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Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in low-weight patients with atrial fibrillation

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Abstract

It remains unclear whether non-vitamin K antagonist oral anticoagulants (NOACs) are more effective and safer than warfarin in low-weight patients with atrial fibrillation (AF). Here, we retrospectively compared the effectiveness and safety of NOACs with those of warfarin in low-weight patients with AF. We extracted the July 2011–September 2022 data of patients with AF treated with a NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) or warfarin at a tertiary hospital. The patients were divided into low-weight (body weight ≤ 60 kg) and non–low-weight (body weight = 60–100 kg) groups. The primary outcomes were hospitalization for ischemic stroke (IS) or systemic embolism (SE) and major bleeding, whereas the secondary outcomes were any ischemic and bleeding events. We used the inverse probability of treatment weighting to balance the baseline characteristics between the groups. In total, 5,044 patients (mean age = 73.7 years, mean CHA2DS2-VASc score = 3.0, mean HAS-BLED score = 2.3) were enrolled and divided into low-weight and non–low-weight groups—containing 1,666 (1,406 NOAC users, 260 warfarin users) and 3,378 (2,978 NOAC users, 400 warfarin users) patients, respectively. NOACs were associated with a lower risk of any bleeding event in the low-weight group (adjusted hazard ratio = 0.61, 95% confidence interval = 0.51–0.73). The between-group differences in the risks of IS/SE, any ischemic event, major bleeding, and any bleeding event were nonsignificant. Thus, the use of NOACs (specifically dabigatran or edoxaban) is associated with a lower risk of any bleeding event than warfarin use in low-weight patients with AF.

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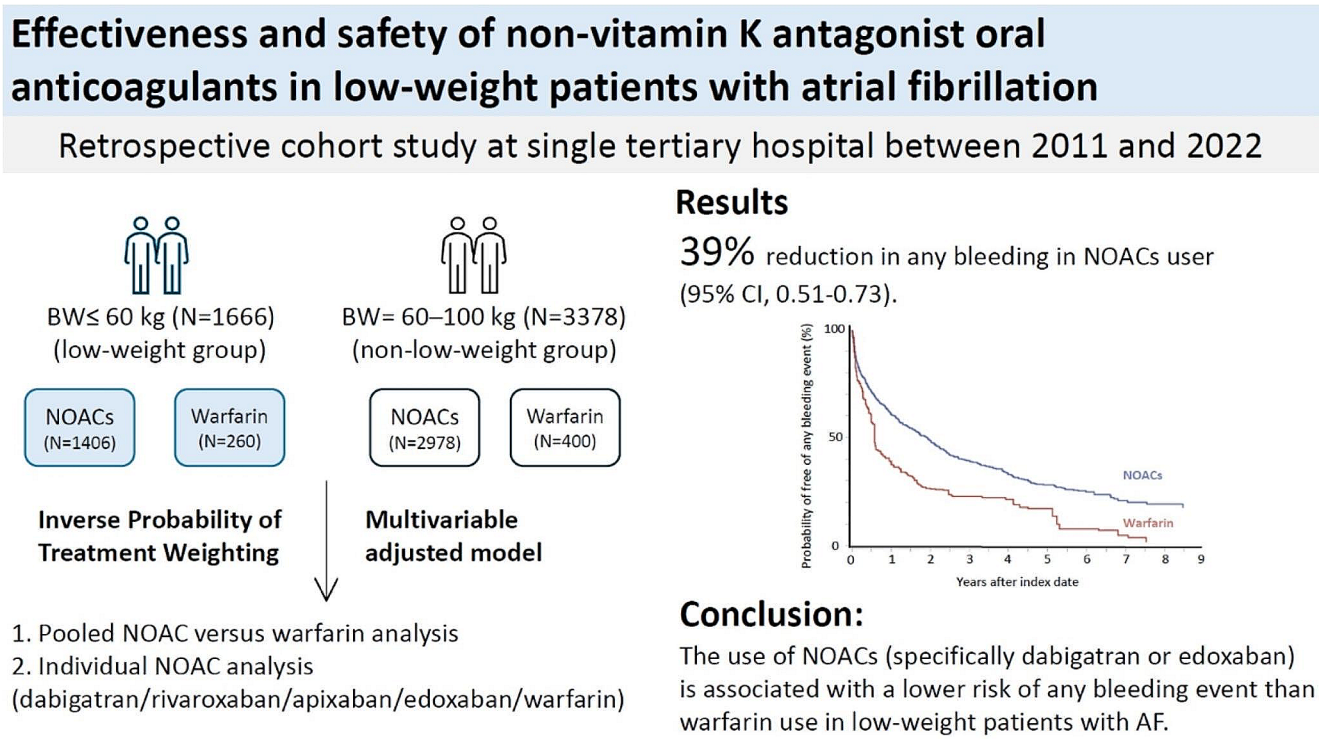
Graphic abstract



Keywords Atrial fibrillation · Low body weight · Non-vitamin K antagonist oral anticoagulant (NOAC)

Introduction

The incidence and prevalence of atrial fibrillation (AF) can increase with age and comorbidity burden [1]. Oral anticoagulant (OAC) therapy facilitates AF management, preventing ischemic stroke (IS) and reducing overall mortality [2]. Warfarin has been used as a primary OAC over several decades; however, its use has been reduced because of its association with a narrow therapeutic range, frequent monitoring requirements, drug–drug interactions, and bleeding complications [3]. The introduction of non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, heralded a transformation in OAC therapy, providing convenient, safe, and effective alternatives to warfarin and leading to broader OAC utilization [4–7]. With the increase in the use of various OACs, their effectiveness and safety warrant evaluation.

Compared with non-underweight patients, underweight patients on a fixed dosage of NOACs may be exposed to higher levels of these medications, which may increase their bleeding risk. The pharmacokinetics of NOACs are strongly linked to their plasma concentrations, which are influenced by the individual's body distribution volume. Extremely low body weight may significantly affect the efficacy and safety profile of NOACs. However, pivotal clinical trials evaluating NOACs have enrolled extremely few low-weight patients; notably, most of these low-weight patients have primarily been of Asian descent [8–11].

NOACs demonstrate superior net clinical benefits over warfarin, particularly in terms of a decrease in intracranial hemorrhage (ICH) occurrence [3]. In the study by Park et al., AF patients taking NOACs who were underweight had an increased risk of major bleeding and all-cause death compared to those who were normal weight or overweight to obese. [12].

