

Impact of Non-Vitamin K Antagonist Oral Anticoagulants on Cardiovascular Outcomes in Diabetes Patients with Atrial Fibrillation: A Single-Center Experience

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Background: Non-vitamin K antagonist oral anticoagulants (NOACs) are widely used to prevent stroke in patients with atrial fibrillation (AF). Diabetes mellitus (DM) increases the risk of stroke in these patients, necessitating the careful selection of anticoagulant therapy. This study compared the effectiveness and safety of different NOACs in patients with both DM and AF.

Methods: This retrospective cohort study included patients with DM and AF treated with NOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) between December 2012 and June 2022 at a tertiary hospital in Taiwan. The primary outcomes were major adverse cardiovascular events (MACEs), all-cause mortality, and major bleeding. Multivariable Cox proportional hazards models were used to assess the risks associated with each NOAC.

Results: After propensity score matching, 700 patients were included in the final analysis. The mean age was 72.71 ± 10.08 years, and the mean CHA₂DS₂-VASc score was 4.96 ± 1.76 . No significant differences were observed among the four NOACs in the risks of acute myocardial infarction, ischemic stroke, or cardiovascular death. Similarly, the risks of intracranial hemorrhage and gastrointestinal bleeding were comparable across groups. However, dabigatran was associated with a significantly lower risk of MACEs (hazard ratio [HR], 0.42; 95% confidence interval [CI], 0.19–0.93; $p = 0.032$) and all-cause mortality (HR, 0.39; 95% CI, 0.15–0.99; $p = 0.047$) compared with apixaban.

Conclusions: In this single-center study, the risk of major bleeding was similar across the four NOACs. In addition, dabigatran was associated with lower risks of MACEs and all-cause mortality compared with apixaban.

Key Words: Atrial fibrillation • Diabetes mellitus • Non-vitamin K antagonist oral anticoagulants • Stroke

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs) such as apixaban, dabigatran, edoxaban, and rivaroxaban are widely used to prevent stroke and systemic embolism in patients with atrial fibrillation (AF) who have specific risk factors.¹ Although vitamin K antagonists (VKAs) are effective for the treatment and prevention of thromboembolism, their use is limited by a significant bleeding risk and the need for close monitoring.² In contrast, NOACs have been shown to reduce the risks of major adverse cardiovascular events (MACEs) and major bleeding

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Abbreviations

AF	Atrial fibrillation
AMI	Acute myocardial infarction
CAD	Coronary artery disease
CHF	Congestive heart failure
cHR	Crude-hazard ratio
CI	Confidence interval
CKD	Chronic kidney disease
DM	Diabetes mellitus
ESRD	End-stage renal disease
GI	Gastrointestinal
HR	Hazard ratio
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10 th Revision, Clinical Modification
ICH	Intracranial hemorrhage
IRB	Institutional Review Board
MACE	Major adverse cardiovascular event
NOACs	Non-vitamin K antagonist oral anticoagulants
SD	Standard deviation
VKAs	Vitamin K antagonists

compared with VKAs in patients with AF, making them a safer, more effective, and more convenient alternative to warfarin.^{1,3,4} To assess stroke risk in patients with AF, the CHA₂DS₂-VASc score was developed to stratify individuals into high-, intermediate-, or low-risk categories.⁵⁻⁷ Patients classified as high-risk, particularly older adults and those with congestive heart failure (CHF), hypertension, diabetes mellitus (DM), stroke, transient ischemic attack, thromboembolism, vascular disease, or female sex, require anticoagulant therapy such as NOACs.

DM significantly increases the risk and worsens the outcomes of stroke through metabolic disturbances such as insulin resistance and hyperglycemia, which contribute to atherosclerosis. These systemic effects further promote stroke development through oxidative stress, inflammation, endothelial dysfunction, arterial plaque formation, and thrombosis.⁸⁻¹⁰ The Framingham Study reported that the incidence of ischemic stroke in patients with DM was 2.5-3.5 times higher than in those without DM, likely due to cerebral ischemia secondary to atherosclerosis.^{11,12} Overall, DM not only increases the risk and severity of stroke but also complicates its management, underscoring the need for targeted therapeutic strategies for this high-risk population.

DM has also been independently associated with an

increased risk of AF.¹³ Previous studies have shown that patients with DM have a 30% to 40% higher risk of developing AF compared with those without DM.^{14,15} Proposed mechanisms include atrial structural, electrical, and mechanical remodeling associated with DM, as well as diabetic autonomic neuropathy and activation of the renin-angiotensin system.¹⁶⁻¹⁸ In addition, chronic hyperglycemia in DM increases oxidative stress, which promotes cardiomyocyte damage and contributes to inflammation and fibrosis of atrial tissue. These changes disrupt normal electrical conduction within the atria, thereby facilitating the development of AF.¹⁹ These findings highlight the important role of DM in increasing AF risk.

Patients with both DM and AF are at a significantly higher risk of stroke compared with those who have either condition alone. These two diseases share common risk factors, including hypertension, ischemic heart disease, and metabolic syndrome, all of which contribute to a prothrombotic state. Furthermore, DM is associated with a hypercoagulable state, characterized by increased platelet aggregation and altered anticoagulant pathways, thereby further increasing the risk of thromboembolism in patients with AF.²⁰⁻²³ Given this elevated risk, effective anticoagulation therapy is crucial for stroke prevention in this population.

