in ensuring compliance to NOACs, but the implications of such an approach warrant further investigations in the local context, especially in terms of its cost-effectiveness. Lastly, validated questionnaires for compliance may be conducted for patients on NOACs to identify drug-related problems and non-compliance.[24]

Despite challenges for NOACs involving compliance and affordability, there are reasons to support their use for NVAF in Singapore. Although NOACs cost more than warfarin, the healthcare resource utilisation was found to be lower for NOACs in several real-world studies.[39] The higher cost of NOACs is usually offset by the lower medical costs incurred from fewer outpatient visits (since NOACs do not necessitate INR monitoring) and lower hospitalisation rates (since NOACs contribute to better clinical outcomes), as compared to warfarin. Furthermore, a meta-analysis by Wang et al. showed that the risks of ischaemic stroke, major bleeding and all-cause mortality were lower among Asians than non-Asians on standard-dose NOACs.[40] Therefore, NOACs can be considered in NVAF management in Singapore due to the financial and clinical benefits, though desirable outcomes were not herein observed.

Several limitations in this study need to be addressed. Firstly, the power of this single-centre study was limited by its small sample size, especially the dabigatran group. Hence, pooled data from various institutions could be obtained subsequently to enhance the quality of results. Secondly, the reasons for switching OAC and its effects were not accounted for and the outcomes were analysed based on the OAC that was first initiated. Ideally, patients enrolled should only be taking a single OAC throughout the entire study period, but the small sample size limited the setting of such an inclusion criterion. Nonetheless, this mirrors the real-world situation whereby adherence to a single OAC is not always achievable. Thirdly, the effects of some baseline characteristics on the outcomes were not evaluated due to inadequate data. These included concomitant medications (e.g. NSAIDs or amiodarone), comorbidities (e.g. hyperlipidaemia, ischaemic heart disease or cancer) and type of AF (e.g. paroxysmal, persistent or permanent). Furthermore, significant differences were noted between the treatment groups for certain baseline

characteristics. For example, the rivaroxaban and dabigatran groups had significantly lower median HAS-BLED scores as compared to the warfarin group, which might have led to an underestimate of the true bleeding risk. Factors contributing to risks of thrombosis and of bleeding were assigned as covariates for survival analyses to mitigate the effect of such differences. Lastly, the impacts on the rates of hospitalisation and healthcare resource utilisation in Singapore were not compared between NOACs and warfarin in this study.

Conclusion

Among patients with NVAF, NOACs were associated with similar rates of stroke and major bleeding as compared to warfarin. Warfarin remains an option for NVAF management when TTR can be optimised.

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