Boriani et al. reported that the pharmacokinetics and pharmacodynamics of edoxaban in low-weight patients (≤ 55 kg, $n = 1082$) are similar to those in other weight groups. Additionally, they observed that low-weight patients using low-dose edoxaban had a lower risk of major bleeding compared to those using warfarin. Furthermore, low-weight patients using high-dose edoxaban had better net clinical outcomes compared to those using warfarin. Therefore, the study suggests using edoxaban in low body weight patients [13]. Hohnloser et al. reported that the use of apixaban, compared to warfarin, shows better efficacy (in terms of stroke/systemic embolism, all-cause death, or myocardial infarction) and safety (major bleeding) in both low-weight (≤ 60 kg;

$n = 1985$, 10.9%) and overweight (> 120 kg; $n = 982$, 5.4%) patients. Therefore, this study supports the use of apixaban across various weight categories. Among the low-weight group (≤ 60 kg), nearly 50% were Asian, and Asians might have a higher risk of bleeding. Consequently, more data is needed to support the efficacy and safety of anticoagulants in the Asian population [14].

Whether NOACs provide benefits in individuals with low body weight, especially those with extremely low body weight, comparable to those in non-underweight individuals remains unclear. Thus, in the present cohort study, we compared the effectiveness and safety profiles of various NOACs with those of warfarin in low-weight patients with AF.

Methods

Data source and study population

In this retrospective cohort study, all patient data were acquired from the electronic medical records of Taipei Veterans General Hospital (TPEVGH), one of the largest medical centers in Taiwan, with approximately 3,000 beds and 10,000 daily outpatient visits. The TPEVGH's database includes data on demographic characteristics, prescription records, laboratory data, and procedure and diagnosis codes for inpatients and outpatient claims. All diagnoses are coded on the basis of the *International Classification of Disease*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) and *International Classification of Disease*, *Ninth/Tenth Revision*, *Clinical Modification* (ICD-10-CM).

The present study, based in part on data from the Big Data Center, TPEVGH, was approved by the TPEVGH's institutional review board (IRB-TPEVGH No.: 2023-01-028CC). The requirement of collecting informed consent from the patients was waived because the study only used deidentified data along with a retrospective design.

We included patients aged > 20 years who were diagnosed as having AF and initially treated with a NOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) or warfarin at some time between July 1, 2012, and September 30, 2021. The exclusion criteria were as follows: strict indication for warfarin [e.g., valvular AF (i.e., moderate-to-severe mitral stenosis or mechanical valve)]; alternative indications for OACs (e.g., undergoing joint replacement surgery or experiencing venous thromboembolic ≤ 6 months before the cohort entry date); HIV infection; absence of body weight, height, or renal function data; and body weight ≥ 100 kg.

At the time of hospital discharge or in inpatient claims, AF diagnoses were coded as ICD-9-CM 427.31 or ICD-10-CM I48. To ensure accuracy, we confirmed the presence of an AF diagnosis when AF codes were used for at least two outpatient claims or one hospital discharge indication.

Exposure and outcome measurement

We divided our patients into low-weight (body weight ≤ 60 kg) and non–low-weight (body weight = 60–100 kg) groups. In the low-weight group, we used the body weight cutoff of 60 kg in accordance with the low-weight thresholds used to define underweight in previous randomized controlled trials and cohort studies [4–7, 14]. Moreover, body weight ≤ 60 kg is a criterion used to indicate apixaban or edoxaban dose reduction; in particular, a patient must meet at least two of three criteria (i.e., age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL) to be eligible for a dose reduction. To accurately elucidate the effectiveness and safety of NOACs in low-weight patients, with non–low-weight patients as comparators, we excluded patients with a body weight of > 100 kg.

All eligible patients were further divided into four groups: low-weight and non–low-weight NOAC users and low-weight and non–low-weight warfarin users. To avoid potential residual confounders and ensure similar backgrounds between the two groups, we used warfarin users as the comparators for NOAC users.

Study outcomes and follow-up periods

The cohort entry date was defined as the date of anticoagulant treatment initiation after AF diagnosis and the first prescription of OAC, with a minimum medication usage duration of 5 days. Patients were followed until the earliest occurrence of any outcome, discontinuation of OACs, switch from NOACs to warfarin, loss of follow-up, occurrence of valve surgery, diagnosis of mitral stenosis, or end of study (September 30, 2022). Discontinuation was defined as a 90-day period since the final day of supply after the last prescription.

Outcomes

The outcomes were assessed by verifying ICD-9-CM or ICD-10-CM codes at each hospitalization and in the records for each outpatient clinic visit (Supplemental Table 1). The definitions of the outcomes are detailed in Supplemental Information.

The primary outcomes were IS or systemic embolism (SE) and major bleeding events resulting in hospitalization; they were identified by the presence of the ICD-9-CM or ICD-10-CM codes in the first and second positions of discharge diagnoses. The secondary effectiveness outcome was any ischemic event (i.e., a composite of hospitalization

outcomes including IS/SE, venous thromboembolism, peripheral vascular disease, transient ischemic attack, and acute myocardial infarction). The secondary safety outcome was any bleeding event (encompassing all events in inpatient and outpatient claims, whichever occurred first).

Covariates

We defined potential baseline confounders in terms of the diagnostic and procedure codes and prescription records within 1 year before the cohort entry date. We evaluated the following baseline characteristics: age, sex, body weight, height, body mass index (BMI), renal function, comorbidities (including hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disease, malignancy, heart failure, chronic renal or liver disease, end-stage renal disease, prior IS, transient ischemic attack, peripheral vascular disease, acute myocardial infarction, ICH, gastrointestinal bleeding, and bleeding at other sites), CHA_2DS_2-VASc and HAS-BLED scores, Charlson comorbidity index, and prior antiplatelet agent use (Supplemental Tables 1–4). Renal function was determined on the basis of creatinine clearance (CrCl) assessed using the Cockcroft–Gault method.

Statistical analysis

To compare the warfarin and pooled NOAC groups, their propensity scores (PSs) were assessed using a logistic regression model with the baseline covariates. To balance the baseline characteristics between the two groups, we used the inverse probability of treatment weighting (IPTW) method with stabilized weights. In brief, these weights were calculated from the PSs by assigning each individual a weight based on the inverse probability of receiving NOACs or warfarin [15, 16]. Given the nonequal sample sizes of NOAC and warfarin users, IPTW was used instead of PS matching to retain the study population and maintain generalizability.

