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Off-label reduced-dose apixaban does not reduce hemorrhagic risk in Taiwanese patients with nonvalvular atrial fibrillation

A retrospective, observational study

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Abstract

East Asians are reportedly at high risk of anticoagulant-related bleeding; therefore, some physicians prefer to prescribe low-dose direct oral anticoagulants (DOACs). Little is known about the therapeutic effectiveness and safety of off-label reduced-dose apixaban in East Asians with nonvalvular atrial fibrillation (AF). We aimed to investigate the effectiveness and safety of off-label reduced-dose apixaban in Taiwanese patients with nonvalvular AF.

This retrospective cohort study enrolled 1073 patients with nonvalvular AF who took apixaban between July 2014 and October 2018 from 4 medical centers in southern Taiwan. The primary outcomes included thromboembolic events (stroke/transient ischemic attack or systemic embolism), major bleeding, and all-cause mortality.

Among all patients, 826 (77%) patients were classified as the "per-label adequate-dose" treatment group (i.e., consistent with the Food and Drug Administration label recommendations) while 247 (23%) patients were the "off-label reduced-dose" treatment group. The mean follow-up period was 17.5 ± 13 months. The "off-label reduced-dose" group did not have a lower major bleeding rate than the "per-label adequate-dose" group (4.8% vs 3.8%, adjusted hazard ratio [HR] 1.20, 95% confidence interval [CI] 0.69–2.09), but had a nonsignificantly higher incidence of thromboembolic events (4.23% vs 3.05%, adjusted HR: 1.29, 95% CI: 0.71–2.34).

An off-label reduced-dose apixaban treatment strategy may not provide incremental benefits or safety for Taiwanese patients with nonvalvular AF.

Abbreviations: AF = atrial fibrillation, CKD = chronic kidney disease, CRNMB = clinically relevant non-major bleeding, DOAC = direct oral anticoagulant, eGFR = estimated glomerular filtration rate, ICH = intracranial hemorrhage, ISTH = International Society on thrombosis and hemostasis, SE = systemic embolism, TIA = transient ischemic attack, VKA = vitamin K antagonist.

Keywords: direct oral anticoagulant, nonvalvular atrial fibrillation, off-label reduced-dose apixaban, stroke

1. Introduction

Atrial fibrillation (AF) is a major cause of morbidity and mortality in adults because it carries a 4- to 5-fold increased risk of stroke.[1–4] Oral anticoagulant therapy is recommended in all AF patients with additional risk factors in order to reduce the risk of stroke or systemic embolism (SE).[3,4] However, compared to Caucasian populations, East Asian patients taking

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vitamin K antagonists (VKAs) have been shown to be vulnerable to bleeding, including intracranial hemorrhage (ICH).[1,5–9]

Direct oral anticoagulants (DOACs) represent a major advance in stroke prevention in patients with AF. Compared with VKAs, DOACs demonstrate equivalent efficacy of stroke and SE prevention but are associated with fewer major or minor bleeding events.[10–14] Nevertheless, although each DOAC has its own dose reduction criteria, many East Asian physicians still prefer to prescribe "reduced-dose" DOACs, which do not comply with dose reduction criteria for stroke prevention in AF patients.[14–16] This practice may be associated with physicians' fear of bleeding based on their previous VKA experience. However, it is shown that inappropriate dose reduction could decrease the efficacy of stroke prevention but it may not reduce major bleeding events.[14–16]

Although nowadays, there are several large population-based database cohort studies investigating the effectiveness and safety of DOACs in Asians,[17–21] it is worth noting that these retrospective nationwide database studies may have many weaknesses and limitations,[22] such as unverified and incorrect diagnosis and/or outcome coding, unmeasured confounding variables, etc. In addition, some studies using the same nationwide data have the opposite results.[19,21] Therefore, to avoid the major limitations of the nationwide database studies, we conducted this retrospective cohort study to carefully review all medical records to investigate the safety and effectiveness of off-label reduced-dose apixaban administration in nonvalvular AF patients in Taiwan. In this study, we focused in particular on clinical outcomes associated with stroke and systemic emboli prevention and bleeding risk.

