

ORIGINAL RESEARCH ARTICLE

Cardiovascular outcomes of non-vitamin K
antagonist oral anticoagulants among patients
with atrial fibrillationYik Ching Hung*

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Abstract

Introduction: Non-vitamin K antagonist oral anticoagulants (NOACs) effectively reduce thromboembolic stroke risk in patients with non-valvular atrial fibrillation. Evidence suggested dabigatran may carry a higher risk of myocardial infarction (MI); however, whether NOACs differ in cardiovascular safety remains unclear.

Objectives: To compare three NOACs (dabigatran, rivaroxaban, and apixaban) on the risk of MI and sudden cardiac death.

Methods: Using a database search of the New Territories West Cluster of the Hospital Authority of Hong Kong, 1,161 patients with non-valvular atrial fibrillation taking the three NOACs before December 31, 2017 were recruited into the study. Four comparison cohorts were established among factor Xa inhibitors, dabigatran, rivaroxaban, and apixaban. Cox proportional hazard regression analyses were performed among the weighted population. The primary endpoint included a combined risk of MI and sudden cardiac death. Secondary endpoints were major adverse cardiovascular events (MACE; MI, cardiovascular death, heart failure hospitalization, and stroke), individual MACE components, and fatal bleeding.

Results: Rivaroxaban, apixaban, and factor Xa inhibitors were collectively associated with an insignificant trend of lower combined risk of MI and sudden death compared to dabigatran (hazard ratios of 0.72, 0.58, and 0.67, respectively). There were no significant differences in the comparison of rivaroxaban and apixaban.

Conclusion: Dabigatran was associated with higher but insignificant cardiovascular outcomes. Cardiovascular safety may differ among NOACs in non-valvular atrial fibrillation patients.

Keywords: Atrial fibrillation; Non-vitamin K antagonist oral anticoagulants; Myocardial infarction

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1. Introduction

Atrial fibrillation (AF) is one of the most significant arrhythmias encountered in medical practice, and has long been recognized as an independent risk factor for thromboembolic stroke.¹ In high-risk individuals—stratified by the CHA₂DS₂-VASc score—oral anticoagulants reduce the incidence of stroke and thromboembolism.² Over the past years, the landscape of anticoagulation has been transformed by non-vitamin K antagonist oral anticoagulants (NOACs), which include direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). In their

respective landmark trials, these drugs demonstrated stroke-prevention efficacy that was either comparable or superior to warfarin, the vitamin K antagonist that remained the mainstay of oral anticoagulation for decades. Furthermore, NOACs are associated with more favorable safety profiles, characterized by lower rates of life-threatening bleeding and a substantial reduction in the incidence of intracranial hemorrhage.³⁻⁶ These advantages, together with the benefits of fixed dosing, the absence of coagulation profile monitoring requirements, and fewer interactions with food and other medications, have made NOACs the first-line anticoagulation of choice in non-valvular AF patients.

Atrial fibrillation is not only linked to stroke but also to increased susceptibility to myocardial infarction (MI). Evidence has characterized AF as a risk factor for MI independently, with reported relative risks reaching up to twofold compared with populations free of the arrhythmia. The absolute estimates of MI risk among AF patients have varied considerably across different study settings, with figures ranging from 0.4% to 2.5%, and with some Eastern cohorts describing lower event rates.⁷⁻¹³ From a clinical standpoint, cardiovascular events in patients with AF complicate disease management. In particular, prescription of antiplatelet therapy in addition to anticoagulants may be required in patients undergoing coronary stenting to reduce the risk of stent thrombosis.

The historical evidence regarding antithrombotic management of patients with prior MI has demonstrated that vitamin K antagonists confer benefit in reducing recurrent ischemic events when compared with aspirin-based strategies.¹⁴⁻¹⁶ On the other hand, certain studies have reported broadly similar MI rates between warfarin-based regimens and dual antiplatelet therapy, with annual MI event rates falling below 1%.¹⁷ Nevertheless, due to bleeding concerns, therapeutic strategies that simply substitute aspirin with warfarin, or that combine warfarin with aspirin, are generally not endorsed in routine clinical practice. Reflecting this balance between ischemic protection and hemorrhagic hazard, recent clinical guidelines place strong emphasis on minimizing the duration of combined antiplatelet and anticoagulant therapy to the greatest extent that is clinically feasible in patients requiring both classes of drugs, thereby limiting the cumulative bleeding exposure to which patients are subjected.²