NOACs have been shown to be both effective and safe in preventing stroke and systemic embolism in patients with AF, including those with DM.^{24,25} Among these agents, apixaban has been associated with a lower risk of gastrointestinal (GI) bleeding compared with other NOACs in patients with AF.^{26,27} In addition, a previous study reported that apixaban reduced the risk of major or clinically relevant non-major bleeding in patients with deep vein thrombosis and/or pulmonary embolism.²⁸ Despite the established benefits of NOACs, a critical evidence gap remains regarding the optimal choice of NOAC for high-risk patients with both DM and AF. Given the distinct pharmacokinetic profiles of NOACs and their differing risks of bleeding and thromboembolism, a direct comparison is essential to guide clinical decision-making in this vulnerable population. Therefore, we conducted this retrospective cohort study using a hospital-wide database to compare the effectiveness and safety of apixaban, dabigatran, edoxaban, and rivaroxaban in patients with both DM and AF.

METHODS

Study design and population

This retrospective cohort study used data from the clinical database of Tri-Service General Hospital, a medical center in northern Taiwan. Patients who had received NOAC therapy for more than three months between December 2012 and June 2022 were eligible for inclusion. Patients with a diagnosis of AF and DM prior to initiating a NOAC were identified using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 427.31 and International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code I48 for AF, and ICD-9-CM code 250 and ICD-10-CM codes E1-E14 for DM. Subjects under 20 years of age, those who received more than one type of NOAC, and those with end-stage renal disease (ESRD; ICD-9-CM code 585.6 and ICD-10-CM code N185) were excluded. The study was approved by the Institutional Review Board (IRB) of Tri-Service General Hospital (IRB number: B2024 05022).

The study population was categorized into four groups according to exposure to apixaban, dabigatran, edoxaban, or rivaroxaban. NOAC prescriptions were guided by clinical indications and contemporary treatment guidelines. The index date was defined as the first day of NOAC prescription, and follow-up continued from the index date until the last visit, death, or June 30, 2022.

Baseline variables

Baseline characteristics of the study population, including age, sex, pre-existing comorbidities, CHA₂DS₂-VASc score, and laboratory tests, were collected at the index date. The presence of comorbidities including hypertension, coronary artery disease (CAD), CHF, chronic obstructive pulmonary disease, chronic kidney disease (CKD), hyperlipidemia, chronic liver disease, ischemic stroke, and cancer was recorded. The CHA₂DS₂-VASc score was calculated for each patient using International Classification of Diseases codes and clinical data available at the index date. Laboratory tests included complete blood count, electrolytes, blood urea nitrogen, creatinine, alanine aminotransaminase, glycated hemoglobin, total cholesterol, low-density lipoprotein, triglycerides, pro-brain natriuretic peptide, and troponin I.

Outcome variables

The study outcomes were MACEs, major bleeding events, and all-cause mortality. MACEs were defined as acute myocardial infarction (AMI; ICD-9-CM codes 410-411 and ICD-10-CM codes I21, I22, I23), ischemic stroke (ICD-9-CM codes 433-434 and ICD-10-CM code I63), or cardiovascular death. Cardiovascular death was defined as mortality resulting from an AMI, sudden cardiac death, or heart failure.²⁹ Major bleeding was defined as GI bleeding or intracranial hemorrhage (ICH) classified as type 3 according to the Bleeding Academic Research Consortium.³⁰ Causes of death were ascertained by reviewing electronic medical records.

Statistical analysis

We performed 1:1 nearest-neighbor propensity score matching on all baseline covariates, ensuring standardized mean differences of < 0.1 for each variable before proceeding to further analysis. The baseline characteristics of the four NOAC groups are presented as counts, means with standard deviation (SD), or percentages. Continuous variables were analyzed using the Student's *t*-test or analysis of variance and are reported as mean $\pm$ SD. Categorical variables were assessed using the chi-square test or Fisher's exact test. Multivariable Cox proportional hazards models were used to examine the associations between NOAC use and the outcomes of interest, expressed as crude hazard ratios (cHRs) with 95% confidence intervals (95% CIs) for comparisons. Statistical analyses were conducted using R software, version 3.4.4, with a significance threshold of $p < 0.05$.

RESULTS

Between December 2012 and June 2022, 7,229 patients were treated with apixaban, dabigatran, edoxaban, or rivaroxaban for more than three months. Of these patients, 1,382 had been diagnosed with DM and AF prior to NOAC exposure. None of the patients were younger than 20 years. We excluded those who received more than one type of NOAC and those diagnosed with ESRD before the index date. The final cohort consisted of 1,320 patients, divided into four groups: 396 (30.0%) received apixaban, 175 (13.3%) received dabigatran, 213 (16.1%) received edoxaban, and 536 (40.6%) received rivaroxa-

ban. After propensity score matching, 700 patients (175 in each group) were included in the final analysis (Figure 1).

