Risk of Major Bleeding and Thromboembolism in Asian Atrial Fibrillation Patients Using Non-vitamin K Oral Anticoagulants Versus Warfarin

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Research Article

Keywords: warfarin, non-vitamin K oral anticoagulants, Asian patients, bleeding, thromboembolism

Posted Date: May 11th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-500778/v1

Version of Record: A version of this preprint was published at International Journal of Clinical Pharmacy on July 29th, 2021. See the published version at https://doi.org/10.1007/s11096-021-01309-z.

Abstract

Background: Bleeding or thromboembolism prevention is important in patients with atrial fibrillation receiving anticoagulants, including non-vitamin K oral anticoagulants and warfarin. Asians have higher risks of bleeding complications when taking anticoagulants. However, evidence that considers laboratory parameters is lacking.

Objective: We aimed to compare the safety and effectiveness between non-vitamin K oral anticoagulants and warfarin in Asian patients with atrial fibrillation.

Setting: Retrospective design using hospital-based data.

Method: This propensity score-matched cohort study included data extracted from the electronic medical records of the En Chu Kong Hospital Research Database.

Main outcome measure: Outcome measures were major bleeding and thromboembolism. Cox proportional hazard models were applied for evaluating hazard ratios with 95% confidence intervals.

Results: Among 1,075 patients with atrial fibrillation, 687 and 388 were administered non-vitamin K oral anticoagulants and warfarin, respectively. After propensity score matching, 264 patient pairs were selected. Compared with warfarin use, non-vitamin K oral anticoagulant use was associated with similar risks for major bleeding and thromboembolism; however, the latter was associated with increased gastrointestinal bleeding risks (adjusted hazard ratio 3.59; 95% confidence interval, 1.31-11.39). Notably, an approximately 10-fold increased risk of gastrointestinal bleeding was observed in 0-6-month non-vitamin K oral anticoagulant users (adjusted hazard ratio 10.13, 95% confidence interval 1.27-80.89).

Conclusion: Non-vitamin K oral anticoagulant use was not associated with major bleeding and thromboembolism occurrence in Asian patients with atrial fibrillation. However, non-vitamin K oral anticoagulant use was associated with increased gastrointestinal bleeding risks, especially when used within 0-6 months.

Impact Of Findings On Practice

- Asians have higher risks of bleeding complications when taking anticoagulants than non-Asians.
- Current guidelines support the use of non-vitamin K oral anticoagulants as non-inferior or even superior to warfarin in Asians with atrial fibrillation, although limited clinical trials involving Asians exist, and there is a lack of laboratory data of blood clotting in most real-world studies.
- Our study supports the finding that there is a comparable risk for any major bleeding event and major thromboembolism between non-vitamin K oral anticoagulants and warfarin in Asian patients with atrial fibrillation, and a high risk of gastrointestinal bleeding was observed in the patients taking non-vitamin K oral anticoagulant for 0–6 months.

- In clinical practice, we observed a low percentage of time in therapeutic range after warfarin treatment and most non-vitamin K oral anticoagulant prescriptions were administered in low doses in Asian patients with atrial fibrillation.

Introduction

Atrial fibrillation (AF) is a leading cause of stroke-related disability and death, affecting approximately 33.5 million people worldwide [1]. For patients with AF, one of the main goals of therapy is the prevention of arterial thromboembolism, particularly stroke [2]. Anticoagulants, including non-vitamin K oral anticoagulants (NOACs) and warfarin, are widely prescribed for thromboembolism prevention in patients with AF. According to the 2019 ACC/AHA/HRS updated guidelines, NOACs are recommended over warfarin in NOAC-eligible patients with AF [3]. Despite their efficacy, anticoagulants are also associated with an increased risk of bleeding that may lead to life-threatening or fatal outcomes, especially in the Asian population [4].

Asian patients with AF are known to have different coagulation profiles from those of non-Asian patients with AF [5]. Asian patients have higher bleeding risks with difficulty in achieving the therapeutic goal of the international normalized ratio (INR) during warfarin treatment [6, 7]. In Asian patients with AF, NOAC might be a more efficacious and safer choice, based on the propensity for stroke and intracranial bleeding when taking warfarin [8]. Furthermore, the subgroup analysis of pivotal NOAC trials indicated that NOACs have favorable effects and safety profiles compared with warfarin in Asian patients with AF [9, 10]. In addition, a meta-analysis of real-world data showed that NOACs may have greater effectiveness and safety than warfarin in a nationwide Asian cohort with AF, despite the lack of laboratory parameters for blood clotting in most included studies [11]. As NOAC use gradually increases [12], more evidence is necessary to support the use of NOACs in the Asian population.