The accumulated evidence concerning the cardiovascular safety of NOACs has proven to be considerably less uniform than the evidence regarding

their efficacy in stroke prevention, and this lack of consistency has been particularly pronounced with respect to MI outcomes. The RE-LY trial (landmark phase III study of dabigatran) compared dabigatran against warfarin and reported a higher but statistically non-significant rate of MI among patients receiving dabigatran. Specifically, the trial documented annual MI rates of 0.72%, 0.74%, and 0.53% per year for dabigatran 110 mg, dabigatran 150 mg, and warfarin, respectively. The rates of fatal MI were similarly low and comparable across the treatment arms.³ Of particular importance, the observed effect on MI was not modified by the presence or absence of a history of prior MI.¹⁸ However, because the absolute count of MI events was small, the trial did not possess sufficient power to establish definitively whether a genuine difference in risk existed between the treatment groups statistically. To reflect this finding, the 2010 Canadian Cardiovascular Society guideline issued a note of caution regarding the use of dabigatran in patients considered to be having an elevated risk of cardiovascular events.¹⁹ Contrary to the dabigatran experience, the landmark phase III trials of rivaroxaban and apixaban did not clearly demonstrate comparable associations with increased MI risk.^{4,5}

Direct head-to-head comparisons among the various NOACs in real-world clinical settings have been notably scarce, leaving an important gap in the evidence base that informs everyday prescribing decisions. In an effort to address this gap, a meta-analysis conducted by Loffredo *et al.*²⁰ that compared MI risk between the two classes of NOACs reported that direct thrombin inhibitors were associated with an absolute increase in MI risk of 0.41% relative to warfarin. Such an association was not observed in the group of patients taking factor Xa inhibitors. It is important to recognize, however, that this represented an indirect comparison, as each class of NOACs was compared against warfarin as a comparator rather than being compared directly against one another. Such indirect comparisons, while informative, are subject to inherent limitations and cannot fully substitute for direct analyses of one agent against another within a single population.

In view of these considerations, the question of comparative cardiovascular safety among the NOACs remains highly relevant to clinical practice, particularly within real-world populations characterized by heterogeneous baseline risk factors that may differ substantially from the carefully selected cohorts enrolled in randomized controlled trials. The objective of the current study was therefore to compare the cardiovascular safety of three NOACs—dabigatran, rivaroxaban, and apixaban—within a defined local population.

2. Methods

2.1. Study population and data source

The current investigation was a retrospective cohort study encompassing patients managed within the New Territories West Cluster of the Hospital Authority of Hong Kong. This cluster serves a substantial catchment population of approximately 1.1 million individuals, thereby providing a sizeable and demographically representative base from which to draw the study sample.²¹ Eligible patients were identified through the Clinical Data Analysis and Reporting System, a comprehensive database that aggregates clinical information across the institutions within the cluster. Detailed clinical information of each patient, encompassing physician clinical notes, laboratory investigation results, and pharmacy drug prescription records, was collected from the electronic patient record system.

The study population included adult patients (aged 18 years or older) who carried a diagnosis of non-valvular AF and who had been prescribed dabigatran, rivaroxaban, or apixaban within the medicine and geriatrics wards or outpatient clinics prior to December 31, 2017. Non-valvular AF was operationally defined by the absence of moderate or above mitral stenosis (irrespective of etiology) and by the absence of prosthetic heart valves, in accordance with conventional definitions. The clinical progress of each eligible patient was subsequently tracked until June 30, 2019, which served as the study end date. This timing ensured assessment of outcomes over a relatively extended follow-up period. There were no guidelines from the hospital to direct clinicians in the choice of NOACs for each patient, except for the practical concern that dabigatran should not be crushed or administered via a feeding tube. Clinicians were advised to follow standard dose reduction criteria for individual NOACs, as published in the respective landmark trials of each NOAC.

To minimize the potential for confounding arising from prior anticoagulant exposure, patients who had a documented history of receiving other oral anticoagulants before the index NOAC were excluded from the analysis. Patients with chronic kidney disease stage 4 or above, assessed using the Chronic Kidney Disease Epidemiology Collaboration equation, were excluded as use of dabigatran was contraindicated in severe renal impairment. Patients were also excluded when NOACs were prescribed for indications other than AF thromboembolic stroke prophylaxis, and when oral anticoagulation was intended for planned short-term use at the time of prescription (for example, for a few months after cardioversion among low-risk patients). Clinical notes were systematically reviewed to identify instances of drug non-compliance and to

ascertain the occurrence and nature of clinical outcomes.