Differences in the risks of the outcomes between the NOAC and warfarin groups were determined using survival analyses with the Kaplan–Meier method (i.e., log-rank test) and the weighted Cox proportional hazards model. Survival rates were calculated based on the weighted number of events during the follow-up period divided by 100 person-years at risk.

The balance of covariates between the two groups was assessed using the absolute standardized difference (ASD) [17, 18]. An ASD of >0.1 was considered to indicate an imbalance in the covariates, prompting its subsequent inclusion in a multivariable Cox proportional hazard regression model. This multivariate Cox proportional hazard regression model, weighted with IPTW, was used to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CI).

Additional analyses were performed for each NOAC, separating the NOAC group included in the main analysis into dabigatran, rivaroxaban, apixaban, and edoxaban cohorts. Each cohort was separately compared with the warfarin group.

Subgroup and sensitivity analyses

Pooled NOAC and warfarin users in the total study population were further compared through stratified analyses according to extremely low body weight (<50 kg), age, and sex. To determine whether the results were robust to patients having an extremely low body weight, a subgroup analysis by body weight (<50 and 50–60 kg) was conducted.

In the ELDERCARE-AF trial, compared with the placebo, low-dosage edoxaban (15 mg, once a day) reduced the IS/SE risk in AF patients aged ≥ 80 years; this indicated the efficacy and safety of low-dose edoxaban in older adults [19]. However, older adults may demonstrate weight loss because of physical aging and digestive comorbidities. Age is also a major risk factor for embolism and bleeding. Furthermore, age and sex can influence body size; women and older adults are generally smaller in size than men and young adults, respectively. To account for these factors, we performed subgroup analyses on the basis of age (<80 and ≥ 80 years) and sex.

Sensitivity analyses were performed to validate the results by (1) exploring BMI as a threshold for the study population, (2) including only on-label dosage NOAC users, (3) limiting the follow-up period to 1 year, (4) restricting the grace period to 30 days, and (5) censoring in the case of changes in the prespecified weight group.

Two-sided $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed on SAS (version 9.4; SAS Institute, Cary, NC, USA).

Results

A total of 5,044 patients with AF were recruited in this study; based on a 60-kg weight threshold, 1,666 (33%) and 3,378 (67%) patients were divided into the low-weight and non–low-weight groups, respectively.

In the low-weight group, 260 patients (15.6%) received warfarin, whereas 1,406 (84.4%) received NOACs; of the patients who received NOACs, 266 (16.0%), 500 (30.0%), 329 (19.7%), and 311 (18.7%) received dabigatran, rivaroxaban, apixaban, and edoxaban, respectively. Before IPTW was applied, the low-weight NOAC users were older, had better renal function, and demonstrated higher IS and ICH

prevalence than the low-weight warfarin users. After IPTW was applied, the low-weight NOAC users had a mean age of 77.8 (SD = 10.7) years, mean weight of 52.2 (SD = 5.6), mean BMI of 21.4 kg/m^2, and mean CrCl of 44.8 (SD = 17.9). Moreover, 63.3% (n = 887) of them were women. Finally, their mean (SD) CHA_2DS_2-VASc and HAS-BLED scores [(3.6 (1.6) and 2.5 (1.3), respectively] indicated a high embolism and moderate bleeding risk, respectively.

After IPTW, the low-weight group had ASDs > 0.1 for age, renal function, cohort entry year, other bleeding events, diabetes, and chronic liver disease. By contrast, the non–low-weight group had ASDs > 0.1 for age, renal function, smoking, cohort entry year, and IS history. These variables were included in the Cox proportional hazards model for adjustments (Tables 1-1 and 1-2).

According to Rosendaal linear interpolation, the time in therapeutic range (TTR) among the warfarin users was 39.2%, with INR of 1.5–3 as the threshold [20, 21]; however, after IPTW, this value became 41.2%. The number of warfarin users with TTR ≥ 70% was 65, which accounted for 25% of all warfarin users.

Clinical outcomes

The incidence rates and aHRs of outcomes during the follow-up duration are listed in Table 2. The Kaplan–Meier survival curve of outcomes after IPTW is presented in Fig. 1.

Among NOAC and warfarin users in the low-weight group, the incidence rates were respectively 1.46 and 1.99 per 100 person-years for IS/SE (p = 0.8437), 3.41 and 5.69 per 100 person-years for any ischemic event (p = 0.9534), 4.02 and 5.53 per 100 person-years for major bleeding events (p = 0.8105), and 38.73 and 69.55 per 100 person-years for any bleeding event (p = 0.0005). Here, only the between-group differences in the incidence rates for any bleeding event were significant.

In our multivariable regression model, compared with warfarin use, NOAC use was associated with a 32% higher IS/SE risk and a 35% higher major bleeding risk [aHRs (95% CIs) = 1.32 (0.39–4.44) and 1.35 (0.71–2.56), respectively]; however, the differences were nonsignificant (p = 0.658 and 0.356, respectively). By contrast, NOAC use was associated with a mere 8% higher risk of any ischemic event [aHR (95% CI) = 1.08 (0.54–2.19), p = 0.827]. Nevertheless, NOAC use was associated with a significantly lower risk of any bleeding event [aHR (95% CI) = 0.61 (0.51–0.73), p < 0.001].

The clinical outcomes in the non–low-weight and low-weight groups were similar. Moreover, the differences between NOAC and warfarin users in terms of IS/SE, any ischemic event, major bleeding, and any bleeding event were nonsignificant.

These results jointly indicated that regardless of patient weight, NOAC use tended to be nonsignificantly associated with low rates of ischemia events and major bleeding.

Individual NOAC analyses

As illustrated in Fig. 2, each NOAC in the low-weight group demonstrated potential associations with lower risks of IS/SE and any ischemic and bleeding event. In particular, the association of each NOAC with any bleeding event was significant.

Major bleeding risk varied among the NOACs. Compared with warfarin use, rivaroxaban use was associated with a higher major bleeding risk [aHR (95% CI) = 1.58 (0.83–2.99)], whereas dabigatran, apixaban, and edoxaban use was associated with a lower major bleeding risk [aHRs (95% CIs) = 0.85 (0.41–1.79), 0.98 (0.54–1.76), and 0.59 (0.28–1.23), respectively].

Compared with warfarin, dabigatran and edoxaban use was associated with a lower IS/SE risk [aHRs (95% CIs) = 0.51 (0.16–1.67) and 0.09 (0.006–1.45), respectively] and with a lower major bleeding risk [aHRs (95% CIs) = 0.85 (0.41–1.79) and 0.59 (0.28–1.23), respectively].