The baseline characteristics of the matched groups are shown in Table 1, and the baseline characteristics of the general subjects ($n = 1,320$) are shown in Supplementary Table 1. Most patients were male (58.6%). The mean age of the entire population was 72.71 ± 10.08 years, with a mean CHA₂DS₂-VASc score of 4.96 ± 1.76 and an average follow-up duration of 1310.43 ± 922.16 days. Among the 700 included patients, 82.3% had hypertension, 71.6% had hyperlipidemia, 45.9% had CAD, and 40.0% had ischemic stroke. The apixaban group received an average daily dose of 7.34 ± 2.57 mg, which was lower than the standard dose of 10 mg/day. For dabigatran, the average daily dose was 237.37 ± 52.70 mg, compared with the standard dose of 300 mg/day. For edoxaban, the average daily dose was 45.00 ± 15.04 mg/day, which was lower than the standard dose of 60 mg/day. Similarly, in the rivaroxaban group, the average daily dose was 12.93 ± 2.59 mg, which was lower than the recommended standard dose of 20 mg/day. The dabigatran group had the longest mean follow-up duration, while the edoxaban group had the shortest. There were no significant differences in sex, mean age, mean CHA₂DS₂-VASc score, baseline comorbidities, or laboratory results among the four NOAC groups.

The study outcomes, including MACEs, major bleeding, and all-cause mortality, are presented in Table 2. Among the four groups, the apixaban group had the highest number of MACEs, AMI, and ischemic stroke events. Conversely, the dabigatran and rivaroxaban groups had the fewest AMI events, while the edoxaban group had the fewest ischemic stroke events. Major bleeding events occurred most frequently in the rivaroxaban group, whereas the edoxaban group had the lowest rate of major bleeding and GI bleeding. Of the 49 deaths during the study period, six were cardiovascular related. The lowest mortality rate was in the dabigatran group.

We used Cox regression models to analyze the risks of MACEs, major bleeding, and all-cause mortality among the patients receiving different NOACs in the propensity score-matched cohort (Table 3). In this high-risk population with both DM and AF, dabigatran was associated with a 61% lower risk of all-cause mortality compared with apixaban (cHR, 0.39; 95% CI, 0.15-0.99; $p = 0.047$). Dabigatran was also associated with a 58% lower risk of MACEs compared with apixaban (cHR, 0.42; 95% CI, 0.19-0.93; $p = 0.032$). Regarding safety, no significant differences were observed in the risks of major bleeding, ICH or GI bleeding among the four groups, although rivaroxaban showed a nonsignificant trend toward higher risks of major bleeding, ICH and GI bleeding compared to apixaban.

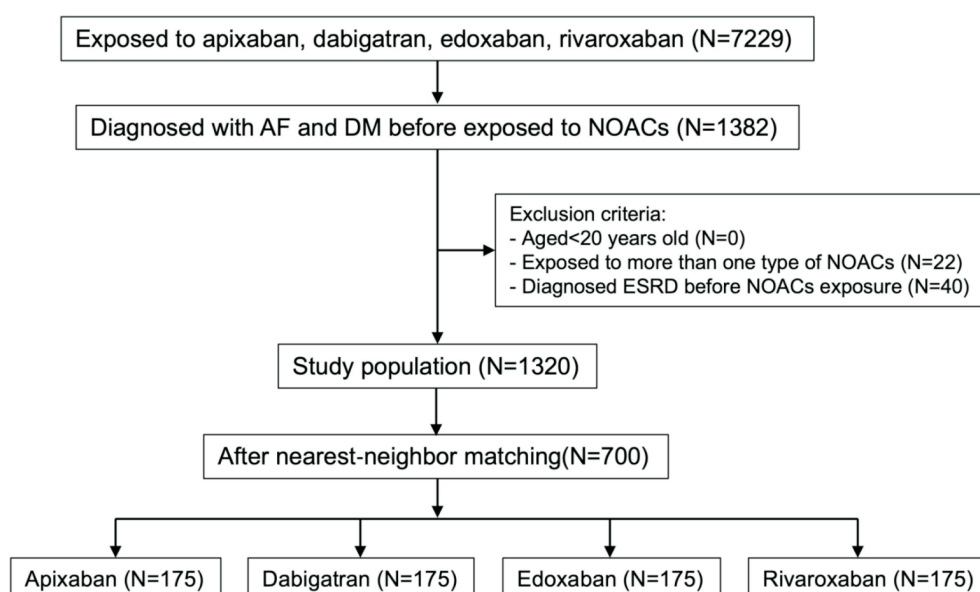


Figure 1. Flowchart of study population enrollment based on the inclusion and exclusion criteria. AF, atrial fibrillation; DM, diabetes mellitus; ESRD, end-stage renal disease; NOACs, non-vitamin K antagonist oral anticoagulants.