2.2. Study cohort

To facilitate meaningful comparisons among the agents, four distinct analytical cohorts were established. These consisted of a comparison of factor Xa inhibitors collectively against dabigatran, a comparison of rivaroxaban against dabigatran, a comparison of apixaban against dabigatran, and a comparison of apixaban against rivaroxaban. For each of these cohorts, the period of inclusion commenced at the point when the later-introduced drug first became available within the Hospital Authority system. This design choice was made deliberately to minimize differences in the duration of drug exposure between the comparator groups, since disparate exposure times could act as a confounding factor and distort the interpretation of comparative outcomes.

2.3. Baseline characteristics

Baselines, including demographics and past medical histories, were collected. These included age, sex, race, prior ischemic or hemorrhagic stroke, previous MI, prior percutaneous coronary intervention, prior coronary arterial bypass grafting, diabetes mellitus, hypertension, peripheral vascular disease (either being diagnosed by a vascular surgeon or by imaging studies), congestive heart failure (defined as left ventricular ejection fraction less than 55% on cardiac imaging), proteinuria (defined as 24-hour urine protein equaled or more than 1 gram per day, or alternatively a spot urine protein to creatinine ratio equaled or more than 1), thyrotoxicosis, cirrhosis (diagnosed by imaging), obstructive sleep apnea (diagnosed by sleep study including overnight oximetry or polysomnography), malignancy (active malignant disease or where the patient had received anti-cancer treatment within the one-year period preceding NOAC initiation), and gout. Smoking and alcohol consumption status were derived from a review of consultation notes. Medication history was reviewed to identify baseline medication, defined as drugs prescribed within one month before the initiation of NOAC. In addition, CHA₂DS₂-VASc and HAS-BLED scores were calculated for each patient, so as to quantify their stroke and bleeding risks, respectively.^{22,23}

2.4. Study outcomes

The primary endpoint of the study was defined as a composite outcome of MI and sudden death. Sudden death was defined as sudden cardiac arrest occurring in the absence of an obvious alternative cause and in the absence of autopsy. This composite endpoint was selected on the recognition that a proportion of sudden deaths in this population may plausibly be attributable to fatal MI that

escapes formal diagnostic confirmation. The secondary endpoints comprised a composite of major adverse cardiovascular events (MACE), which incorporated MI, cardiovascular death, hospitalization for congestive heart failure, and ischemic or hemorrhagic stroke, together with the individual constituent components of MACE, as well as the outcome of fatal bleeding considered separately.

2.5. Statistical analysis

Categorical variables were summarized as percentages, and continuous variables were reported as mean values accompanied by standard deviations. To achieve improved balance between the groups, thereby reducing the influence of confounding by indication, propensity score methodology in conjunction with inverse probability of treatment weighting (IPTW) was employed. The propensity score of the weighting system was estimated by generalized boosted models constructed on the basis of 10,000 regression trees. Weights were subsequently derived to estimate the population average treatment effect. The model took into account patient demographic characteristics, comorbid conditions, and baseline medications. The CHA₂DS₂-VASc and HAS-BLED scores were excluded within the propensity score model, given that several of the constituent elements of these scores were already represented among the aforementioned baseline characteristics, and their inclusion would have introduced redundancy. The adequacy of balance achieved between groups was assessed by means of the absolute standardized mean difference, with a value of less than 0.1 being regarded as indicative of satisfactory balance. The equality of distribution of continuous variables was further evaluated using the Kolmogorov–Smirnov statistic.

Both crude and weighted event incidence rates were reported as the number of events per 100 person-years. The 95% confidence intervals (CI) were estimated using Poisson regression. Survival analyses were conducted using the Cox proportional hazards regression model, with hazard ratios (HR) and their associated 95% CI reported. A *p*-value of less than 0.05 was interpreted as statistically significant. If baseline characteristics remained imbalanced despite the application of weighting, these variables were incorporated as covariates within the survival analysis, in accordance with the method of doubly robust estimation.²⁴ The proportional hazards assumption underlying the Cox regression models was verified through calculation of the Schoenfeld residuals.

All statistical analyses were performed using R version 3.6.1 (R Core Team, Austria) and the Statistical Package for Social Sciences version 26 (IBM Corp, United States).

3. Results

Altogether 2,420 patients were identified to have at least one prescription of one of the studied NOACs. Among them, 1,161 were included in the next step of analyses. The detailed reasons for exclusion of the remaining patients and the dose distribution are summarized in Tables S1 and S2, respectively.