AIM OF THE STUDY

This observational study among Taiwanese patients with AF aimed to compare the safety and effectiveness between NOAC and warfarin in a hospital care setting, by analyzing their risks of bleeding and thrombotic events. Furthermore, we aimed to determine the dosage of NOACs and the time in therapeutic range (TTR) after warfarin therapy in clinical practice in Asia.

ETHICS APPROVAL

This investigation was approved by the Institutional Review Committee on Human Research of En Chu Kong Hospital (Registration no. ECKIRB1081201).

Method

Study design and data source

We conducted a retrospective cohort study using data obtained from electronic medical records of patients admitted to En Chu Kong Hospital, which a >500-bed regional teaching hospital and the main referral hospital in the Sanxia district in Taiwan [13], from January 1, 2014 to December 31, 2019. Unlike administrative data, the electronic medical records contain extensive laboratory data, which can provide a less biased estimate of the association between exposures and outcomes [14].

Study cohort identification

The study cohort included patients aged ≥20 years, who were newly treated with NOACs (dabigatran or rivaroxaban) or warfarin between January 2015 and December 2018 for AF, diagnosed according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 427.31 and ICD-10-CM codes of I48.0, I48.2, and I48.91. We defined the cohort entry date as the first prescribed date of the anticoagulant drug. To improve the impact of prevalent user bias, patients with any anticoagulant prescription in the year before the cohort entry date were excluded [15]. To ensure data quality and avoid loss to follow up, we excluded patients with <1 year of records in the year before the cohort entry date and those without any following record after the cohort entry date.

Patients were classified as either NOAC initiators or warfarin initiators, with the two groups further categorized into the exposure and reference groups, respectively. NOACs and warfarin are similar in treatment indications, which helps mitigate the risk of confounding factors such as differences in indication, disease severity, and unmeasured confounding factors in the evaluation of NOACs [16]. We followed each individual of the cohort from the cohort entry date until the first occurrence of the study outcome, treatment discontinuation, switching to a different anticoagulant group, an add-on of other anticoagulants, or the study end date (December 31, 2019) for as-treated analysis, whichever came first. Termination of treatment was defined as a period between two successive prescriptions exceeding 30 days .

Outcome measures

The primary safety outcome was any major bleeding, which was the composite of intracranial, gastrointestinal tract, or other bleeding events, from inpatients or emergency room visits. The primary effectiveness outcome was major thromboembolism, which was defined as arterial thromboembolism (for example, ischemic stroke, transient ischemic attack, and peripheral embolism), myocardial infarction, and venous thromboembolism from inpatients or emergency room visits. Secondary outcomes separately analyzed a number of individual outcomes among the composite outcomes. Definitions of outcomes were described previously [17] and are reported in Online Resource 1.

Covariate measurement

We extracted five classes of confounders according to a literature review, including demographics, laboratory data, occurrence of the study outcomes, comorbidities, and comedications in the year before cohort entry. Specifically, we identified INR, activated partial thromboplastin time (APTT), serum

creatinine, aspartate aminotransferase, and alanine aminotransferase to measure parameters of blood coagulation, renal function, and liver function. Despite the therapeutic INR range being between 2.0 and 3.0 for American or European subjects, we set the normal range of INR between 1.8 and 2.4 because the cut-off value is more sensitive to warfarin for Asians [18]. We estimated the CHA2DS2-VASc and HAS-BLED scores as risk predictors of bleeding and thrombotic events. The HAS-BLED score could not be reliably calculated because of the unavailability of blood pressure measurements. We evaluated the presence of comorbidities using frequently observed diagnoses in patients with AF, including cardiovascular disease, diabetes, and dyslipidemia. In addition, we identified comedications for these conditions, such as antiarrhythmic drugs, antiplatelet monotherapy, dual antiplatelet therapy, and antidiabetic drugs.

Statistical analysis

To control for imbalances of multiple covariates in patient characteristics between the two groups, we calculated a propensity score (PS) for each subject as the predicted probability of receiving NOACs using a multiple logistic regression model with predictors of all potential confounders listed in Table 1. We used 1:1 matching of the cohorts on their estimated PS using a caliper width equal to 0.05 of the PS scale without replacement. Categorical variables were analyzed using the chi-square test and Fisher's exact test, and continuous variables were analyzed using the independent t-test or Wilcoxon test. Before and after PS matching, the covariate balance between the NOAC and warfarin groups was assessed, and a two-sided p-value < 0.05 was considered statistically significant. Cox regression models were employed for the hazard ratios (HRs) with 95% confidence intervals (CIs) for outcomes of bleeding or thromboembolism. The variables were adjusted in the regression model if the variables had significant associations with the outcome in the bivariate analysis at each time period. We assessed the proportional hazards assumption by testing means of Schoenfeld residuals and the graphical methods and confirmed that the assumption was not violated. The analyses were performed using SAS software version 9.4 (College Station, TX, USA) for data management and statistical analyses were performed using STATA software version 15 (Cary, NC, USA).