Similar to that in the low-weight group results, the interaction p values for the four NOACs in the non–low-weight group was not statistically significant despite inconsistency in the risks among all four NOACs (Supplemental Fig. 2).

Sensitivity analyses and subgroup analyses

In the sensitivity analysis, we segmented the sample by BMI instead of high versus low body weight. Specifically, the patients were segmented into groups with BMI values of < 18.5 kg/m^2 (underweight, 4% of the sample), 18.5–22.9 kg/m^2 (normal weight, 28% of the sample), 23–24.9 kg/m^2 (overweight, 22% of the sample), and ≥ 25 kg/m^2 (46% of the sample). The underweight, normal-weight, overweight, and obese groups included, respectively, 99.5%, 71.0%, 28.3%, and 6.2% of the patients from the original low-weight group and 0.5%, 29.0%, 71.7%, and 93.8% of the patients from the original non–low-weight group.

In the underweight and normal-weight groups, NOAC use was associated with a lower risk of any bleeding event [aHRs (95% CIs) = 0.55 (0.34–0.88) and 0.77 (0.61–0.97), respectively]. The differences in the other outcomes were nonsignificant, likely because our sample size was small.

No significance was observed in other sensitivity and subgroup analyses (Supplemental Tables 5–7 and Supplemental Figs. 1–3). Nevertheless, the results of these analyses tended to be consistent with the main findings across all clinical outcomes.

Table 1-1 Baseline characteristics of the low-weight group before and after inverse probability of treatment weighting (IPTW)

Variables	Before weighting		ASD	After weighting		ASD
	DOACs (*N* = 1,406)	Warfarin (*N* = 260)		DOACs (*N* = 1,402)	Warfarin (*N* = 263)	
Demographics						
Age, mean (SD), yr	78.3 (10.5)	72.6 (13.4)	0.48	77.8 (10.7)	79.1 (12.2)	0.11
Female sex, No. (%)	872 (62.0)	172 (66.2)	0.09	887 (63.3)	158 (60.2)	0.06
Weight, mean (SD), kg	52.3 (5.7)	51.8 (5.8)	0.09	52.2 (5.6)	52.0 (6.5)	0.02
BMI, mean (SD), kg/m^2	21.4 (2.7)	21.3 (2.6)	0.04	21.4 (2.7)	21.3 (3.0)	0.06
Estimated GFR, mean (SD), mL/min	45.7 (17.5)	41.1 (24.5)	0.21	44.8 (17.9)	41.5 (22.2)	0.16
Smoking, No. (%)			0.06			0.06
Current non-smoker	1366 (97.2)	250 (96.2)		1362 (97.1)	257 (97.0)	
Current smoker	35 (2.5)	9 (3.5)		35 (2.5)	5.8 (2.8)	
Unknown	5 (0.3)	1 (0.3)		5 (0.3)	0.6 (0.2)	
Year of cohort entry, No. (%)			0.84			0.11
2012	25 (1.8)	22 (8.5)		45 (3.2)	7 (2.7)	
2013	60 (4.3)	46 (17.7)		89 (6.4)	17 (6.6)	
2014	91 (6.5)	31 (11.9)		101 (7.3)	21 (8.0)	
2015	114 (8.1)	37 (14.2)		127 (9.1)	21 (8.0)	
2016	196 (13.9)	34 (13.1)		189 (13.5)	35 (13.3)	
2017	221 (15.7)	29 (11.2)		205 (14.7)	41 (15.5)	
2018	208 (14.8)	30 (11.5)		205 (14.7)	45 (17.2)	
2019	183 (13.0)	19 (7.3)		169 (12.1)	27 (10.3)	
2020	195 (13.9)	9 (3.5)		170 (12.1)	30 (11.7)	
2021	113 (8.0)	3 (1.2)		97 (6.9)	18 (6.7)	
Comorbidities, No. (%)						
CHA_2DS_2-VASc score, mean (SD)	3.5 (1.6)	3.4 (1.7)	0.08	3.6 (1.6)	3.6 (1.6)	0.01
HAS-BLED score, mean (SD)	2.5 (1.3)	2.4 (1.4)	0.04	2.5 (1.3)	2.5 (1.3)	0.01
Quan-Charlson Cormobidity Index, mean (SD)	1.5 (1.9)	1.9 (2.0)	0.23	1.5 (1.9)	1.5 (1.8)	0.04
Ischemic stroke	320 (22.8)	47 (18.1)	0.12	307 (21.9)	50 (19.0)	0.07
Transient ischemic attack	21 (1.5)	5 (1.9)	0.03	23 (1.7)	1.8 (0.7)	0.09
Intracranial hemorrhage	108 (7.7)	8 (3.1)	0.21	96 (6.9)	13 (5.2)	0.07
Gastrointestinal hemorrhage	49 (3.5)	13 (5.0)	0.08	63 (4.5)	7.8 (3.0)	0.08
Other site bleeding†	55 (3.9)	15 (5.8)	0.09	56 (4.0)	19 (7.2)	0.14
Cancer	198 (14.1)	26 (10.0)	0.13	186 (13.3)	27 (10.3)	0.09
Congestive heart failure	344 (24.5)	105 (40.4)	0.35	383 (27.3)	70 (26.7)	0.01
Myocardial infraction	37 (2.6)	11 (4.2)	0.09	41 (2.9)	6 (2.3)	0.04
Peripheral vascular disease	23(1.6)	10 (3.9)	0.14	28 (2.0)	3 (1.2)	0.06
Chronic obstructive pulmonary disease	129 (9.2)	19 (7.3)	0.07	123 (8.8)	19 (7.4)	0.05
Diabetes mellitus	262 (18.6)	41 (15.8)	0.08	257 (18.4)	63 (23.9)	0.14
Hypertension	713 (50.7)	130 (50.0)	0.01	713 (50.9)	121 (46.0)	0.10
Dyslipidemia	223 (15.9)	32 (12.3)	0.10	210 (15.0)	47 (17.8)	0.07
Chronic liver disease	73 (5.2)	10 (3.9)	0.06	68 (4.9)	5 (2.0)	0.16
Chronic renal disease	73 (5.2)	35 (13.5)	0.29	98 (7.0)	24 (9.2)	0.08
End-stage renal disease	39 (2.8)	41 (15.8)	0.46	71 (5.1)	10 (4.1)	0.05
Prior antiplatelets use	618 (44.0)	113 (43.5)	0.01	628 (44.8)	127 (48.2)	0.07

ASD: Absolute standardized difference

†Other site bleeding consist of hematuria, hemopericardium, hemothorax, hemoperitoneum, respiratory bleeding, retinal hemorrhage, vitreous hemorrhage, conjunctival hemorrhage, etc.