The analysis consisted of 954 patients in the rivaroxaban vs. dabigatran cohort, 826 in the apixaban vs. dabigatran cohort, and 438 in the apixaban vs. rivaroxaban cohort. Apixaban and rivaroxaban were respectively introduced into the local cluster in November 2013 and April 2014. As a result, these dates were designated as the inclusion start dates for the relevant cohorts to minimize differences in exposure time as far as possible. The patient baseline characteristics of each cohort are summarized in Tables S3 to S6.

3.1. Factor Xa inhibitors vs. dabigatran

The mean follow-up period was 886 ± 465 days. The analysis showed trends that favored factor Xa inhibitors in terms of both the combined risk of MI plus sudden death and the risk of MI considered in isolation. The HR for the combined endpoint was 0.67 (95% CI: 0.42 to 1.05, *p* = 0.082), while the HR for MI alone was 0.62 (95% CI: 0.29 to 1.35, *p* = 0.229). Neither of these reached the threshold for statistical significance, although a consistent direction of effect was demonstrated. With regard to safety, the use of dabigatran showed a statistically significantly lower rate of fatal bleeding, with an HR of 3.58 (95% CI: 1.22 to 10.48, *p* = 0.020) in favor of dabigatran (Table 1).

3.2. Rivaroxaban vs. dabigatran

The mean follow-up period was 912 ± 486 days. Rivaroxaban was associated with a lower rate of the primary endpoint, with an HR of 0.72 (95% CI: 0.44 to 1.18, *p* = 0.195), and likewise with a lower rate of the secondary endpoint of MI, with an HR of 0.46 (95% CI: 0.18 to 1.18, *p* = 0.106). These findings did not attain statistical significance; however, they were directionally consistent with a signal favoring use of rivaroxaban. Conversely, rivaroxaban was linked with a greater fatal bleeding incidence, with an HR of 3.82 (95% CI: 1.17 to 12.50, *p* = 0.026) (Table 2).

3.3. Apixaban vs. dabigatran

The mean follow-up period was 810 ± 414 days. The primary endpoint demonstrated a trend in favor of apixaban use, with an HR of 0.58 (95% CI: 0.23 to 1.45, *p* = 0.242). In addition, the apixaban arm was associated with statistically significantly fewer MACEs, with an HR of 0.67

Table 1. Results of factor Xa inhibitors vs. dabigatran

Variables	Event rate after			
	FXa inhibitor	Dabigatran (Reference)	Hazard ratio (CI)	p-value
<i>n</i>	446	715	-	-
MI + SCD	1.22 (0.84–1.68)	1.81 (1.35–2.41)	0.67 (0.42–1.05)	0.082
MACE	9.15 (7.99–10.43)	10.59 (9.33–12.02)	0.88 (0.73–1.05)	0.158
MI	0.75 (0.47–1.13)	1.21 (0.84–1.72)	0.62 (0.29–1.35)	0.229
CVD	1.41 (1.03–1.95)	0.97 (0.64–1.42)	1.44 (0.71–2.91)	0.314
Hospitalization for CHF	6.08 (5.16–7.14)	6.52 (5.54–7.60)	0.94 (0.75–1.18)	0.593
Stroke	2.91 (2.30–3.63)	2.89 (2.28–3.64)	1.02 (0.73–1.41)	0.920
Fatal bleed	0.59 (0.35–0.94)	0.17 (0.06–0.41)	3.58 (1.22–10.48)	0.020

Notes: Data presented as number of events per 100 person-years. $p < 0.05$ is considered significant.

CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular death; IPTW: Inverse probability of treatment weighting; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; SCD: Sudden cardiac death.

Table 2. Results of rivaroxaban vs. dabigatran

Variables	Event rate after IPTW			
	Rivaroxaban	Dabigatran (Reference)	Hazard ratio (CI)	p-value
<i>n</i>	239	715	-	-
MI + SCD	1.19 (0.79–1.69)	1.70 (1.21–2.32)	0.72 (0.44–1.18)	0.195
MACE	10.22 (8.91–11.72)	10.4 (9.05–11.9)	1.04 (0.85–1.26)	0.702
MI	0.51 (0.28–0.87)	1.13 (0.75–1.66)	0.46 (0.18–1.18)	0.106
CVD	1.51 (1.04–2.05)	0.95 (0.60–1.42)	1.66 (0.60–3.80)	0.227
Hospitalization for CHF	6.85 (5.79–8.08)	6.52 (5.49–7.71)	1.11 (0.87–1.40)	0.410
Stroke	2.96 (2.31–3.75)	2.82 (2.18–3.63)	1.08 (0.76–1.54)	0.673
Fatal bleed	0.58 (0.34–0.99)	0.16 (0.05–0.40)	3.82 (1.17–12.5)	0.026

Notes: Data presented as number of events per 100 person-years. $p < 0.05$ is considered significant.

CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular death; IPTW: Inverse probability of treatment weighting; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; SCD: Sudden cardiac death.

(95% CI: 0.52 to 0.85, $p < 0.001$). The observed difference in MACE was driven in part by differences in the rate of hospitalization for congestive heart failure, which carried an HR of 0.72 (95% CI: 0.43 to 1.20, $p = 0.205$), and in part by differences in MI, which carried an HR of 0.77 (95% CI: 0.27 to 2.20, $p = 0.632$) (Table 3).

3.4. Apixaban vs. rivaroxaban

The mean follow-up period was 919 ± 427 days. The survival analyses for the two groups in terms of the composite of MI and sudden death, and in terms of MI alone, were statistically similar. However, apixaban was associated with fewer MACE, with an HR of 0.63 (95%

CI: 0.46 to 0.87, $p = 0.005$), as well as with a lower rate of hospitalization for congestive heart failure, with an HR of 0.57 (95% CI: 0.34 to 0.97, $p = 0.038$) (Table 4).

The specific causes of cardiovascular mortality and the causes of fatal bleeding across the study population are respectively summarized in Tables S7 and S8.

4. Discussion

4.1. Summary of principal findings

This retrospective cohort study compared the cardiovascular safety of three NOACs used in clinical practice among adult non-valvular AF patients. Across

Table 3. Results of apixaban vs. dabigatran

Variables	Event rate after IPTW			
	Apixaban	Dabigatran (Reference)	Hazard ratio (CI)	<i>p</i> -value
<i>n</i>	207	619 ^a	-	-
MI + SCD	1.09 (0.65–1.76)	1.81 (1.27–2.50)	0.58 (0.23–1.45)	0.242
MACE	7.46 (6.10–9.08)	11.16 (9.68–12.88)	0.67 (0.52–0.85)	<0.001
MI	0.91 (0.49–1.49)	1.09 (0.70–1.67)	0.77 (0.27–2.20)	0.632
CVD	1.04 (0.60–1.67)	1.01 (0.61–1.52)	1.015 (0.34–3.03)	0.979
Hospitalization for CHF	4.99 (3.92–6.34)	7.08 (5.91–8.40)	0.72 (0.43–1.20)	0.205
Stroke	2.60 (1.83–3.53)	2.79 (2.08–3.62)	0.94 (0.61–1.44)	0.772
Fatal bleed	0.79 (0.44–1.40)	0.20 (0.06–0.47)	3.94 (0.75–20.57)	0.105

Notes: Data presented as number of events per 100 person-years. $p < 0.05$ is considered significant. ^aSome of the patients in the dabigatran group were excluded.

CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular death; IPTW: Inverse probability of treatment weighting; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; SCD: Sudden cardiac death.

Table 4. Results of apixaban vs. rivaroxaban

Variables	Event rate after IPTW			
	Apixaban	Rivaroxaban (Reference) ^a	Hazard ratio (CI)	<i>p</i> -value
<i>n</i>	207	231	-	-
MI + SCD	1.21 (0.59–2.09)	1.80 (1.13–2.68)	0.71 (0.33–1.53)	0.381
MACE	7.84 (6.03–10.03)	11.31 (9.39–13.52)	0.63 (0.46–0.87)	0.005
MI	0.99 (0.50–1.93)	1.00 (0.54–1.71)	1.16 (0.46–2.93)	0.750
CVD	1.06 (0.50–1.93)	2.06 (1.33–2.99)	0.42 (0.19–0.92)	0.029
Hospitalization for CHF	4.87 (3.49–6.62)	7.97 (6.41–9.87)	0.57 (0.34–0.97)	0.038
Stroke	2.70 (1.72–4.01)	2.97 (2.08–4.10)	0.85 (0.49–1.47)	0.559
Fatal bleed	0.62 (0.27–1.43)	0.61 (0.30–1.25)	1.05 (0.33–3.35)	0.929

Notes: Data presented as number of events per 100 person-years. $p < 0.05$ is considered significant. ^aSome of the patients in the rivaroxaban group were excluded.