Table 1
Clinical characteristics of NOAC users and matched warfarin users

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Age, mean ± SD	75.5 (10.8)	72.5 (11.9)	0.000	73.5 (11.6)	74.4 (11.1)	0.375
Sex, male no. (%)	310 (45.1)	183 (47.2)	0.519	112 (45.5)	113 (45.9)	0.928
Entry year (%)						
2015	276 (40.2)	261 (67.3)	0.000	145 (58.9)	146 (59.4)	0.984
2016	136 (19.8)	46 (11.9)		38 (15.5)	35 (14.2)	
2017	141 (20.5)	50 (12.9)		38 (15.5)	39 (15.9)	
2018	134 (19.5)	31 (8.0)		25 (10.2)	26 (10.6)	
Serum creatinine (mg/dL)			0.000			0.683
≤ 1.4	494 (71.9)	233 (60.1)		158 (64.2)	152 (61.8)	
> 1.4	88 (12.8)	72 (18.6)		35 (14.2)	42 (17.1)	
Unknown	105 (15.3)	83 (21.4)		53 (21.5)	52 (21.1)	
GOT (IU/L)			0.009			0.681
≤ 38	299 (43.5)	135 (34.8)		98 (39.8)	100 (40.7)	
> 38	56 (8.2)	28 (7.2)		20 (8.1)	15 (6.1)	

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Unknown	332 (48.3)	225 (58.0)		128 (52.0)	131 (53.3)	
GPT (IU/L)			0.043			0.775
≤ 41	458 (66.7)	253 (65.2)		152 (61.8)	154 (62.6)	
> 41	59 (8.6)	20 (5.2)		19 (7.7)	15 (6.1)	
Unknown	170 (24.8)	115 (29.6)		75 (30.5)	77 (31.3)	
APTT (s)			0.000			0.911
< 22.5	12 (1.75)	4 (1.03)		5 (2.0)	3 (1.2)	
22.5–32.5	244 (35.5)	69 (17.8)		53 (21.5)	55 (22.4)	
> 32.5	58 (8.4)	37 (9.5)		27 (11.0)	27 (11.0)	
Unknown	373 (54.3)	278 (71.7)		161 (65.5)	161 (65.5)	
INR			0.000			0.000
< 1.8	232 (33.8)	134 (34.5)		59 (24.0)	87 (35.4)	
1.8–2.4	13 (1.9)	81 (20.9)		4 (1.6)	47 (19.1)	
> 2.4	8 (1.2)	41 (10.6)		4 (1.6)	23 (9.4)	

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Unknown	434 (63.2)	132 (34.0)		179 (72.8)	89 (36.2)	
CHA_2DS_2–VASc score			0.000			0.672
0–2	113 (16.5)	101 (26.0)		55 (22.4)	47 (19.1)	
3–4	233 (33.9)	146 (37.6)		88 (35.8)	91 (37.0)	
≥ 5	341 (49.6)	141 (36.3)		103 (41.9)	108 (43.9)	
HAS-BLED score			0.000			0.786
0–2	306 (44.5)	237 (61.1)		129 (52.4)	132 (53.7)	
≥ 3	381 (55.5)	151 (38.9)		117 (47.6)	114 (46.3)	
Previous bleeding						
Intracranial	123 (17.9)	16 (4.1)	0.000	15 (6.1)	16 (6.5)	0.853
Gastrointestinal bleedings	66 (9.6)	34 (8.8)	0.647	22 (8.9)	21 (8.5)	0.873
Other bleedings	40 (5.8)	21 (5.4)	0.780	15 (6.1)	14 (5.7)	0.848
Previous thromboembolism						
Myocardial infarction	19 (2.8)	5 (1.3)	0.115	2 (0.8)	3 (1.2)	0.653
Arterial thromboembolisms	265 (38.6)	106 (27.3)	0.000	86 (35.0)	90 (36.6)	0.707

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Venous thromboembolisms	29 (4.2)	10 (2.6)	0.166	9 (3.7)	9 (3.7)	1.000
Comorbidity						
Heart failure	333 (48.5)	209 (53.9)	0.089	125 (50.8)	125 (50.8)	1.000
Hypertension	483 (70.3)	260 (67.0)	0.261	166 (67.5)	171 (69.5)	0.628
Cerebrovascular disease	347 (50.5)	121 (31.2)	0.000	103 (41.9)	108 (43.9)	0.649
Other ischemic heart disease	229 (33.3)	130 (33.5)	0.954	80 (32.5)	77 (31.3)	0.772
Dyslipidemia	249 (36.2)	223 (57.5)	0.000	105 (42.7)	110 (44.7)	0.650
Diabetes mellitus	226 (32.9)	106 (27.3)	0.057	70 (28.5)	76 (30.9)	0.554
Asthma	59 (8.6)	40 (10.3)	0.349	17 (6.9)	21 (8.5)	0.499
COPD	122 (17.8)	91 (23.5)	0.025	52 (21.1)	52 (21.1)	1.000
Pneumonia	109 (15.9)	56 (14.4)	0.531	36 (14.6)	37 (15.0)	0.899
Psychiatric disorders	82 (11.9)	62 (16.0)	0.062	35 (14.2)	34 (13.8)	0.897
Fracture	62 (9.0)	31 (8.0)	0.562	23 (9.4)	18 (7.3)	0.415
Osteoarthritis	134 (19.5)	89 (22.9)	0.183	57 (23.2)	55 (22.4)	0.830