Discussion

The management of AF patients in 2012 has been adapted to incorporate recent evidence and guideline recommendations. Over 80% of eligible patients receive oral anticoagulant therapy, primarily with VKAs or NOACs [22]. In this retrospective cohort study, we observed that NOAC and warfarin have become more and less commonly used, respectively, in recent years among patients with AF; a similar trend has

Table 1-2 Baseline characteristics of the non-low-weight group before and after inverse probability of treatment weighting (IPTW)

Variables	Before weighting		ASD	After weighting		ASD
	DOACs (*N* = 2,978)	Warfarin (*N* = 400)		DOACs (*N* = 3,012)	Warfarin (*N* = 365)	
Demographics						
Age, mean (SD), yr	72.4 (12.4)	68.1 (12.9)	0.33	71.7 (12.9)	69.5 (11.6)	0.18
Female sex, No. (%)	710 (23.8)	75 (18.8)	0.12	691 (22.9)	89 (24.4)	0.03
Weight, mean (SD), kg	72.6 (9.1)	72.8 (9.1)	0.03	72.7 (9.2)	72.8 (9.2)	0.01
BMI, mean (SD), kg/m^2	26.5 (3.3)	26.2 (3.3)	0.09	26.4 (3.3)	26.6 (3.3)	0.05
Estimated GFR, mean (SD), mL/min	65.8 (25.3)	61.6 (33.2)	0.14	64.7 (26.1)	70.9 (34.0)	0.20
Smoking, No. (%)			0.14			0.16
Current non-smoker	2806 (94.2)	372 (94.8)		2839 (94.2)	339 (92.9)	
Current smoker	161 (5.4)	19 (4.8)		162 (5.4)	24.6 (6.8)	
Unknown	11 (0.4)	2 (0.4)		11 (0.4)	1.4 (0.3)	
Year of cohort entry, No. (%)			0.77			0.24
2012	55 (1.9)	51 (12.8)		95 (3.2)	12 (3.6)	
2013	185 (6.2)	69 (17.3)		222 (7.4)	31 (8.5)	
2014	184 (6.2)	48 (12.0)		252 (8.4)	33 (9.0)	
2015	283 (9.5)	53 (13.3)		291 (9.7)	36 (9.8)	
2016	372 (12.5)	39 (9.8)		361 (12.0)	56 (15.2)	
2017	398 (13.4)	35 (8.8)		384 (12.8)	63 (17.3)	
2018	524 (17.6)	46 (11.5)		498 (16.5)	50 (13.7)	
2019	383 (12.9)	28 (7.0)		359 (11.8)	41 (11.2)	
2020	352 (11.8)	21 (5.3)		328 (10.8)	28 (7.7)	
2021	242 (8.1)	10 (2.5)		222 (7.4)	15 (4.0)	
Comorbidities, No. (%)						
CHA_2DS_2-VASc score, mean (SD)	2.7 (1.6)	2.6 (1.8)	0.06	2.7 (1.6)	2.5 (1.5)	0.09
HAS-BLED score, mean (SD)	2.3 (1.3)	2.3 (1.3)	0.01	2.3 (1.3)	2.2 (1.1)	0.08
Quan-Charlson Cormobidity Index, mean (SD)	1.2 (1.7)	1.5 (1.7)	0.20	1.2 (1.8)	1.2 (1.6)	0.04
Ischemic stroke	461 (15.5)	62 (15.5)	0.001	461 (15.3)	42 (11.6)	0.11
Transient ischemic attack	40 (1.3)	6 (1.5)	0.01	41 (1.4)	3.7 (1.0)	0.03
Intracranial hemorrhage	131 (4.4)	5 (1.3)	0.19	118 (3.9)	11 (3.0)	0.05
Gastrointestinal hemorrhage	74 (2.5)	15 (3.8)	0.07	124 (4.1)	14 (3.7)	0.02
Other site bleeding†	92 (3.1)	15 (3.8)	0.04	94 (3.1)	12 (3.3)	0.01
Cancer	348 (11.7)	34 (8.5)	0.11	336 (11.2)	42 (11.6)	0.01
Congestive heart failure	513 (17.2)	111 (27.8)	0.25	595 (19.8)	73 (20.1)	0.01
Myocardial infraction	61 (2.1)	19 (4.8)	0.15	69 (2.3)	10 (2.8)	0.03
Peripheral vascular disease	60 (2.0)	22 (5.5)	0.18	83 (2.8)	10.5 (2.9)	0.01
Chronic obstructive pulmonary disease	234 (7.9)	41 (10.3)	0.08	239 (8.0)	24 (6.6)	0.05
Diabetes mellitus	615 (20.7)	97 (24.3)	0.09	630 (20.9)	75 (20.6)	0.01
Hypertension	1638 (55.0)	229 (57.3)	0.05	1687 (56.0)	199 (54.6)	0.03
Dyslipidemia	631 (21.2)	77 (19.3)	0.05	626 (20.8)	70 (19.3)	0.04
Chronic liver disease	133 (4.5)	20 (5.0)	0.03	134 (4.5)	17 (4.8)	0.02
Chronic renal disease	144 (4.8)	55 (13.8)	0.31	214 (7.1)	20 (5.7)	0.06
End-stage renal disease	87 (2.9)	57 (14.3)	0.41	165 (5.5)	17 (4.9)	0.03
Prior antiplatelets use	1401 (47.0)	213 (53.3)	0.12	1430 (47.5)	170 (46.6)	0.02

ASD: Absolute standardized difference

†Other site bleeding consist of hematuria, hemopericardium, hemothorax, hemoperitoneum, respiratory bleeding, retinal hemorrhage, vitreous hemorrhage, conjunctival hemorrhage, etc.