CHF: Congestive heart failure; CI: Confidence interval; CVD: Cardiovascular death; IPTW: Inverse probability of treatment weighting; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; SCD: Sudden cardiac death.

comparisons, factor Xa inhibitors as a class showed trends toward a lower rate of MI and sudden death composite outcomes compared with dabigatran, but these trends did not reach statistical significance. Among individual comparisons, rivaroxaban showed trends toward a lower rate of MI but also increased fatal bleeding relative to dabigatran. Apixaban demonstrated statistically significant reductions in MACE compared with dabigatran. Taken together, these findings support that cardiovascular safety profiles may not be identical across NOACs in real-world populations.

4.2. Association between atrial fibrillation and myocardial infarction

Atrial fibrillation is characterized by systemic markers of inflammation that are capable of promoting a pro-thrombotic state throughout the vascular system. Moreover, the risk factors that commonly accompany AF—including hypertension, diabetes mellitus, and hyperlipidemia—are each independently linked with activation of platelets, a process that plays a crucial role in the pathogenesis of MI.^{25,26} Supporting this conceptual framework, higher levels of biomarkers indicative of platelet activation, including P-selectin, beta-thromboglobulin, and soluble CD40 ligand, were demonstrated among AF patients.²⁷ Furthermore, a positive association has been demonstrated between the occurrence of MI and plasma concentrations of soluble CD40 ligand.²⁸

Beyond the contributions of atherosclerosis and platelet activation, AF possesses additional pathways through which it may precipitate MI. During episodes of rapid ventricular response, the heightened myocardial oxygen demand may produce a demand–supply mismatch that culminates in type 2 MI. In addition, thromboembolic material originating within the left atrium may embolize directly into the coronary vasculature, thereby producing coronary occlusion and infarction through a mechanism analogous to that of embolic stroke.

4.3. Dabigatran

Beyond the post hoc analysis of the RE-LY trial, additional evidence accumulated regarding the relationship between dabigatran and MI. A separate meta-analysis showed a higher risk of MI among patients taking dabigatran, compared to placebo, warfarin, or enoxaparin.²⁹ This elevated risk was found to be particularly pronounced for the 150 mg twice-daily dosing regimen.^{30,31} In the phase II trial evaluating use of dabigatran against placebo among acute coronary syndrome patients taking double antiplatelets, dabigatran was not associated with any reduction in ischemic events but was instead shown to cause more bleeding among the studied patients.³²

Considerable debate has surrounded the question of whether the apparent association between dabigatran and MI reflects a protective effect of warfarin that is lost upon its discontinuation, or alternatively a directly deleterious effect attributable to dabigatran itself.^{30,33} A Danish cohort study demonstrated a significant trend toward increased MI risk within 60 days of switching from a vitamin K antagonist to dabigatran, when compared to patients who were newly initiated on dabigatran. The HRs in this analysis were 3.01 for the 110 mg twice-daily dosing and 2.97 for the 150 mg twice-daily dosing.³⁴ This finding suggests that switching from warfarin to dabigatran may unmask the cardiovascular stabilizing effects that warfarin had previously been exerting. This was in contrast to the findings of the RE-LY trial, in which half of the enrolled population was naive to vitamin K antagonist therapy. Additionally, the numerical rise in MI seen in the dabigatran group was not modified by a history of prior vitamin K antagonist use in the RE-LY trial.³⁵

Further complicating the interpretation, the post hoc analysis of the RE-LY trial showed that approximately one third of the MI events occurred at a time when the study drug had been discontinued. An excess of events persisted within the dabigatran group even beyond 90 days following treatment cessation. This temporal pattern raises the possibility that the observed difference in MI risk may have arisen from an underlying and unrecognized imbalance between the treatment groups, rather than from a direct pharmacological effect of dabigatran.¹⁸ Adding yet another dimension to the evidence, a separate Danish registry study found that the risk of MI was actually lower with high-dose and low-dose dabigatran compared to warfarin.³⁶

These apparently contradictory findings may to a considerable extent reflect the inevitable differences that exist between the controlled environment of clinical trials and the more variable conditions of real-world clinical practice. Within trials, patients are subject to more rigorous and frequent follow-up, and the time in therapeutic range for the warfarin group is more tightly controlled than is typically achievable in routine care. It was demonstrated that a time in therapeutic range exceeding 65% is associated with reduction in cardiovascular events among AF patients receiving warfarin.^{18,37} These considerations may well account, at least in part, for the discrepancies observed between the various published analyses and the findings of the present study.