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Anemia	71 (10.3)	40 (10.3)	0.990	20 (8.1)	26 (10.6)	0.353
Thyroid disease	58 (8.4)	66 (17.0)	0.000	29 (11.8)	25 (10.2)	0.564
Cancer	31 (4.5)	15 (3.9)	0.615	8 (3.3)	8 (3.3)	1.000
Comedication						
Diuretics	189 (27.5)	61 (15.7)	0.000	53 (21.5)	54 (22.0)	0.913
Angiotensin- converting enzyme inhibitors/ Angiotensin receptor blockers	141 (20.5)	48 (12.4)	0.001	36 (14.6)	38 (15.5)	0.801
Beta blockers	128 (18.6)	49 (12.6)	0.011	40 (16.3)	36 (14.6)	0.618
Calcium channel blockers	155 (22.6)	59 (15.2)	0.004	45 (18.3)	51 (20.7)	0.495
Lipid-lowering agents	93 (13.5)	36 (9.3)	0.039	18 (7.3)	26 (10.6)	0.206
Antiarrhythmic Drugs	108 (26.2)	49 (12.6)	0.000	45 (18.3)	45 (18.3)	1.000
Mono-antiplatelet therapy	204 (29.7)	41 (10.6)	0.000	47 (19.1)	40 (16.3)	0.408
Dual-antiplatelet therapy	24 (3.5)	5 (1.3)	0.032	3 (1.2)	4 (1.6)	0.703
Diabetic medications	95 (13.8)	27 (7.0)	0.001	23 (9.4)	25 (10.2)	0.761

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

Characteristics*	Before matching, no. (%)			After matching, no. (%)		
	NOACs (n = 687)	Warfarin (n = 388)	p-value‡	NOACs (n = 246)	Warfarin (n = 246)	p-value‡
Steroids	62 (9.0)	24 (6.2)	0.099	17 (6.9)	19 (7.7)	0.729
NSAIDs	161 (23.4)	64 (16.5)	0.007	53 (21.5)	45 (18.3)	0.367
Proton pump Inhibitors	65 (9.5)	19 (4.9)	0.007	16 (6.5)	16 (6.5)	1.000

Abbreviations: NOACs, non-vitamin K oral anticoagulants; SD, standard deviation; no., number; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; APTT, activated partial thromboplastin time; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; COPD, chronic obstructive pulmonary disease.

*All comorbidities, CAD severity indicators, COPD severity indicators, and comedications were measured in the year before the cohort entry date.

‡ p-value with < 0.05 represents meaningful differences between two groups.

We analyzed the data of the patients receiving treatments within 0-6 months, 6 months-1 year, and 1-2 years to determine the risks of any major bleeding or thromboembolic event. In addition, we conducted three sensitivity analyses to examine the robustness of our findings. First, we re-evaluated the analyses by an intention-to-treat definition to account for the probability that censorship was associated with the outcome. In the intention-to-treat approach, we assumed that patients continuously used their initial anticoagulant during the entire follow-up period, regardless of any discontinuation or switching that occurred. Second, we excluded patients with a history of any major bleeding or thromboembolic event before cohort entry date. Finally, we performed PS-weighted analysis to maximize the representative cohort in a sensitivity analysis. Furthermore, we calculated the dosage of NOAC therapy and the TTR value for warfarin therapy using the Rosendaal method to determine whether an ideal therapeutic range was achieved [19]. We defined low-dose NOACs as dabigatran 110 mg twice daily or rivaroxaban 10 mg/day [20, 21]. A TTR level of ≥0.65 was considered to represent good clinical outcomes to minimize possible bleeding or thromboembolic complications in warfarin users [22].