2. Methods

2.1. Study design and participants

In this multicenter, retrospective cohort study, we enrolled consecutive eligible nonvalvular AF patients taking apixaban at 4 hospitals in southern Taiwan, including National Cheng Kung University Hospital, Tainan Municipal Hospital, Kaohsiung Medical University Chung-Ho Memorial Hospital, and Chi-Mei Medical Center, between July 2014 and October 2018. This study adhered to the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of the National Cheng Kung University Hospital (IRB number: B-ER-108–096). Because this was a retrospective study and all data were fully anonymized, the Human Research and Ethics Committee of National Cheng Kung University Hospital waived the requirement for informed consent.

The included patients have to meet all the following inclusion criteria:

1. age $\geq$ 20 years,
2. diagnosis of nonvalvular AF,
3. oral anticoagulation with apixaban, and
4. follow-up for at least 3 months or longer after the first prescription of apixaban.

Those patients would be excluded if one of the following exclusion criteria was met:

1. chronic kidney disease (CKD), stage 5 (estimated glomerular filtration rate [eGFR] $<$ 15 mL/min/1.73 m^2), with or without on dialysis,
2. metallic heart valve implantation,
3. rheumatic mitral stenosis,
4. moderate or severe mitral stenosis,
5. severe hepatic disease,
6. high risk for thrombophilia, and
7. severe thrombocytopenia (platelet count $<$ 20,000/μL).

Those eligible patients were categorized into 2 groups:

1. The per-label adequate-dose group (defined as apixaban 5 mg twice daily or 2.5 mg twice daily per the Food and Drug Administration label recommendations: in patients having at least 2 of the following criteria: age $\geq$ 80 years, body weight $\leq$ 60 kg, or serum creatinine value $\geq$ 1.5 mg/dL) and
2. The off-label reduced-dose group (defined as apixaban 2.5 mg twice daily, but not consistent with Food and Drug Administration label recommendations).

All clinical information on co-morbidities, medical history, laboratory test results, current medication, and the CHA2DS2-VASc and HAS-BLED scores was obtained by careful review of the medical records of each patient. The clinical endpoint events were collected by medical chart reviews or phone calls to medical records.

2.2. Clinical outcomes

2.2.1. Primary and secondary effectiveness endpoints. The primary effectiveness endpoint was defined as the occurrence of a composite outcome of stroke, including ischemic or hemorrhagic, transient ischemic attack (TIA), or SE. The secondary endpoints were the occurrence of all-cause mortality and each component of the primary endpoints.

2.2.2. Primary safety endpoint. According to the criteria of the International Society on thrombosis and hemostasis (ISTH),[23] the primary safety endpoints were major bleeding, defined as:

1. clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red blood cells,
2. the occurrence of bleeding at a critical site, or
3. resulting in death.

The occurrence of clinically relevant non-major bleeding (CRNMB) and minor bleeding events were also recorded and compared between these 2 groups. CRNMB included clinically overt bleeding that did not meet the criteria for major bleeding but did lead to hospitalization, physician-guided medical or surgical treatment, or a change in antithrombotic therapy, as described previously.[23]

2.2.3. Outcome measures for high risk bleeding groups. Because elderly nonvalvular AF patients, the patients with moderate to severe renal impairment (defined as CKD, stage 3 and 4) or previous stroke are more prone to embolism and major bleeding,[24–28] we did subgroup analyses to investigate the effectiveness of treatment for stroke/SE prevention and the bleeding risk associated with off-label reduced-dose apixaban for these high-risk patients.

2.3. Statistical analyses

All the variables were presented as the mean $\pm$ standard deviation. The dichotomous data were presented as numbers (percentages). We compared demographic and clinical baseline

Table 1

Baseline demographic and clinical characteristics of overall AF population.