Table 1. Baseline characteristics of the study population

	Total	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	p value
No. of patients	700 (100%)	175 (25%)	175 (25%)	175 (25%)	175 (25%)	
Mean duration (days)	1310.43 ± 922.16	1374.30 ± 848.47	1617.53 ± 1102.82	969.39 ± 610.31	1278.36 ± 942.73	< 0.001
Average dose (mg/day)		7.34 ± 2.57	237.37 ± 52.70	45.00 ± 15.04	12.93 ± 2.59	
Mean CHA ₂ DS ₂ VASc score	4.96 ± 1.76	4.90 ± 1.79	4.78 ± 1.71	5.06 ± 1.64	5.08 ± 1.90	0.341
Mean age (years)	72.71 ± 10.08	72.65 ± 10.42	72.31 ± 9.66	73.30 ± 9.85	72.57 ± 10.42	0.825
Sex						0.753
Male	410 (58.6%)	106 (60.6%)	106 (60.6%)	98 (56.0%)	100 (57.1%)	
Female	290 (41.4%)	69 (39.4%)	69 (39.4%)	77 (44.0%)	75 (42.9%)	
Comorbidities (n, %)						
HTN	576 (82.3%)	144 (82.3%)	143 (81.7%)	146 (83.4%)	143 (81.7%)	0.972
CAD	321 (45.9%)	81 (46.3%)	80 (45.7%)	81 (46.3%)	79 (45.1%)	0.996
CHF	172 (24.6%)	48 (27.4%)	39 (22.3%)	41 (23.4%)	44 (25.1%)	0.701
COPD	167 (23.9%)	42 (24.0%)	37 (21.1%)	40 (22.9%)	48 (27.4%)	0.565
CKD	73 (10.4%)	20 (11.4%)	18 (10.3%)	19 (10.9%)	16 (9.1%)	0.911
Hyperlipidemia	501 (71.6%)	126 (72.0%)	125 (71.4%)	133 (76.0%)	117 (66.9%)	0.306
Chronic liver disease	167 (23.9%)	45 (25.7%)	44 (25.1%)	38 (21.7%)	40 (22.9%)	0.794
Ischemic stroke	280 (40.0%)	64 (36.6%)	74 (42.3%)	68 (38.9%)	74 (42.3%)	0.634
Cancer	84 (12.0%)	27 (15.4%)	17 (9.7%)	22 (12.6%)	18 (10.3%)	0.340
Laboratory tests						
WBC (10 ³ /uL)	7.32 ± 2.65	7.48 ± 2.59	7.30 ± 2.39	7.25 ± 2.58	7.26 ± 2.98	0.900
Hb (g/dL)	12.93 ± 2.17	12.73 ± 2.11	13.43 ± 2.22	12.73 ± 2.23	12.92 ± 2.07	0.055
Platelet (10 ³ /uL)	205.75 ± 71.11	206.46 ± 70.73	216.60 ± 76.51	198.98 ± 57.57	202.79 ± 78.43	0.286
Na (mmol/L)	138.23 ± 3.25	138.02 ± 3.17	138.97 ± 2.40	138.32 ± 3.26	137.78 ± 3.78	0.173
K (mmol/L)	4.00 ± 0.52	3.94 ± 0.51	4.02 ± 0.49	4.00 ± 0.59	4.04 ± 0.44	0.610
BUN (mg/dL)	21.61 ± 14.40	21.77 ± 17.95	19.98 ± 8.53	20.97 ± 12.33	23.37 ± 15.66	0.572
Creatinine (mg/dL)	1.05 ± 0.42	1.07 ± 0.46	1.03 ± 0.33	1.06 ± 0.46	1.01 ± 0.37	0.645
ALT (U/L)	20.30 ± 24.44	21.56 ± 17.68	17.66 ± 12.86	18.80 ± 11.34	23.16 ± 44.25	0.396
HbA1c (%)	6.95 ± 1.42	6.93 ± 1.16	7.07 ± 1.64	6.99 ± 1.63	6.80 ± 1.13	0.526
Total cholesterol (mg/dL)	148.72 ± 39.37	149.70 ± 36.31	149.77 ± 33.22	142.97 ± 38.12	155.73 ± 48.00	0.141
LDL (mg/dL)	85.02 ± 30.44	85.10 ± 26.86	86.49 ± 27.66	80.82 ± 30.16	90.26 ± 36.05	0.159
Triglyceride (mg/dL)	117.66 ± 62.63	123.00 ± 59.55	129.61 ± 77.16	114.01 ± 59.90	107.15 ± 54.71	0.097
Pro-BNP (pg/mL)	1992.05 ± 2746.24	2186.01 ± 2263.76	1594.08 ± 2504.16	2267.71 ± 3735.80	1673.14 ± 1376.04	0.190
Troponin I (pg/mL)	411.26 ± 3068.81	220.21 ± 1015.10	484.87 ± 2044.51	84.79 ± 299.10	1072.88 ± 6044.11	0.261

ALT, alanine aminotransaminase; BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; HbA1c, glycated hemoglobin; HTN, hypertension; LDL, low-density lipoprotein; Pro-BNP, pro-brain natriuretic peptide; WBC, white blood cell.

Table 2. Events of complications and mortality in patients with atrial fibrillation and diabetes receiving NOACs

Complications	Total (N = 700)	Apixaban (N = 175)	Dabigatran (N = 175)	Edoxaban (N = 175)	Rivaroxaban (N = 175)
Total MACE	51	19	10	10	12
Acute myocardial infarction	15	5	3	4	3
Ischemic stroke	32	14	7	5	6
Cardiovascular death	6	1	1	1	3
Major bleeding events	40	10	11	4	15
Intracranial hemorrhage	7	1	1	1	4
Gastrointestinal bleeding	34	9	10	4	11
All-cause mortality	49	13	8	14	14

MACE, major adverse cardiovascular event; NOACs, non-vitamin K antagonist oral anticoagulants.