Results

Before PS matching, we identified 687 NOAC and 388 warfarin initiators (Fig. 1). NOAC initiators were slightly younger and had better renal functions; lower APTT and INR; and greater thromboembolic and bleeding risks as measured by the CHA2DS2–VASc score and HAS-BLED score, respectively; moreover, they were more likely to have comorbidities and comedications at baseline than warfarin initiators

(Table 1). After PS matching, all baseline characteristics were balanced prior to cohort entry between NOAC and warfarin users. There were 264 pairs of NOAC and warfarin initiators. The two groups showed similar characteristics at baseline. The mean follow-up period was 183.1 (standard deviation [SD], 237.5) and 187.1 (SD, 241.7) days, respectively, for the examination of new NOAC and warfarin therapies and any associated major bleeding and thromboembolic event. The rates of occurrence of any major bleeding event were 0.43 and 0.25 events per 1,000 person-years for NOAC and warfarin users, respectively, and the rates of occurrence of major thromboembolic events were 0.39 and 0.23 events per 1,000 person-years for NOAC and warfarin users, respectively (Table 2).

Table 2
The hazard ratios for NOACs versus warfarin after propensity score matching

	NOACs (n = 246)		Warfarin (n = 246)			
	No. of events	Incidence rate (events/1000 patient years)	No. of events	Incidence rate (events/1000 patient years)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Primary analysis by as-treated exposure definition						
Any bleeding	18	0.43 (0.27–0.68)	12	0.25 (0.14–0.44)	1.61 (0.77–3.37)	1.64 (0.73–3.68)
Intracranial	5	0.11 (0.04–0.25)	4	0.08 (0.03–0.22)	1.18 (0.32–4.42)	1.07 (0.24–4.82)
Gastrointestinal	11	0.25 (0.14–0.46)	4	0.08 (0.03–0.22)	3.12 (0.98–9.91)	3.59 (1.13–11.39)[b]
Other	4	0.08 (0.03–0.22)	4	0.08 (0.03–0.22)	0.99 (0.25–3.99)	0.95 (0.21–4.41)
Any thromboembolism	17	0.39 (0.24–0.62)	11	0.23 (0.13–0.41)	1.64 (0.77–3.53)	1.68 (0.75–3.78)
Arterial	7	0.14 (0.07–0.30)	12	0.27 (0.15–0.47)	1.69 (0.66–4.31)	1.79 (0.68–4.71)
Myocardial infarction	4	0.08 (0.03–0.22)	6	0.13 (0.06–0.29)	1.67 (0.46–6.01)	1.70 (0.43–6.71)
Venous	1	0.02 (0.00-0.15)	0	NA	NA	NA

Abbreviations: NOACs, non-vitamin K oral anticoagulants; HR, hazard ratio; CI, confidence interval

[a] djusted for covariates that were measured with SD > 0.1 between NOACs and warfarin as shown in Table 1.

[b] $p < 0.05$

In the primary analysis, the overall use of NOACs showed no association with risks of any major bleeding and thromboembolic events compared with the use of warfarin among Asian patients with AF. In the secondary analysis, new use of NOACs was associated with a higher risk of gastrointestinal bleeding

than new use of warfarin in the matched population, with an adjusted HR of 3.69 (95% CI, 1.13–11.39). No other statistically significant difference was observed in other individual components of the composite outcomes (Table 2).

The results according to the different time period analyses are shown in Table 3. In the period of 0–6 months, the use of NOACs was associated with an increased risk of gastrointestinal bleeding (adjusted HR 10.13, 95% CI 1.27–80.89) compared to the use of warfarin, albeit no increased risk was observed at 6 months-1 year and 1–2 years. Reanalysis of the cohort with intention-to-treated definition showed results that were consistent with those of the main analysis for all outcomes. In addition, after excluding patients with a history of any major bleeding and thromboembolic events before cohort entry date, the results were very similar to the main finding. Using the whole cohort with PS-weighted analysis also resulted in HRs that were comparable to those of the primary analysis with PS matching (Fig. 2). Further, after warfarin treatment, the median TTR value was 0.32, ranging from 0.01 to 0.92. The percentage of patients with low-dose NOAC was 91.9% in this study.

Table 3
The time period analysis for NOACs versus warfarin

	NOACs	Warfarin			
	No. of events	No. of events	P-value	Crude HR	Adjusted HR[a]
0–6 months					
Any bleeding	12	8	0.361	1.41 (0.57–3.47)	1.64 (0.58–4.67)
Intracranial	2	4	0.686	0.44 (0.08–2.44)	0.36 (0.06–2.02)
Gastrointestinal	8	1	0.037	7.67 (0.95–61.68)	10.13 (1.27–80.89)[b]
Other	2	3	1.000	0.61 (0.10–3.73)	0.55 (0.09–3.32)
Any thromboembolism	11	9	0.648	1.13 (0.47–2.70)	1.28 (0.50–3.22)
Arterial	10	6	0.309	1.54 (0.57–4.17)	1.80 (0.63–5.13)
Myocardial infarction	2	3	1.000	0.62 (0.10–3.80)	0.74 (0.09–6.07)
Venous	1	0	1.000	NA	NA
6 months-1 year					
Any bleeding	1	1	1.000	1.30 (0.09–18.72)	0.77 (0.06–10.51)
Intracranial	1	0	1.000	NA	NA
Gastrointestinal	0	0	NA	NA	NA
Other	0	1	1.000	NA	NA
Any thromboembolism	1	0	1.000	NA	NA
Arterial	1	0	1.000	NA	NA

Abbreviations: NOACs, non-vitamin K oral anticoagulants; HR, hazard ratio; CI, confidence interval; NA, not available

[a]Adjusted for covariates that were measured with SD > 0.1 between NOACs and warfarin after stratification.