	Per-label adequate dose N = 826 (77%)	Off-label reduced dose N = 247 (23%)	*P*
Age (yr)	75.1 ± 10.5	76.5 ± 8.3	.07
Male (%)	53%	52%	.67
Body weight (kg)	62.4 ± 12.4	63.3 ± 11.7	.31
Age ≧75yr	457 (55.3%)	165 (66.8%)	.001
History of CAD	193 (23.4%)	60 (24.3%)	.76
History of CHF	236 (28.6%)	62 (25.1%)	.29
History of diabetes	258 (31.2%)	95 (38.5%)	.03
History of hypertension	607 (73.5%)	196 (79.4%)	.06
History of stroke/TIA	286 (34.6%)	98 (39.7%)	.15
History of liver cirrhosis	17 (2.1%)	9 (3.6%)	.16
Use of antiplatelet drug	56 (6.8%)	18 (7.3%)	.78
Creatinine clearance	68.2 ± 28.5	65.1 ± 26.1	.13
Renal impairment (eGFR <50 mL/min/1.73 m^2)	226 (27.4%)	69 (27.9%)	.86
CHA_2DS_2-VASc	4.1 ± 1.8	4.5 ± 1.6	.02
HAS-BLED score	2.3 ± 1.1	2.5 ± 1.1	.02

CAD = coronary artery disease, CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category, $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, CHF = congestive heart failure, eGFR = estimated glomerular filtration rate, HAS-BLED = hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, older adult (age ≥75 years), drugs and alcohol, TIA = transient ischemic attack.

characteristics among the patients of these 2 groups by using Pearson Chi-Squared test/Fisher exact test and Student *t* test for categorical variables and continuous variables, respectively. If more than one endpoint occurred within the follow-up period, only the first event was considered for analysis. The Kaplan–Meier method was used with a log-rank test to compare survival rates between strata. Cumulative events of clinical outcomes were assessed using the Cox proportional hazards model. To control for confounding factors, we performed a multi-variate Cox regression model as following: univariate Cox regression analysis was performed to evaluate factors in relation to the primary effectiveness endpoint and the primary safety endpoint. Factors with $P < .1$ on univariate analysis were considered in the multivariate Cox regression analysis to estimate the adjusted hazard ratio (HR) with 95% confidence intervals (CI). Differences were considered statistically significant at a *P* value of $< .05$. All statistical analyses were performed using SPSS software (Version 24.0, SPSS Inc., Chicago, IL).

3. Results

A total of 1073 patients were included in this study; 826 (77%) patients (age 75.1 ± 10.5 years, male 53%) were classified into the per-label adequate-dose group and 247 (23%) patients (age 76.5 ± 8.3 years, male 52%) were classified into the off-label reduced-dose group. There was no significant difference in most baseline demographic and clinical characteristics between these 2 groups. Nevertheless, those patients taking off-label reduced-dose apixaban had a higher prevalence of diabetes mellitus, and higher CHA_2DS_2-VASc and HAS-BLED scores (Table 1).

3.1. Clinical outcomes

3.1.1. Primary and secondary effectiveness outcomes. The median follow-up duration was 15.1 months (interquartile range, 7.7–25.6). Compared with the per-label adequate-dose group, the off-label reduced-dose group had a higher risk of the primary effectiveness outcome of stroke/TIA or SE (per-label adequate-dose vs off-label reduced-dose: 3.05% vs 4.23%; HR: 1.45, 95% CI: 0.80–2.61; adjusted HR: 1.29, [after adjusting for age, diabetes mellitus, and CHA_2DS_2-VASc score], 95% CI: 0.71–2.34), the difference of the primary effectiveness endpoint did not reach statistical significance though (Table 2 and Fig. 1). Furthermore, for the secondary endpoints, including all-cause mortality (per-label adequate-dose vs off-label reduced-dose: 3.30% vs 2.46%; HR: 0.78, 95% CI: 0.39–1.57) and each component of the primary effectiveness outcomes, there was no significant difference, neither (Table 2).

3.1.2. Safety outcomes. Importantly, compared to the per-label adequate-dose group, the off-label reduced-dose group did not have a lower bleeding risk (Table 2 and Fig. 1). The risks of major bleeding (per-label adequate-dose vs off-label reduced-dose: 3.81% vs 4.76%; HR: 1.25, 95% CI: 0.72–2.16; adjusted HR:

Table 2

Effectiveness and safety outcomes of overall AF population.