Table 2 The incidence rates and aHRs of outcomes during their follow-up time after applying IPTW

Outcome	DOACS group		Warfarin group		aHR [b] (95% CI)
	Events	Incidence [a] (95% CI)	Events	Incidence [a] (95% CI)	
Low-weight group					
IS/SE	45	1.46 (1.09,1.95)	7	1.99 (0.95,4.18)	1.32 (0.39–4.44)
Major bleeding	120	4.02 (3.36,4.80)	19	5.53 (3.53,8.67)	1.35 (0.71–2.56)
Any ischemia	102	3.41 (2.81,4.14)	19	5.69 (3.63,8.93)	1.08 (0.54–2.19)
Any bleeding	735	38.73 (36.03,41.63)	157	69.55 (59.48,81.33)	0.61 (0.51–0.73)
Non-low-weight group					
IS/SE	87	1.19 (0.97,1.47)	16	2.74 (1.68,4.46)	0.65 (0.33–1.31)
Major bleeding	254	3.61 (3.19,4.08)	30	5.43 (3.80,7.77)	0.74 (0.49–1.14)
Any ischemia	296	4.29 (3.83,4.81)	36	6.43 (4.64,8.92)	1.20 (0.74–1.95)
Any bleeding	1564	37.50 (35.69,39.41)	199	58.65 (51.04,67.39)	0.87 (0.74–1.02)

DOACs, direct oral anticoagulants; IS, ischemic stroke; SE, systemic embolism; aHR, adjusted hazard ratio; CI, confidence interval.

[a] Incidence, per 100 person-years.

b Weighted with inverse probability of treatment weighting and adjusted for age, renal function, other site bleeding history, year of cohort entry, diabetes mellitus, liver disease in low-weight group; adjusted for age, renal function, year of cohort entry, smoking status in non-low-weight group.

been observed previously [23–25]. Moreover, the main findings of the present study were as follows:

(1) Among low-weight (≤60-kg) patients with AF, compared with warfarin use, NOAC use was associated with lower risks of any bleeding event; however, NOAC and warfarin use demonstrated comparable risks of IS/SE, any ischemic event, and major bleeding.
(2) All four NOAC types demonstrated similar trends in terms of IS/SE, any ischemic and bleeding event, and major bleeding risks.
(3) When BMI is used as the grouping criterion, a significant reduction was noted exclusively in the risk of any bleeding event in our underweight and normal-weight patients.

The average age of our patient population was 73 years. Moreover, compared with the non–low-weight group, the low-weight group was older, had more women, and demonstrated poorer renal function (all $p < 0.001$). Consistent with previous findings [13, 25], our low-weight group also demonstrated a higher incidence of previous IS, ICH, gastrointestinal bleeding, and bleeding in other sites.

Furthermore, compared with warfarin users, NOAC users in both the body-weight–based groups had a higher mean age before IPTW (78.3 vs. 72.6 years in the low-weight group; 72.4 vs. 68.1 years in the non–low-weight group). This contradicts the age-related trend proposed by the SAMe-TT2R$_2$ score, suggesting a potential improvement in the safety profile of NOACs among older adults in recent years [26, 27]. Warfarin has a considerable number of extensive food–drug interactions; therefore, its use warrants strict medication adherence to attain the target therapeutic standard (TTR ≥ 70%) [28].

Older patients often experience polypharmacy and are therefore prone to be affected by potential drug interactions. Clinicians may prefer prescribing NOACs over warfarin to these patients because NOACs have fewer drug–drug interactions and monitoring requirements.

Clinical outcomes

In this study, we noted a 39% reduction in the risk of any bleeding event in low-weight NOAC users compared with low-weight warfarin users [aHR (95% CI) = 0.61 (0.51–0.73)]. Nevertheless, no significant differences were observed in the risks of IS/SE, any ischemic event, or major bleeding—which differs from previous findings.

A Korean study, which used actual body weight as the defining criterion, explored and compared the effectiveness and safety of NOAC and warfarin in patients with AF [14]; NOAC users weighing ≤ 60 kg were noted to demonstrate significantly lower stroke, major bleeding, ICH, and all-cause mortality risks than their warfarin-using counterparts; this advantage extended to NOAC users weighing ≤ 50 kg. By contrast, we noted a substantial reduction only in the risk of any bleeding event in low-weight NOAC users with AF. This discrepancy may be due to the inclusion of patients with an IS, ICH, or gastrointestinal bleeding history in our study; this increased the relevance of our results in terms of real-world clinical scenarios. We also evaluated warfarin effectiveness based on the average TTR, included more edoxaban users, and ensured a balanced representation of all four NOACs. As such, we were able to assess the effectiveness and safety of the NOACs in low-weight patients comprehensively and then compare them with those of warfarin, consequently addressing the knowledge gaps in previous studies.