4.4. Other direct thrombin inhibitors

An important and unresolved question concerns whether the association between dabigatran and MI represents

a class effect common to all direct thrombin inhibitors. The evidence on this point is mixed. Bivalirudin, a direct thrombin inhibitor which was administered parenterally, was shown to result in a lower composite risk of death or MI, compared to heparin among patients with acute coronary syndrome.³⁸ Wallentin *et al.*³⁹ reported that the combination of aspirin with ximelagatran, another oral direct thrombin inhibitor that is no longer available in clinical practice, was more effective in preventing MI than aspirin administered alone, although it must be acknowledged that this study did not reflect contemporary practice as patients with recent or planned percutaneous coronary intervention were excluded. In contrast, another study demonstrated that ximelagatran was associated with a higher risk of MI than warfarin among patients with deep vein thrombosis.⁴⁰ A further meta-analysis, which pooled data on the two oral direct thrombin inhibitors dabigatran and ximelagatran, found that this combined group was linked to a higher risk of MI, yielding an odds ratio of 1.35.³³

4.5. The thrombin paradox and platelet reactivity

The precise mechanism underlying the apparently elevated rate of myocardial events associated with dabigatran remains incompletely understood. One possible explanation invokes the thrombin paradox, whereby thrombin is capable of exerting either pro-coagulant or anti-coagulant effects depending upon the prevailing circumstances.⁴¹ Furugohri *et al.*⁴² showed that melagatran promoted thrombin generation within plasma at a lower concentration. The opposite effect was observed at higher concentrations. It is believed that this enhancement of thrombin generation arises from suppression of the thrombin–thrombomodulin-induced negative feedback system, which occurs through inhibition of activation of protein C.⁴² In addition, dabigatran was also shown to enhance platelet reactivity by increasing expression of the thrombin receptor.^{43,44} Dale *et al.*⁴⁵ revealed a greater reduction in both thrombin potential and generation among patients receiving warfarin compared with those receiving dabigatran. In contrast, factor Xa inhibitors have been demonstrated to produce consistent and dose-dependent inhibition of thrombin generation, without the paradoxical effects observed with the direct thrombin inhibitors.⁴²

4.6. Factor Xa inhibitors

In the present study, the favorable trends observed for the two factor Xa inhibitors, whether assessed collectively or individually, accord well with the existing body of evidence regarding the cardioprotective properties of rivaroxaban and apixaban. The phase III studies of both of these drugs

did not demonstrate any increase in MI risk relative to warfarin.^{4,5}

The cardiovascular benefits of rivaroxaban have been explored at lower doses, namely 5 mg twice daily and 2.5 mg twice daily, in phase III trials targeting the reduction of cardiovascular outcomes among patients without AF. In the COMPASS study, the combination of rivaroxaban and aspirin was associated with lower cardiovascular mortality compared with aspirin alone among patients with stable atherosclerosis, specifically coronary artery disease or peripheral arterial disease. The rate of MI in this trial was numerically lower with the combination regimen, although the difference was not statistically significant.⁴⁶ In a separate population of patients with recent MI, rivaroxaban administered on top of standard therapy led to a lower risk of MI and a lower risk of coronary stent thrombosis compared to placebo. The 2.5 mg twice-daily regimen even caused reductions in both cardiovascular death and all-cause death. Conversely, both dosing regimens of rivaroxaban were associated with an increase in major bleeding and intracranial hemorrhage, although the rate of fatal bleeding remained similar between groups.⁴⁷ This latter observation is consistent with the finding in the current study that rivaroxaban was associated with a greater incidence of fatal bleeding compared with dabigatran.

As for apixaban, the primary endpoint of MI plus sudden death exhibited a trend that favored apixaban use in the current study, while the rate of MI considered in isolation was statistically similar between the two groups. Although post-mortem autopsies were not performed, it is reasonable to suppose that a proportion of the sudden deaths may be attributable to fatal MI. From a historical perspective, apixaban was somewhat less successful in reducing ischemic events among patients with recent MI than its NOAC counterparts. The APRAISE-2 was terminated early because of an excess of clinically important bleeding together with the absence of any significant reduction in cardiovascular events. Nonetheless, even within that study, the rate of stent thrombosis was lower among patients in the apixaban arm, and the rate of MI was also numerically lower than that observed in the warfarin group, with an odds ratio of 0.93.⁴⁸ A further meta-analysis indicated that apixaban demonstrated a trend toward lower cardiovascular mortality when compared with warfarin.⁴⁹

Beyond the difference between the two classes of NOACs, the data also raised the possibility of intra-factor Xa inhibitor heterogeneity. The difference in risk of MI between apixaban and rivaroxaban did not reach statistical significance, yet apixaban was associated with a lower incidence of MACE, which was mainly contributed by the lower rate of hospitalization for heart failure. The

observation is difficult to explain on a pharmacological basis, and other real-world cohorts did not report similar findings. This apparent association should be interpreted with caution, as it may be attributable to the limited size of the study population and consequently insufficient statistical power to detect or exclude a genuine difference.