Table 3. Hazard ratios for complications and mortality in patients with atrial fibrillation and diabetes receiving NOACs

	Medication	HR (95% CI)	p value
MACE	Apixaban	1.00	
	Dabigatran	0.42 (0.19-0.93)	0.032
	Edoxaban	0.70 (0.32-1.52)	0.365
	Rivaroxaban	0.65 (0.32-1.35)	0.251
Acute myocardial infarction	Apixaban	1.00	
	Dabigatran	0.49 (0.12-2.04)	0.324
	Edoxaban	1.19 (0.31-4.57)	0.800
	Rivaroxaban	0.68 (0.16-2.83)	0.591
Ischemic stroke	Apixaban	1.00	
	Dabigatran	0.52 (0.21-1.29)	0.157
	Edoxaban	0.48 (0.17-1.34)	0.160
	Rivaroxaban	0.52 (0.20-1.35)	0.177
Cardiovascular death	Apixaban	1.00	
	Dabigatran	0.51 (0.03-9.56)	0.650
	Edoxaban	1.55 (0.09-26.04)	0.762
	Rivaroxaban	2.58 (0.26-25.96)	0.421
Major bleeding	Apixaban	1.00	
	Dabigatran	0.94 (0.40-2.24)	0.890
	Edoxaban	0.52 (0.16-1.68)	0.275
	Rivaroxaban	1.61 (0.72-3.60)	0.242
Intracranial hemorrhage	Apixaban	1.00	
	Dabigatran	0.78 (0.05-12.59)	0.859
	Edoxaban	1.71 (0.11-27.79)	0.706
	Rivaroxaban	4.42 (0.49-39.55)	0.184
Gastrointestinal bleeding	Apixaban	1.00	
	Dabigatran	0.89 (0.36-2.21)	0.801
	Edoxaban	0.59 (0.18-1.93)	0.384
	Rivaroxaban	1.22 (0.50-2.94)	0.664
All-cause mortality	Apixaban	1.00	
	Dabigatran	0.39 (0.15-0.99)	0.047
	Edoxaban	1.75 (0.81-3.78)	0.154
	Rivaroxaban	1.06 (0.49-2.28)	0.878

CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular event; NOACs, non-vitamin K antagonist oral anticoagulants.

Additional stratified analyses were conducted to explore whether the effects of different NOACs varied across clinically relevant patient subgroups (Table 4, Figure 2). With respect to MACEs, dabigatran was associated with a significantly lower risk compared to apixaban in several subgroups. Notable reductions were observed among females (hazard ratio [HR], 0.17; 95% CI, 0.03-0.87; $p = 0.034$), patients aged ≥ 70 years (HR, 0.31; 95% CI, 0.12-0.83; $p = 0.019$), those without heart failure (HR, 0.25; 95% CI, 0.09-0.74; $p = 0.012$), and those without CKD (HR, 0.38; 95% CI, 0.16-0.90; $p = 0.028$). Among the patients with a CHA₂DS₂-VASc score between 7-9,

dabigatran was also associated with a significantly lower risk of MACEs (HR, 0.06; 95% CI, 0.01-0.62; $p = 0.018$). In terms of major bleeding, no significant differences were observed across subgroups when comparing the other NOACs to apixaban. HRs were largely nonsignificant and CIs were wide, likely due to the limited number of bleeding events in each subgroup. For all-cause mortality, dabigatran again demonstrated a lower risk compared with apixaban in certain subgroups. Significant associations were observed in male patients (HR, 0.30; 95% CI, 0.09-0.96; $p = 0.043$), patients aged ≥ 70 years (HR, 0.34; 95% CI, 0.12-0.99; $p = 0.049$), and those without

Table 4. Hazard ratios for MACE and all-cause mortality among NOAC groups, stratified by baseline characteristics