	Per-label adequate dose N = 826 (77%)	Off-label reduced dose N = 247 (23%)	Crude HR (95% CI)	Adjusted HR* (95% CI)
Stroke/TIA or SE, n (%)	36 (3.05)	16 (4.23)	1.45 (0.80–2.61)	1.29 (0.71–2.34)
Ischemic stroke, n (%)	22 (1.86)	10 (2.64)	1.24 (0.58–2.66)	
Hemorrhagic stroke, n (%)	10 (0.85)	5 (1.32)	1.52 (0.52–4.47)	
All cause death, n (%)	39 (3.30)	10 (2.64)	0.78 (0.39–1.57)	
Stroke/TIA/SE and all cause death, n (%)	74 (6.27)	26 (6.87)	1.04 (0.66–1.63)	
Major bleeding, n (%)	45 (3.81)	18 (4.76)	1.25 (0.72–2.16)	1.20 (0.69–2.09)
Fatal bleeding, n (%)	9 (0.76)	1 (0.26)	0.33 (0.04–2.58)	
ICH, n (%)	10 (0.85)	4 (1.06)	1.20 (0.38–3.86)	
GI bleeding, n (%)	31 (2.62)	14 (3.70)	1.24 (0.65–2.35)	
Clinically relevant non-major bleeding, n (%)	81 (6.86)	28 (7.40)	0.96 (0.62–1.48)	
Minor bleeding, n (%)	109 (9.23)	34 (8.98)	0.84 (0.57–1.24)	
Net clinical outcome Stroke/TIA or SE or major bleeding, n (%)	71 (6.01)	30 (7.93)	1.20 (0.78–1.85)	
Stroke/TIA or SE or major bleeding or all cause death, n (%)	102 (8.64)	38 (10.04)	1.09 (0.75–1.59)	

GI bleeding = gastrointestinal bleeding, HR = hazard ratio, ICH = intracranial hemorrhage, TIA = transient ischemic attack, SE = systemic embolism.
* Adjusted for age, diabetes mellitus, CHA_2DS_2-VASc and HAS-BLED scores.