[b]$p < 0.0$

	NOACs	Warfarin			
Myocardial infarction	0	0	NA	NA	NA
Venous	0	0	NA	NA	NA
1–2 years					
Any bleeding	3	2	1.000	2.07 (0.38–11.26)	1.98 (0.37–10.59)
Intracranial	1	0	1.000	NA	NA
Gastrointestinal	2	2	1.000	1.50 (0.24–9.54)	1.48 (0.23–9.38)
Other	2	0	0.499	NA	NA
Any thromboembolism	2	1	1.000	2.98 (0.29–30.54)	2.36 (0.24–23.64)
Arterial	1	0	1.000	NA	NA
Myocardial infarction	2	0	0.499	NA	NA
Venous	0	0	NA	NA	NA
Abbreviations: NOACs, non-vitamin K oral anticoagulants; HR, hazard ratio; CI, confidence interval; NA, not available					
[a]Adjusted for covariates that were measured with SD > 0.1 between NOACs and warfarin after stratification.					
[b]$p < 0.0$					

Discussion

This study was based on routinely collected data for clinical care from Asian patients with AF. We observed a similar risk for any major bleeding and major thromboembolic events in both hospitalized inpatients and those who visited the emergency room between NOAC and warfarin initiators, even after carefully controlling for numerous confounders and considering various clinical backgrounds. Notably, those who received NOAC treatment for a period of 0–6 months had an approximately 10-fold increased risk of gastrointestinal bleeding compared to those who initiated warfarin treatment. These findings remained consistent in multiple sensitivity analyses.

NOACs are non-inferior to warfarin in decreasing the risks of stroke and bleeding [23, 24]. Compared with warfarin, safety profiles showed an increased risk of gastrointestinal bleeding with rivaroxaban, edoxaban, and dabigatran (150 mg twice daily) [25]. There are several potential mechanisms to explain

why NOACs cause gastrointestinal bleeding. A possible explanation is the incomplete absorption of active NOACs in the upper gastrointestinal tract, with increased risks of bleeding on the gastrointestinal mucosa; moreover, NOACs may inhibit healing of the mucosa [26, 27]. In addition, dabigatran etexilate contains tartaric acid, which is assumed to lead to direct caustic injury [26]. According to our findings and current evidence on NOAC-related gastrointestinal bleeding in patients with AF, we suggest close monitoring of gastrointestinal bleeding symptoms, such as darker and sticky stools or coughing up blood, especially within 0–6 months of NOAC use.

A higher prevalence of low-dose NOAC prescription and lower TTR for warfarin treatment were found in the present cohort. Notably, these patterns of prescription seem to be common in clinical practice [28, 29]. Clinicians might prefer to use low-dose NOAC in Asians for various reasons. For example, a high percentage of anticoagulant users are elderly patients, who are more likely to present with multiple comorbidities and renal insufficiency [30]. Furthermore, Asian patients with AF taking oral anticoagulants have a lower body mass index and higher bleeding risk than non-Asian patients [6, 7, 31]. Moreover, most patients with AF receive a combination of antiplatelet and anticoagulant therapies [5], which may induce a higher risk of bleeding complications. Because oral anticoagulation is an important strategy for thrombosis prevention in Asian patients with AF, clinical professionals tend to underdose NOACs to avoid major bleeding side effects. Similarly, a lower TTR implies that warfarin is underused to prevent bleeding or therapy compliance is poor in real-world practice in Asia. However, adjusted-dose anticoagulants are like a double-edged sword, with the consideration for excessive bleeding risks of anticoagulants comes the possible depletion of drug efficacy. It is about striking a balance between bleeding risks and thromboembolism prevention through the adjustment of the NOAC dosage and TTR of warfarin. However, we observed that low-dose NOAC usage rate and TTR during warfarin treatment were 91.9% and 32% in our analysis using real-world data. The use of both anticoagulants may be associated with low efficacy or negative consequences. We suggest a time-varied re-evaluation of the benefits and risks for anticoagulants in Asian patients with AF based on their baseline probability for developing dangerous blood clots. Future studies evaluating the optimal dosing and TTR still need to be conducted in Asian patients with AF.