Stratified variable	Medication	MACE		All-cause mortality	
		HR (95% CI)	p value	HR (95% CI)	p value
Female (N = 290)	Apixaban	1.00		1.00	
	Dabigatran	0.17 (0.03-0.87)	0.034	0.73 (0.15-3.64)	0.705
	Edoxaban	1.10 (0.37-3.27)	0.864	5.75 (1.56-21.23)	0.009
	Rivaroxaban	1.01 (0.37-2.75)	0.985	2.01 (0.50-8.08)	0.328
Male (N = 410)	Apixaban	1.00		1.00	
	Dabigatran	0.65 (0.26-1.63)	0.364	0.30 (0.09-0.96)	0.043
	Edoxaban	0.46 (0.15-1.46)	0.189	0.51 (0.14-1.88)	0.313
	Rivaroxaban	0.39 (0.12-1.21)	0.102	0.74 (0.28-1.95)	0.544
Age < 70 (N = 278)	Apixaban	1.00		1.00	
	Dabigatran	0.85 (0.21-3.41)	0.821	0.73 (0.10-5.21)	0.750
	Edoxaban	0.51 (0.09-2.80)	0.440	0.00 (0.00-Inf)	0.998
	Rivaroxaban	0.97 (0.24-3.87)	0.961	2.12 (0.39-11.63)	0.388
Age ≥ 70 (N = 422)	Apixaban	1.00		1.00	
	Dabigatran	0.31 (0.12-0.83)	0.019	0.34 (0.12-0.99)	0.049
	Edoxaban	0.79 (0.33-1.89)	0.594	2.20 (0.98-4.93)	0.057
	Rivaroxaban	0.56 (0.24-1.34)	0.192	0.92 (0.38-2.21)	0.851
No CHF (N = 528)	Apixaban	1.00		1.00	
	Dabigatran	0.25 (0.09-0.74)	0.012	0.24 (0.07-0.83)	0.024
	Edoxaban	0.71 (0.28-1.80)	0.469	1.42 (0.53-3.74)	0.484
	Rivaroxaban	0.56 (0.23-1.37)	0.204	1.26 (0.53-2.98)	0.605
CHF (N = 172)	Apixaban	1.00		1.00	
	Dabigatran	1.09 (0.33-3.58)	0.884	0.98 (0.22-4.38)	0.979
	Edoxaban	0.77 (0.19-3.11)	0.715	2.81 (0.78-10.21)	0.116
	Rivaroxaban	0.94 (0.26-3.36)	0.927	0.40 (0.04-3.55)	0.407
No CKD (N = 627)	Apixaban	1.00		1.00	
	Dabigatran	0.38 (0.16-0.90)	0.028	0.35 (0.12-1.00)	0.051
	Edoxaban	0.77 (0.34-1.76)	0.537	1.95 (0.81-4.69)	0.136
	Rivaroxaban	0.69 (0.32-1.49)	0.345	1.32 (0.58-3.00)	0.511
CKD (N = 73)	Apixaban	1.00		1.00	
	Dabigatran	0.95 (0.16-5.73)	0.955	0.97 (0.16-5.83)	0.973
	Edoxaban	0.35 (0.04-3.41)	0.370	1.13 (0.23-5.60)	0.881
	Rivaroxaban	0.43 (0.04-4.14)	0.465	0.00 (0.00-Inf)	0.999
CHA ₂ DS ₂ VASc score = 1-3 (N = 159)	Apixaban	1.00		1.00	
	Dabigatran	0.98 (0.14-6.97)	0.983	0.00 (0.00-Inf)	0.999
	Edoxaban	2.34 (0.39-14.04)	0.353	0.00 (0.00-Inf)	0.999
	Rivaroxaban	0.91 (0.13-6.47)	0.923	3.66 (0.41-32.83)	0.246
CHA ₂ DS ₂ VASc score = 4-6 (N = 403)	Apixaban	1.00		1.00	
	Dabigatran	0.63 (0.23-1.71)	0.364	0.46 (0.14-1.52)	0.202
	Edoxaban	0.70 (0.25-1.99)	0.507	1.79 (0.63-5.12)	0.275
	Rivaroxaban	0.88 (0.33-2.37)	0.801	0.61 (0.18-2.11)	0.437
CHA ₂ DS ₂ VASc score = 7-9 (N = 138)	Apixaban	1.00		1.00	
	Dabigatran	0.06 (0.01-0.62)	0.018	0.31 (0.06-1.77)	0.189
	Edoxaban	0.28 (0.03-2.35)	0.243	2.68 (0.79-9.03)	0.112
	Rivaroxaban	0.30 (0.07-1.21)	0.091	1.13 (0.33-3.80)	0.850

CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular event; NOAC, non-vitamin K antagonist oral anticoagulant.

CHF (HR, 0.24; 95% CI, 0.07-0.83; $p = 0.024$). Interestingly, edoxaban was associated with a significantly higher risk of mortality among females (HR, 5.75; 95% CI, 1.56-21.23; $p = 0.009$); however, the interaction p value did

not reach statistical significance ($p = 0.058$).

Despite these subgroup-specific findings, none of the interaction p values across the stratified variables were statistically significant. This suggests that the ob-