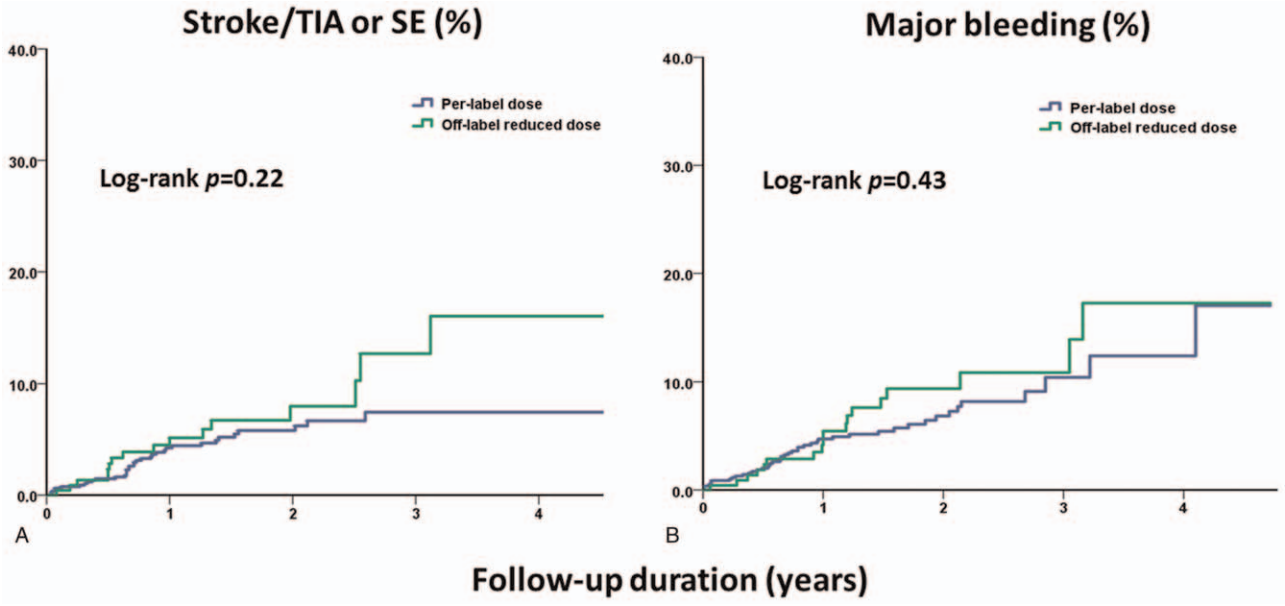

Figure 1. The cumulative incidence curves of stroke/transient ischemic attack (TIA) or systemic emboli (SE) and major bleeding for all atrial fibrillation (AF) patients. (A) Compared with the per-label dose group (blue line), the off-label reduced-dose group (green line) had a higher but nonsignificant risk of the composite outcome of stroke/TIA or SE. (B) The major bleeding rate was not lower in the off-label reduced-dose group.

1.20, [after adjusting for age, diabetes mellitus and HAS-BLED score], 95% CI: 0.69–2.09), CRNMB (per-label adequate-dose vs off-label reduced-dose: 6.86% vs 7.40%; HR: 0.96, 95% CI: 0.62–1.48), and minor bleeding (per-label adequate-dose vs off-label reduced-dose: 9.23% vs 8.98%; HR: 0.84, 95% CI: 0.57–1.24) were similar between these 2 groups (Table 2).

3.2. Effectiveness and safety outcomes of high risk bleeding groups (Fig. 2)

3.2.1. Elderly patients (age ≥ 80 years). There were 432 elderly patients (age ≥ 80 years) in this study. The majority (n = 344, 80% of the elderly patients) took per-label adequate-dose apixaban for stroke/SE prevention. There were no significant differences in the incidence of either major bleeding or CRNMB between the per-label adequate-dose apixaban group and the off-label reduced-dose apixaban group. However, those elderly patients taking off-label reduced-dose apixaban seemed to have more ischemic stroke events than those elderly patients taking per-label adequate-dose apixaban (per-label adequate-dose vs off-label reduced-dose: 1.32% vs 4.32%; HR: 3.29, 95% CI: 1.00–10.81; $P = .05$) (Fig. 2).

3.2.2. Patients with moderately to severely impaired renal function (eGFR < 50 mL/min/1.73m^2 and ≥ 15 mL/min/1.73 m^2). We included 295 patients with moderately to severely impaired renal function. Those CKD patients (stage 3 and 4) taking off-label reduced-dose apixaban (n = 69, 23%) had fewer major bleeding events than those in the per-label adequate-dose group (n = 226, 77%), mainly resulting from less major GI bleeding. However, owing to the limited number of CKD patients, the difference was not statistically significant. No significant difference was found between the per-label adequate-dose and off-label reduced-dose groups in endpoints for stroke/TIA or SE (Fig. 2).

3.2.3. Patients with previous stroke/TIA. We enrolled 384 patients with previous stroke or TIA. 286 patients (74%) took per-label adequate-dose apixaban and 98 (26%) took off-label reduced-dose apixaban. The prevalence of liver cirrhosis (per-label adequate-dose vs off-label reduced-dose: 2.1% vs 7.1%; $P = .017$) and HAS-BLED score (per-label adequate-dose vs off-label reduced-dose: 2.9 ± 1.0 vs 3.2 ± 1.0; $P = .007$) were significantly higher in the off-label reduced-dose group than in the per-label adequate-dose group. No significant difference was found in measures of stroke/TIA or SE prevention between these 2 groups (per-label adequate-dose vs off-label reduced-dose: 5.02% vs 6.05%; HR: 1.12, 95% CI: 0.53–2.4; $P = .76$). Owing to the limited numbers of hemorrhagic stroke events, the difference of hemorrhagic stroke between the off-label reduced-dose and the per-label adequate-dose groups did not reach the statistical significance (per-label adequate-dose vs off-label reduced-dose: 1.37% vs 0.61%; HR: 0.47, 95% CI: 0.06–3.89; $P = .48$) (Fig. 2). Furthermore, ICH occurred in 6 patients in the per-label adequate-dose group, but no ICH occurred in the off-label reduced-dose group.