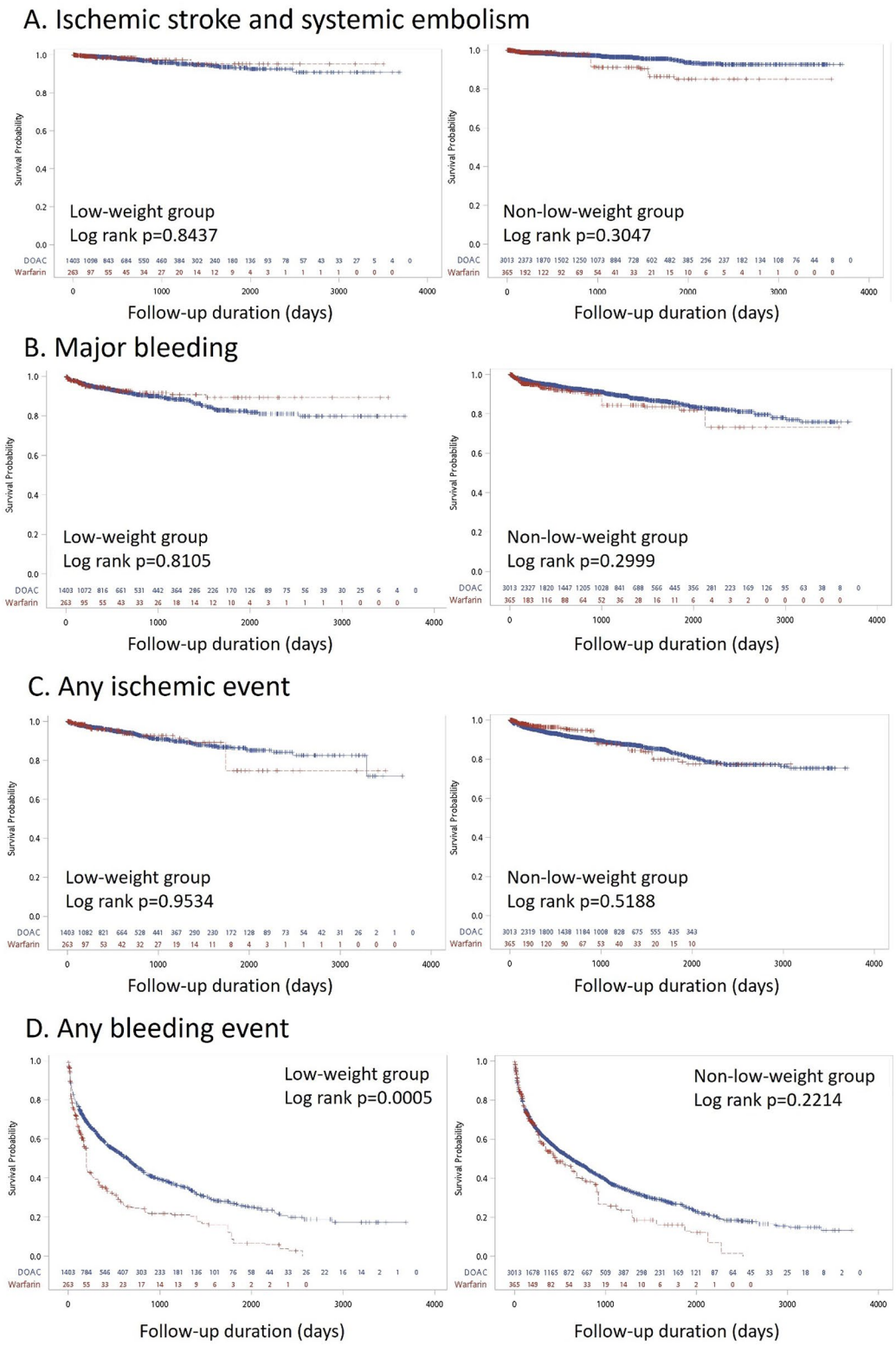


Fig. 1 Kaplan-Meier survival curve of outcomes after utilizing IPTW

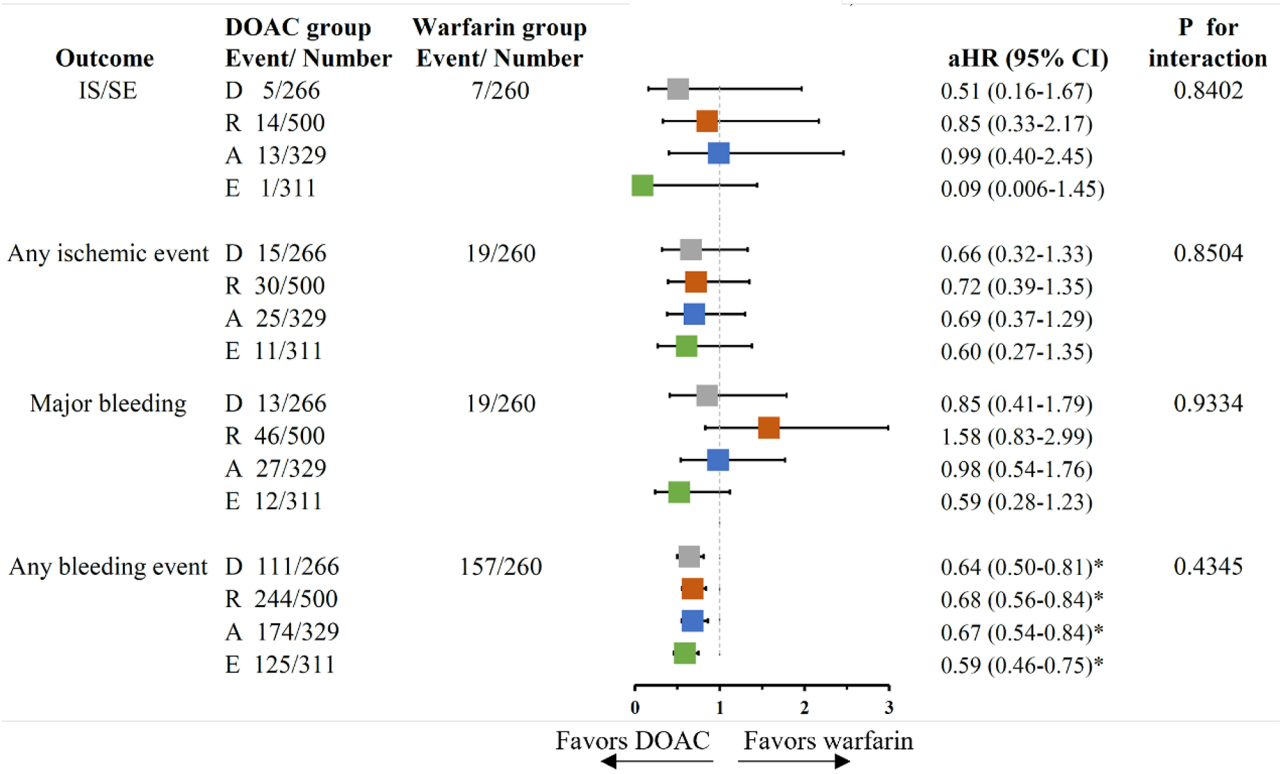


Fig. 2 Individual DOAC analysis in the low-weight group

Individual NOAC analyses

Compared with warfarin, the NOACs of dabigatran, rivaroxaban, apixaban, and edoxaban were associated with a significantly lower risk of any bleeding event [aHRs (95% CIs) = 0.64 (0.50–0.81), 0.68 (0.56–0.84), 0.67 (0.54–0.84), and 0.59 (0.46–0.75), respectively]. Moreover, relative to rivaroxaban or apixaban, dabigatran and edoxaban were associated with a lower risk of IS/SE [aHRs (95% CIs) = 0.51 (0.16–1.67) and 0.09 (0.01–1.45), respectively] and major bleeding [aHRs (95% CIs) = 0.85 (0.41–1.79) and 0.59 (0.28–1.23), respectively]; however, these differences were nonsignificant. Therefore, in low-weight patients with AF, dabigatran and edoxaban might be more effective and safer NOACs than warfarin. However, further research confirming this finding is warranted.

In the low-weight group, the NOAC types were associated with varying differences in the risks of major bleeding compared with warfarin. The variation may be attributable to two factors: (i) The incidence rate of any bleeding event was higher in the low-weight group than in the non–low-weight group. (ii) After IPTW, ICH and gastrointestinal bleeding prevalence was higher in low-weight NOAC users than in low-weight warfarin users (6.9% vs. 5.2% for ICH; 4.5% vs. 3.0% for gastrointestinal bleeding).