The present study had some strengths. Our study is based on routinely collected data in a hospital with additional information on INR, liver function, and renal function. We could therefore apply new-user designs and PS-matched analysis to correct for the imbalance of measured confounders in baseline characteristics, which would have decreased potential biases. Despite these strengths, our investigation also had many limitations. First, the study had a relatively small sample size, although we made an effort to perform a sensitivity analysis using PS weighting to recollect all data of AF patients and obtained very similar results. Second, similar to all observational studies, the present study possibly had unmeasured confounding factors, which always leads to biased effect estimates. Third, it was not possible to exclude long-term differences in risks of any major bleeding and thromboembolic events between the NOAC and warfarin groups because of the relatively short follow-up period. Lastly, our sample was recruited from a general hospital, which belongs to regional pharmacoepidemiology; hence, the included patients may not

be representative of the general population because of selection bias, despite all our efforts of eliminating this bias.

Conclusion

NOACs and warfarin are comparable in their risks for any major bleeding and thromboembolic events in Asian patients with AF. The use of NOACs was associated with an increased risk of gastrointestinal bleeding, especially when used within a period of 0–6 months. We found a high prevalence of low-dose NOAC prescription and lower TTR for warfarin treatment among Asian patients with AF in the clinical setting. Close monitoring for any signs of gastrointestinal bleeding is necessary when NOACs are administered within 0–6 months.

Declarations

Acknowledgements: We would like to express our greatest appreciation to En Chu Kong Hospital for allowing us to use their analyzed claims database and Mrs. You-Meei Lin for giving administrative support. We also thank Professor Yi-Ting Hwang, affiliated to the Department of Statistics, National Taipei University, for the assistance in the statistical analysis.

COMPLIANCE WITH ETHICAL STANDARDS

Funding: This study was supported in part by a grant from the En Chu Kong Hospital, New Taipei City, Taiwan (ECKH_D10802). The funder did not participate in study design, collection, analysis, data interpretation, or manuscript writing.

Conflict of interests: The authors declare that they have no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and there are no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: The current study analyzed data from the electronic medical records of En Chu Kong Hospital. The study was examined by the Institutional Review Committee on Human Research of En Chu Kong Hospital (Registration no. ECKIRB1081201).

Consent to participate: This study is a de-identified database-based study, and, therefore, was exempt from a full review of the Institutional Review Committee on Human Research of En Chu Kong Hospital (Registration no. ECKIRB1081201), and the need for obtainining participant informed consent was waived.

Availability of Data and Material: The authors are restricted from sharing the analyzed data in this study because public access to the electronic medical records is forbidden by the current laws of Taiwan. To request access to the data, En Chu Kong Hospital, Taiwan should be contacted (https://www.eck.org.tw/).

Code Availability: Not applicable

Authors' Contributions: All authors conceptualized and designed the current study; Chen CY acquired the analyzed dataset; Huang YL analyzed the data; all authors interpreted the data; Huang YL and Chen CY drafted the manuscript; all authors made critical revisions of the manuscript and gave final approval of the submitted manuscript.

Transparency: The lead author (Huang YL) confirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Figures