4. Discussion

This study is the first to investigate the effectiveness of stroke/TIA or SE prevention and the bleeding risk associated with off-label reduced-dose apixaban, a prominent DOAC, in East Asian patients with nonvalvular AF. The results showed that, compared to those patients taking per-label adequate-dose apixaban, the patients treated with off-label reduced-dose apixaban had no reduced risk of major bleeding and CRNMB but tended to have more embolic events. Our results suggest that off-label reduced-dose apixaban may not reduce either major or minor bleeding risk but may increase embolic events in East Asians, even though these patients may be prone to higher bleeding risk.

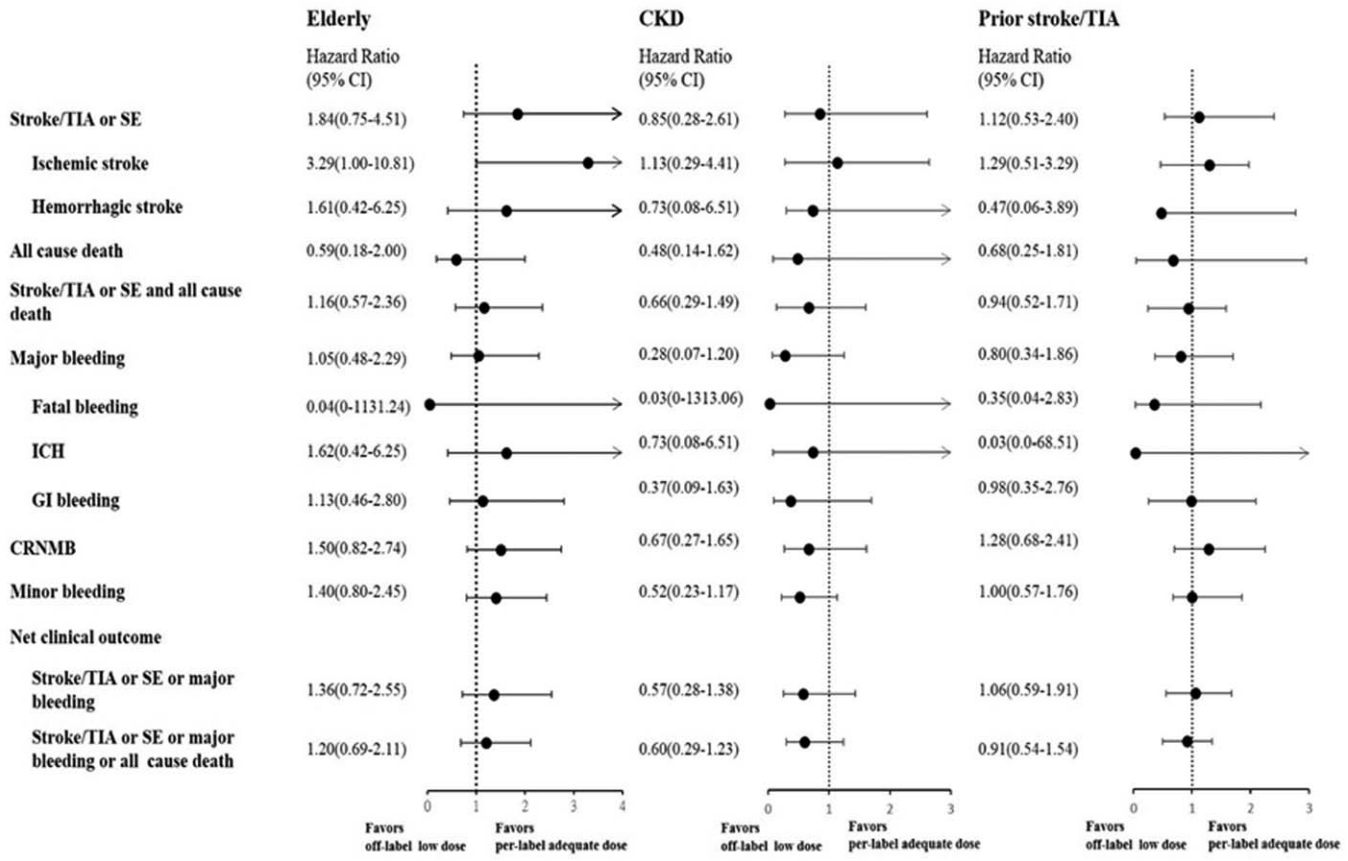

Figure 2. Efficacy and safety outcomes of high-risk bleeding groups. Compared to the per-label dose group, these high bleeding risk patients taking off-label reduced dose apixaban did not have better efficacy outcomes or lower bleeding rates. The net clinical outcome was not better in the off-label reduced dose group. TIA = transient ischemic attack, SE = systemic embolism, ICH = intracranial hemorrhage, GI bleeding = gastrointestinal bleeding.

Although the prescription of DOACs has changed the landscape for stroke/SE prevention in nonvalvular AF patients, in real-world practice, the prescription of off-label reduced-dose DOACs is common, especially in East Asian countries. This may be because East Asians with nonvalvular AF have a higher major bleeding risk, especially ICH, than Caucasians.[11,12] Therefore, East Asian physicians tend to prescribe "reduced-dose" DOACs for stroke/SE prevention. Nevertheless, it is still uncertain whether reduced-dose DOACs for East Asian patients will decrease the effectiveness of stroke/SE prevention or provide any safety benefits.[15,29–33] Li et al[31] showed that, compared with warfarin, apixaban 2.5 mg twice daily was associated with a lower risk of stroke/SE and major bleeding after 1:1 propensity score matching. Additionally, data from the Taiwan National Health Insurance Database, which represents 99% of the Taiwanese population, showed that lower doses of DOACs, including apixaban, were also associated with a reduced risk of ischemic stroke, SE, death, and intracranial bleeding, compared with warfarin.