A Taiwanese retrospective study suggested that lower-BMI dabigatran users with nonvalvular AF patients demonstrate a higher major bleeding risk [29]. Furthermore, the use of dose adjustment criteria resulted in a 50% dosage reduction for apixaban and edoxaban; by contrast, no weight-adjusted dosage changes were made for dabigatran and rivaroxaban. Even at lower dosages (around 25% reduction from the standard dosage), dabigatran (e.g., 110 mg, twice a day) and rivaroxaban (e.g., 15 mg, once a day) led to high drug exposure, potentially increasing bleeding risk. These results emphasize the need for careful consideration of NOAC selection in low-weight populations. In this study, the dosage of NOACs mostly conforms to the European Heart Rhythm Association (EHRA) guidelines. Based on the results of the J-ROCKET AF trial, the standard clinical dosage of rivaroxaban in Taiwan is currently 15/20 mg QD, with an adjusted dosage of 10 mg QD for patients with CrCl 15–30 mL/min. The dosages of dabigatran, apixaban, and edoxaban conform to the standard dosages outlined in the EHRA guidelines. Considering the comparability between the warfarin and DOAC groups, and the clinical experience of using DOACs in patients with renal failure [30], this study did not exclude patients with renal failure and included those diagnosed with end-stage renal disease ($n = 80$ in the low-weight group, $n = 144$ in the non-low weight group).

Most studies have used pooled data for all four NOACs to compare the differences in their effectiveness and safety with respect to body weight and OAC use. However, this approach may have led to potential inconsistencies among the individual NOAC types being overlooked because of the differences in their pharmacokinetics and renal elimination rates. GARFIELD-AF researchers are currently developing a risk prediction tool, along with innovative observational studies and artificial intelligence methodologies. Therefore, future studies should focus on the variations in effectiveness and safety among individual NOAC types in low-weight individuals.

Sensitivity and subgroup analyses

In Asian countries, NOACs are commonly prescribed at lower doses [31–34]. In this study, we used age, weight, and renal function as criteria for adjusting the dosage of NOACs. In the overall, low-weight, and non–low-weight groups, 62.1%, 63.2%, and 61.6% of the patients received on-label dosing, respectively; approximately 32%, 25.2%, and 35.2% of the patients received off-label underdosing, respectively; and 5.3%, 11.6%, and 3.2% of the patients received off-label overdosing, respectively. These proportions are consistent with the results of a previous Asian study: 60.4% for on-label dosing and 31.2% for underdosing [32]. Our low-weight group also demonstrated a lower proportion of underdosing than the non–low-weight group, suggesting that fewer low-weight patients than non–low-weight patients are prescribed NOACs at lower doses.

Among all NOAC types, rivaroxaban (43.3%) was most frequently off-label underdosed, followed by apixaban (21.7%), dabigatran (18%), and edoxaban (17%). By contrast, dabigatran (42.5%) was most frequently off-label overdosed, followed by edoxaban (27.4%), apixaban (16.2%), and rivaroxaban (13.9%). However, our cohort of low-weight patients with AF was small and differed substantially among themselves; this hindered any subgroup analysis of different NOAC dosages. Therefore, the effectiveness and safety of off-label underdosed NOACs in low-weight patients with AF remains unclear.

Finally, our subgroup analyses demonstrate that weight thresholds, sex, and age differences did not affect the assessed outcomes.

Study strengths and limitations

This study has several strengths. First, we obtained detailed laboratory data of our patients, such as weight, height, and CrCl, to investigate the differences in the effectiveness and safety of NOAC and warfarin use across weight groups. Second, we presented more real-world data related to dabigatran and edoxaban use in underweight patients; we also extracted comprehensive data regarding their embolism and bleeding history. Edoxaban is a recently introduced NOAC, and dabigatran is associated with a high gastrointestinal bleeding risk; therefore, real-world data on edoxaban and dabigatran use in low-weight patients with AF risk has been limited thus far. Third, we performed NOAC-specific analyses to explore differences between the effects of using each NOAC and those of using warfarin. Fourth, In the ORBIT-AF study, nearly 30% of patients experienced an OAC interruption event within a median follow-up period of two years, mostly due to routine discontinuation before surgery. In our study, only 10% of patients experienced an OAC interruption event, for similar reasons. Finally, we performed several sensitivity and subgroup analyses to assess various hypotheses, and our findings remained generally consistent with the main result.

This study also has some limitations. First, different NOACs were introduced at various timepoints over 2011–2022, and over time, this may have led to selection bias. Nevertheless, to resolve this problem, we included the cohort entry year as a variable in the IPTW model. Second, to monitor the study outcomes continually, we analyzed the prescribed anticoagulants and dosages as exposure on the cohort entry date and ignored variations in types and dosages during the follow-up period. Third, all data used here were extracted from a single tertiary hospital; this resulted in a limited sample size and fewer outcome events, particularly in the case of warfarin users. Due to database limitations, it is not possible to directly obtain information on the patients' ethnicity. However, this study uses a database from a single tertiary hospital, where clinical experience has shown that the majority of the hospital's patients are Asian. This limitation may affect the comprehensiveness of the baseline characteristics and restrict our results' generalizability to other ethnicities. Fourth, the TTR value after IPTW calculation was only 41.2%, which did not meet the international benchmark (TTR ≥ 70%). Additionally, due to the limitations of a retrospective study, it was not possible to obtain regular monitoring TTR values for warfarin users. The study also included a relatively small number of warfarin users, meaning that any variations in factors could significantly impact the study results. In the RE-LY, ROCKET AF, and ENGAGE AF-TIMI phase III clinical trials, the average TTR for the Asian population was 54.5%, 47.1%, and 67.1%, respectively, indicating the instability of TTR control with warfarin in the Asian population. Furthermore, in a retrospective study conducted in Japan, the average TTR was below 50%, highlighting the difficulty of maintaining proper TTR control with warfarin in clinical practice [3]. This makes it challenging to determine if the appropriate therapeutic concentration of warfarin is achieved, and

therefore, it is impossible to conclude whether this study's results underestimate or overestimate the efficacy of warfarin. Finally, because this was a retrospective observational study, we could not collect data related to patient medication adherence; as such, we could not eliminate potential residual confounders from our analyses.

Conclusion

In low-weight patients with AF, NOACs reduced the risk of any bleeding more significantly than warfarin. The individual analyses of NOACs and warfarin indicate that dabigatran and edoxaban appear to have lower rates of IS/SE and major bleeding. However, these differences did not reach statistical significance and require further research to confirm.

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Declarations

Declarations of conflicts of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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