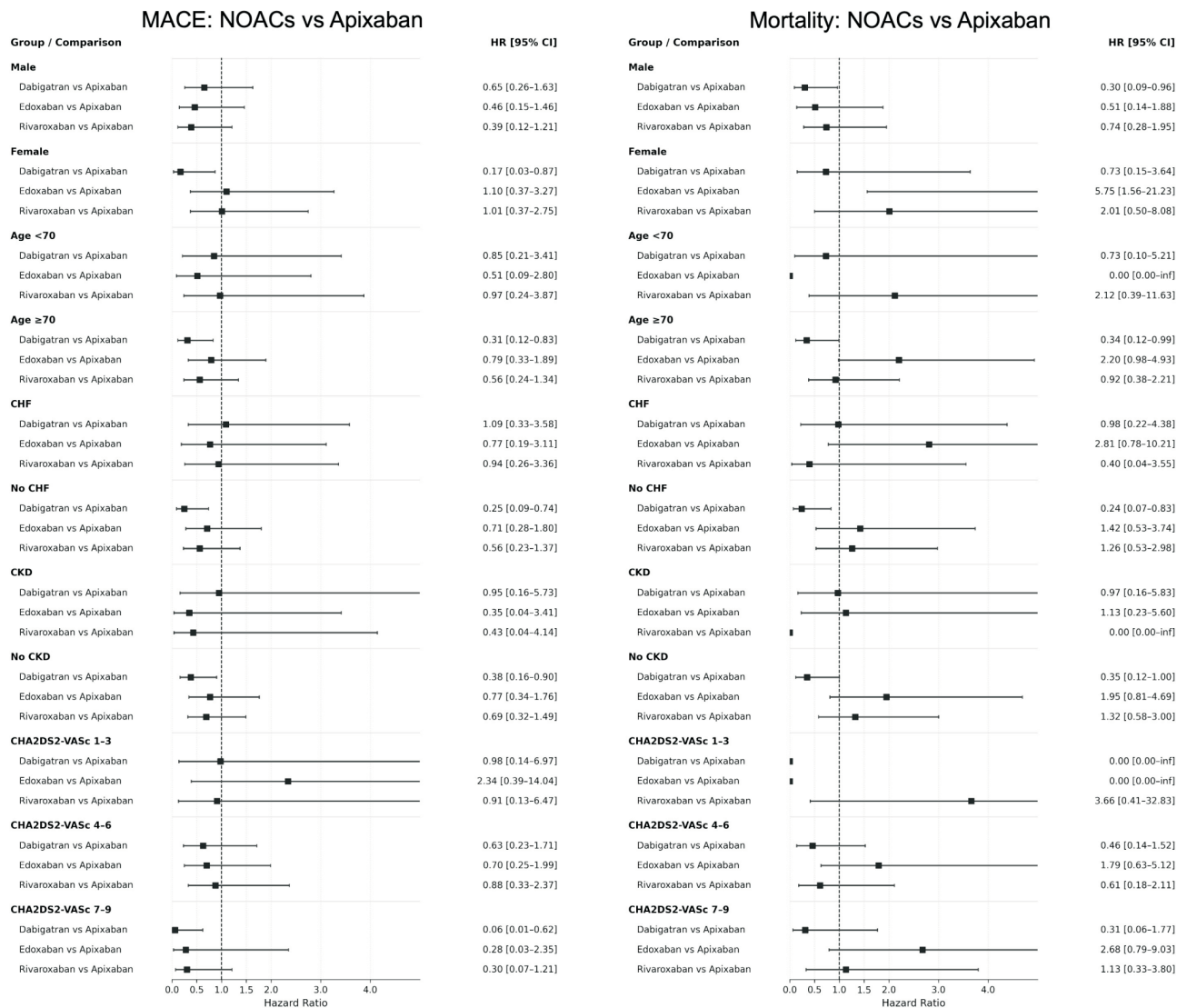


Figure 2. Forest plot of hazard ratios for MACE and all-cause mortality among NOAC groups, stratified by baseline characteristics. CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular event; NOACs, non-vitamin K antagonist oral anticoagulants.

served treatment effects were generally consistent across subgroups, and no clear evidence of heterogeneity was found.

DISCUSSION

This study evaluated the occurrence of MACEs and safety outcomes among four NOACs in a high-risk Asian population with both DM and AF. The study population had a mean CHA₂DS₂-VASc score of 4.96, indicating a substantial need for anticoagulation therapy. Our find-

ings demonstrated that dabigatran was associated with a significantly lower risk of all-cause mortality and MACEs compared with apixaban. There were no significant differences in the risks of major bleeding, ICH or GI bleeding across the groups. Although not statistically significant, rivaroxaban showed a trend toward higher risks of major bleeding, ICH and GI bleeding compared with apixaban.

A meta-analysis of ten independent retrospective studies comparing apixaban and rivaroxaban in patients with nonvalvular AF reported that apixaban was associated with a lower risk of stroke or systemic embolism.³¹

Similarly, a nationwide cohort study by Grymonprez et al. found that all NOACs effectively reduced thromboembolic risk in patients with AF, with dabigatran and apixaban showing significantly lower risks of stroke or systemic embolism compared with rivaroxaban.³² In patients with both DM and AF, a retrospective study by Gregory et al. suggested that apixaban was associated with a lower risk of stroke or systemic embolism compared with dabigatran and rivaroxaban.³³ In contrast, a cohort study by Hsu et al. in patients with DM and AF reported no significant differences between dabigatran and rivaroxaban in the risks of ischemic stroke, thromboembolism, or myocardial infarction.³⁴ Collectively, these studies support the use of NOACs, particularly apixaban, for their favorable efficacy in preventing critical cardiovascular events in patients with AF.

Our results further demonstrated that dabigatran was associated with a significantly lower risk of all-cause mortality compared with apixaban. Grymonprez et al. also reported that dabigatran and edoxaban were associated with a lower risk of all-cause mortality than apixaban in patients with AF.³² In addition, Hsu et al. reported that dabigatran was associated with a significantly lower risk of all-cause mortality compared with rivaroxaban in diabetic patients with non-valvular AF.³⁴ These retrospective studies suggest potential differences in the effectiveness of NOACs for reducing mortality risk.

We found no significant difference in the risk of major bleeding among the four groups; however, rivaroxaban showed a trend toward higher risks of major bleeding, ICH and GI bleeding compared with apixaban. A population-based study in Taiwan reported no significant differences in ICH and GI bleeding between dabigatran and rivaroxaban, aligning with our findings.³⁴ In contrast, a meta-analysis comparing apixaban and rivaroxaban found that apixaban was associated with significantly lower risks of major bleeding and GI bleeding.³¹ Grymonprez et al. further reported that dabigatran and apixaban were associated with significantly lower risks of major bleeding than rivaroxaban and edoxaban, with apixaban exhibiting the lowest risk among the NOACs.³² Likewise, Gregory et al. reported that, among patients with AF and DM, apixaban and dabigatran were associated with significantly lower risks of major bleeding compared with rivaroxaban.³³ Taken together, these findings suggest that apixaban and dabigatran may provide more fa-

vorable bleeding safety profiles than rivaroxaban, consistent with the trend observed in our study.