[17] In contrast, a Korean cohort study suggested that the off-label use of reduced DOAC doses in a subgroup of younger patients (< 75 years of age) without CKD had no beneficial effects over warfarin.[20] Nevertheless, we have to recognize that because the Taiwanese physicians used to prescribe lower doses of warfarin and the time in therapeutic range was low, we could not obtain very informative results when we used National Health Insurance Database data to compare the effectiveness and safety outcomes between the following 2 groups: standard dose DOACs vs warfarin and reduced dose DOACs vs warfarin.

We showed that approximately 23% of patients with nonvalvular AF from southern Taiwan took off-label reduced-dose apixaban. The prevalence of off-label reduced-dose DOAC prescriptions was not extremely high and was even lower than the reported data.[34,35] Notably, in this study, the reported risk of stroke/TIA or SE and major bleeding per year for apixaban in the per-label adequate-dose treatment group were 3.05% and 3.81%, respectively, which were higher than those in the East Asian subgroup analysis of the ARISTOTLE trial,[36] (2.52% and 2.02% per year, respectively). In a Japanese postmarketing surveillance study, the STANDARD study,[37] the incidence rate of ischemic stroke/TIA or SE and major hemorrhage was 1.00% and 2.36% per year, respectively, in the overall nonvalvular AF patients treated with apixaban. These results may imply a higher risk of emboli as well as bleeding in the cohort of the present study, which is compatible with the higher CHA_2DS_2-VASc and HAS-BLED scores of our patients. Notwithstanding, in most of the previously published studies, these enrolled Asian patients were not categorized into 2 groups based on whether they took per-label reduced-dose apixaban or off-label reduced-dose apixaban. Therefore, it would be difficult to determine whether the "reduced-dose" DOAC strategy is a good option for Asian patients.