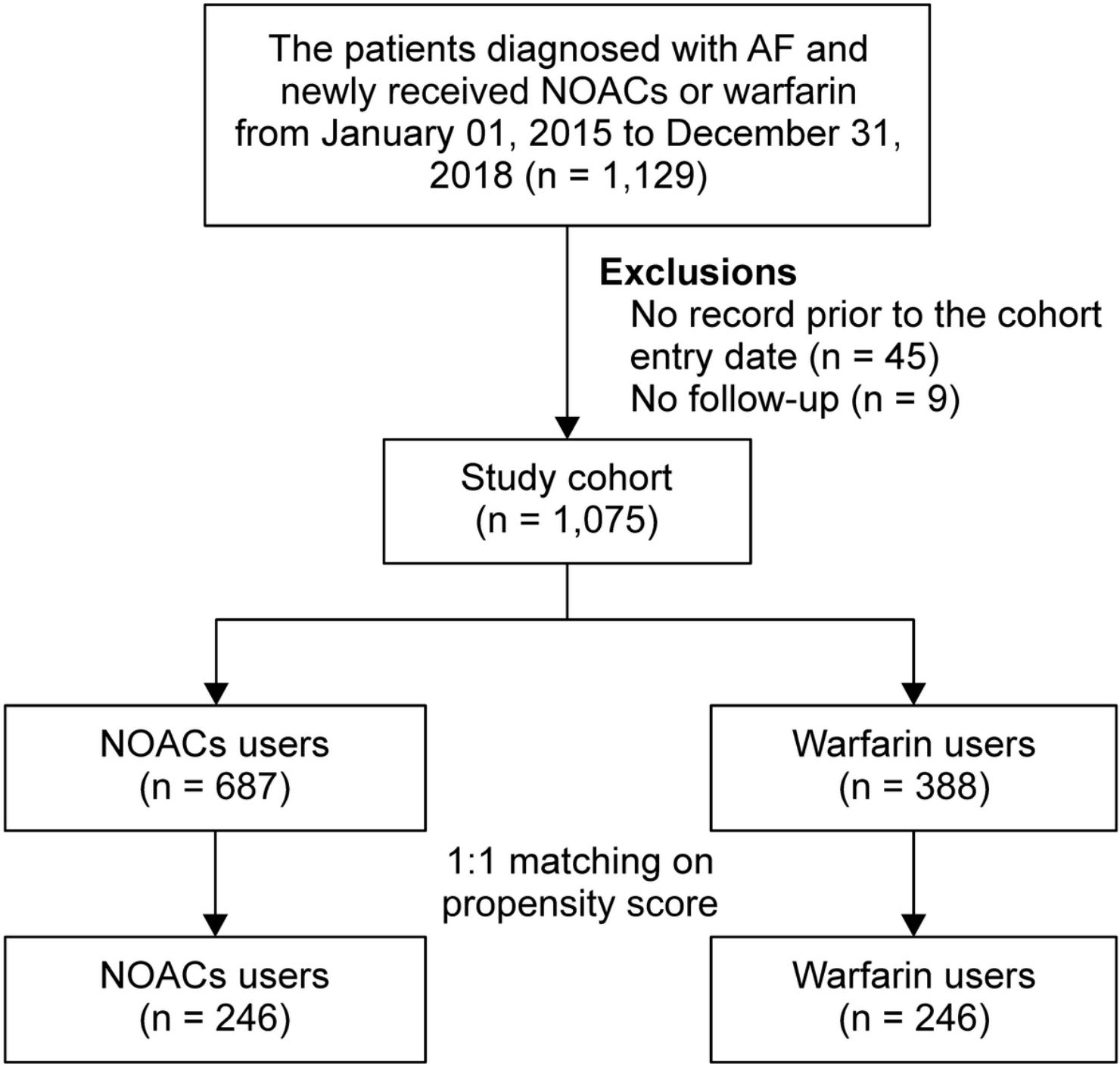

Figure 1

The study flowchart

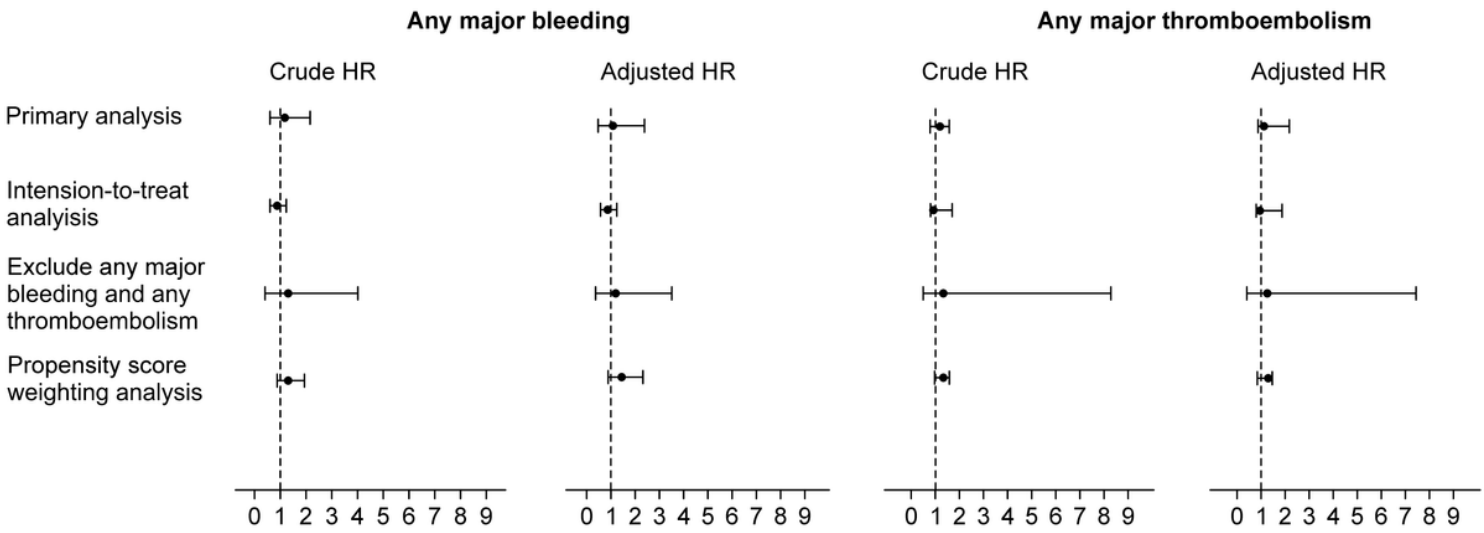

Figure 2

The sensitivity analysis for non-vitamin K oral anticoagulants versus warfarin

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