The biological plausibility for the potential association between dabigatran with reduced mortality and bleeding in patients with DM and AF compared to other NOACs is rooted in both the unique prothrombotic state of diabetes and pharmacologic properties of dabigatran. Diabetes is characterized by increased thrombin generation, endothelial dysfunction, and increased platelet activation, all of which amplify the risk of thromboembolic and bleeding complications. As a direct thrombin inhibitor, dabigatran targets the final step of the coagulation cascade by directly neutralizing thrombin activity, which is particularly elevated in diabetes, potentially providing more effective suppression of thrombosis than factor Xa inhibitors.³⁵ Clinically, dabigatran has been shown to reduce all-cause mortality and major bleeding compared with rivaroxaban in patients with AF and diabetes, and it has demonstrated a favorable safety profile compared with warfarin.^{33,34} Its predictable pharmacokinetics, minimal hepatic metabolism, and fewer drug-drug interactions are advantageous in diabetic patients, who often have renal impairment and polypharmacy. These factors, combined with the greater absolute risk reduction for thromboembolic events in patients with diabetes, support the observed improved outcomes with dabigatran in this high-risk group.^{34,36}

Our stratified analyses revealed that dabigatran was consistently associated with lower risks of MACEs and all-cause mortality compared with apixaban across multiple clinically relevant subgroups, particularly among older patients and those without heart failure or CKD. These findings suggest that dabigatran may provide favorable cardiovascular and survival outcomes in selected high-risk patients with DM and AF. Although some subgroup effects reached statistical significance, the absence of significant interaction *p* values indicates that treatment effects were generally consistent across strata. Furthermore, no substantial differences in bleeding risk were observed between NOACs in any subgroup, supporting the safety of dabigatran in this population. Nonetheless, the limited number of events in certain subgroups warrants cautious interpretation and underscores the need for confirmation in larger prospective studies.

There are several limitations to this study. First, it was conducted at a single center with a limited sample

size and relatively low event rates, which may limit the generalizability of our findings. In addition, while dabigatran was associated with lower risks of MACEs and all-cause mortality compared with apixaban, these associations should be interpreted with caution owing to wide confidence intervals and the potential influence of multiple comparisons. Validation in larger, multicenter cohorts is essential to substantiate these findings. Second, the retrospective design introduces potential biases and unmeasured confounders that could not be fully controlled. For example, NOAC dose, treatment discontinuation, and medication adherence are key factors influencing bleeding and thromboembolic outcomes; however, they were not available in this retrospective study. A randomized controlled trial would be necessary to evaluate their impact across different NOACs. Finally, missing laboratory data may have reduced the statistical power of some analyses. Despite these limitations, this study provides valuable real-world evidence to guide anticoagulation strategies in high-risk patients with AF and DM.

New knowledge gained

This single-center study provides new insights into the comparative effectiveness and safety of NOACs in high-risk Asian patients with both DM and AF. Dabigatran was associated with lower risks of MACEs and all-cause mortality compared with apixaban, while rivaroxaban showed trends toward higher risks of major bleeding, ICH, and GI bleeding. These findings underscore the importance of individualized anticoagulation strategies that balance thromboembolic prevention and bleeding risk in patients with AF and DM.

CONCLUSION

This single-center study compares the efficacy and safety of four NOACs in patients with concomitant DM and AF. Dabigatran was associated with lower risks of MACEs and all-cause mortality compared with apixaban. However, as these findings are derived from a single-center cohort, further multicenter and prospective studies are warranted to validate our results and refine anticoagulation strategies for this high-risk population.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Baseline characteristics of the general subjects and subjects with propensity score matching

	General subjects	Subjects with propensity score matching
No. of patients	1320	700
Mean duration (days)	1211.50 ± 890.27	1310.43 ± 922.16
Mean CHA ₂ DS ₂ VASc score	5.22 ± 1.75	4.96 ± 1.76
Mean age (years)	75.23 ± 10.60	72.71 ± 10.08
Sex		
Male	739 (56.0%)	410 (58.6%)
Female	581 (44.0%)	290 (41.4%)
Comorbidities (n, %)		
HTN	1158 (87.7%)	576 (82.3%)
CAD	662 (50.2%)	321 (45.9%)
CHF	448 (33.9%)	172 (24.6%)
COPD	378 (28.6%)	167 (23.9%)
CKD	272 (20.6%)	73 (10.4%)
Hyperlipidemia	953 (72.2%)	501 (71.6%)
Chronic liver disease	324 (24.6%)	167 (23.9%)
Ischemic stroke	575 (43.6%)	280 (40.0%)
Cancer	202 (15.3%)	84 (12.0%)
Laboratory tests		
WBC (10 ³ /uL)	7.46 ± 3.74	7.32 ± 2.65
Hb (g/dL)	12.58 ± 2.23	12.93 ± 2.17
Platelet (10 ³ /uL)	206.90 ± 74.04	205.75 ± 71.11
Na (mmol/L)	138.28 ± 3.73	138.23 ± 3.25
K (mmol/L)	4.03 ± 0.55	4.00 ± 0.52
BUN (mg/dL)	24.44 ± 16.05	21.61 ± 14.40
Creatinine (mg/dL)	1.15 ± 0.62	1.05 ± 0.42
ALT (U/L)	23.28 ± 55.88	20.30 ± 24.44
HbA1C (%)	6.95 ± 1.40	6.95 ± 1.42
Total cholesterol (mg/dL)	147.57 ± 37.99	148.72 ± 39.37
LDL (mg/dL)	83.75 ± 29.47	85.02 ± 30.44
Triglyceride (mg/dL)	116.93 ± 66.58	117.66 ± 62.63
Pro-BNP (pg/mL)	2898.68 ± 5049.21	1992.05 ± 2746.24
Troponin I (pg/mL)	525.32 ± 3488.77	411.26 ± 3068.81

ALT, alanine aminotransaminase; BUN, blood urea nitrogen; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; HbA1C, glycated hemoglobin; HTN, hypertension; LDL, low-density lipoprotein; Pro-BNP, pro-brain natriuretic peptide; WBC, white blood cell.