A Real-Life study,[38] an Israeli health care database, showed the underdosing apixaban group was not associated with increased risk of ischemic stroke/SE compared with the standard dose apixaban group after controlling for confounders. However, the risk of major bleeding was still higher in the underdosing apixaban group. Furthermore, according to the results of a subanalysis of the STANDARD study,[39] the incidences of thromboembolic and major hemorrhagic events were numerically highest in the recommended reduced-dose group (1.69% and 3.30% per year) followed by the non-recommended reduced-dose group (0.95% and 2.50% per year) and the standard-dose group (0.70% and 2.00% per year). In a multivariate analysis, apixaban dose was not independently associated with these outcome events.[39] On the contrary, a recently published Korean nationwide claims database[40] had the opposite results, showing higher risks of ischemic stroke, all-cause death, and composite clinical outcomes in the off-label underdosed apixaban group than the on-label standard dose group, but both had comparable risks of major bleeding. These trials all used the standard-dose apixaban group as the reference but yielded different and diverse results. In the present study, differently, we compared the clinical outcomes between per-label adequate-dose and off-label reduced-dose apixaban groups and tried to figure out whether Asian patients could get benefits from the "off-label reduced-dose" DOAC strategy.

There are several major limitations of these nationwide database studies, including misclassification bias, that is, coding errors and intentionally "upcoding" of the underlying comorbidities, diagnosis and outcomes, and significant but unmeasured variables.[22] Therefore, these studies easily led to different results and different conclusions. To overcome these limitations of large database studies, we conducted a real-world retrospective cohort study to generate real-world evidence. We carefully reviewed all the medical records of every enrolled patient so that we were able to clearly distinguish any difference between off-label and per-label reduced-dose apixaban treatment groups, which could not be achieved in the large nationwide cohort research. We showed that off-label reduced-dose apixaban treatment was associated with a nonsignificantly higher thromboembolic event rate and did not decrease either major or minor bleeding events.

Different from the global randomized control studies, the value of real-world observation is to provide clinical evidences in patients who were excluded at the beginning.[41,42] Given that the scanty evidence was available to investigate the "reduced-dose" DOACs strategy in patients with AF and co-morbidities. In the subgroup analysis, we focused on 3 special populations including patients with nonvalvular AF and concomitant old age (age $\geq$80 years), moderate to severe CKD (15 mL/min/1.73m2 $\leq$ eGFR $<$ 50 mL/min/1.73m^2) or previous stroke/TIA. Previous literature revealed that these populations were at a higher risk of recurrent thromboembolism and bleeding.[43,44] As a result, the balance between stroke prevention and bleeding risk in such patients is crucial and challenging. In our subgroup analysis, the off-label reduced-dose apixaban group did not have a decreased bleeding risk compared with the per-label adequate-dose group. Furthermore, our results indicated that the elders receiving off-label reduced-dose apixaban tended to have more ischemic stroke events than those receiving per-label adequate-dose apixaban (Fig. 2). The previous evidences[44] demonstrate that as age increases, the risk of stroke increases more rapidly than the risk of bleeding. However, when treatment with VKA, the bleeding risk starts to outweigh ischemic stroke at around the age of 55, and this trend increases steeply at around the age of 75.[44] Nonetheless, this phenomenon varied in different DOACs. According to the results of global trials, apixaban and edoxaban showed consistently lower rates of major bleeding compared to warfarin in all age groups but dabigatran and rivaroxaban did not. Therefore, based on our findings, we cannot recommend the off-label reduced-dose apixaban strategy for East Asians, especially Taiwanese, even though they are at high risk of bleeding.

4.1. Limitations

This study has several limitations, including that the sample size was limited, which may have decreased the statistical power to reach reliable conclusions. The study is also retrospective and does not allow the inference of causality. A higher rate of prevalent diabetes mellitus and higher CHA_2DS_2-VASc as well as HAS-BLED scores in the off-label reduced-dose group may have affected the present results. However, the sample size was not sufficient for propensity score matching. Therefore, we performed multivariate Cox regression models that were adjusted for age, diabetes mellitus, and CHA_2DS_2-VASc score or HAS-BLED score. Finally, the possibility of selection bias and incomplete patient records could not be excluded. Additional prospective studies are warranted to confirm the results of this study.

5. Conclusions

Applying an off-label reduced-dose apixaban treatment strategy may not provide incremental benefits or safety for Taiwanese patients with NVAF. Further studies are warranted to identify the optimal dose of DOACs in Asian individuals with NVAF.

Author contributions

Conceptualization: I-Chih Chen, Yen-Wen Liu.
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Writing – review & editing: Yen-Wen Liu.

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