4.7. Comparison to other real-world studies

The present study suggests that the various NOACs may possess differing cardiovascular safety profiles. This conclusion does not agree with the findings of the study by Lee *et al.*,⁵⁰ which did not identify significant differences among the NOACs. In that study, the annual rate of MI among NOAC users ranged from 1.1% to 1.2%. Several important differences in patient comorbidities were noted between the two studies. The population in the current study carried a greater burden of prior stroke, diabetes, and percutaneous coronary intervention, and exhibited a higher CHA₂DS₂-VASc score, reflecting fundamental differences in vascular burden between the two populations that render direct comparison difficult. Of particular importance, the present study featured a substantially longer follow-up period than the one-year duration employed in the study by Lee's group. It is plausible that the cardiovascular adverse effects of the NOACs are related to the duration of exposure, such that differences may only become apparent over extended periods of observation.

4.8. Clinical practice

The 2MACE score was developed to identify AF patients at high cardiovascular risk. This score incorporates the presence of metabolic syndrome, age, a history of MI or coronary revascularization, a history of congestive heart failure, and a history of stroke; a score of three or above identifies patients who are at elevated risk of major adverse cardiovascular outcomes.⁵¹ The score has been validated in a study comprising more than 2,000 patients. At present, however, there are no trials that have evaluated tailored treatment regimens—such as the addition of aspirin or a statin—according to risk stratification by the 2MACE score. The 2MACE score was not incorporated into the present study, owing to the fact that the status of metabolic syndrome could not be reliably determined in the absence of waist circumference measurements.

4.9. Strengths and weaknesses

A major strength of this study is the use of real clinical records that include both clinical notes and laboratory-linked information. Many registry studies rely heavily on diagnostic codes for outcome ascertainment, a method that would require further validation within local practice settings before its reliability could be assured. In contrast,

this study accessed actual clinical documentation, supporting better characterization of events and increasing validity when evaluating cardiovascular safety outcomes such as MI and fatal bleeding. The review of clinical notes also enabled assessment of drug non-compliance, an important factor because adherence to oral anticoagulants is often suboptimal in real-world practice.

Several limitations nonetheless warrant acknowledgment. The first relates to the relatively small size of the study population. Despite this constraint, the analysis was able to demonstrate trends in the differences among the NOACs with respect to cardiovascular safety.

Secondly, this study did not analyze dose-specific effects of the studied NOACs (e.g., standard vs. low dose of a particular NOAC, or low dose direct thrombin inhibitor vs. low dose factor Xa inhibitor). Such an analysis would require a considerably larger sample size in order to avoid the introduction of a heterogeneous population that would compromise meaningful comparison, particularly given that the different NOACs are subject to distinct dose-reduction criteria. One may need a reduced dose for one NOAC but not the other. Further research on this topic, especially within Eastern populations, would be highly desirable.

Another limitation arises from the assumption inherent in the propensity score model and the subsequent weighting. The methodology assumes that confounders that affect outcome are fully measured and included in the model. As in all observational studies, it would not be possible to completely exclude residual confounding caused by unmeasured variables. However, regardless of the sophistication of the methodology employed, it must be recognized that residual confounding from unmeasured variables, such as frailty, over-the-counter medication use, socioeconomic status, etc., cannot be entirely excluded.

The definition of sudden death did not include post-mortem autopsy confirmation or independent adjudication by blinded reviewers. Therefore, misclassification may have occurred (for example, some sudden deaths might have been fatal MI, while other sudden cardiac events might have been due to non-MI causes). This may affect interpretation of the composite endpoint. Nevertheless, the MI-only results were reported as secondary endpoints and were directionally aligned with the primary composite endpoint.

5. Conclusion

In this retrospective comparative cohort study, dabigatran was associated with numerically higher, though not statistically significant, cardiovascular outcomes relative

to the factor Xa inhibitors. The findings indicate that meaningful intra-class differences exist among the NOACs with respect to their cardiovascular safety profiles in patients with non-valvular AF. Further studies are warranted to investigate this important clinical issue more comprehensively and to inform the optimal selection of anticoagulant therapy for individual patients.

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Conflict of interest

The author declares no competing interests.

Author contributions

This is a single-authored article

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of the New Territories West Cluster of the Hospital Authority (NTWC/REC/19104).

Consent for publication

Not applicable.

Availability of data

All data are available from the corresponding author upon request.

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