

Apixaban outcomes in AF patients with single dose-reduction criterion: ASPIRE 1-year results

Short title: Clinical outcomes of ASPIRE study

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5 (Supplemental Table 1).

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Abstract

Aims: This study, using a prospective cohort, evaluated the effectiveness and safety of off-label reduced-dose apixaban versus the on-label dose in atrial fibrillation (AF) patients meeting a single dose reduction criterion.

Methods and results: The efficacy and Safety of apixaban In Real-world practice in Korean frail patients with AF (ASPIRE) study is a multicenter, prospective observational cohort involving AF patients who met a single dose reduction criterion of apixaban. Patients were divided into two groups: on-label standard dose (5 mg twice daily) and off-label reduced dose (2.5 mg twice daily). The primary effectiveness outcome was stroke/systemic embolism (SSE), and the primary safety outcome was major bleeding. Of 1,944 patients (mean age 74.3 ± 7.9 years, 56% women), 997 (51%) were receiving off-label reduced dose apixaban. The off-label reduced dose group was older, had more comorbidities, higher concomitant antiplatelet use, and higher CHA₂DS₂-VASc and HAS-BLED scores. During follow-up (1.0 ± 0.2 year), crude incidence rates were 0.9 vs. 0.7 per 100 person-years for SSE and 0.5 vs. 1.0 for major bleeding in the on-label vs. off-label groups. After inverse probability of treatment weighting, the off-label reduced dose group showed no significant differences in the risk of SSE (HR 0.67, 95% CI 0.28-1.59, $p=0.370$) and major bleeding (HR 1.38, 95% CI 0.44-4.35, $p=0.578$) compared to the on-label standard dose group.

Conclusion: In Korean patients with AF meeting a single dose reduction criterion of apixaban, off-label reduced-dose apixaban showed no significant differences in SSE and major bleeding compared to the on-label standard dose. These findings suggest that individualized anticoagulation strategies, such as reduced dose apixaban, may be beneficial for patients with a

high risk of bleeding.

Keywords: atrial fibrillation, apixaban, on-label standard dose, off-label reduced dose

Introduction

Oral anticoagulants (OACs), particularly direct oral anticoagulants (DOACs), are recommended for stroke prevention in atrial fibrillation (AF) patients.(1-3) The primary recommendation for reducing the dosage of DOACs is based on the officially published and approved criteria for dose reduction.(4) In the pivotal ARISTOTLE trial, Apixaban at the standard dose (5 mg twice daily) was compared with warfarin in patients with AF, while a reduced dose of apixaban (2.5 mg twice daily) was reserved for those meeting at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.(5) In the ARISTOTLE trial, a total of 428 patients received apixaban 2.5mg or placebo (4.7% in the apixaban group) according to the above dose reduction criteria. Despite guidelines advising against reducing DOAC doses solely due to bleeding concerns, off-label underdosing is common in clinical practice.(6-8) Several retrospective studies have suggested that off-label reduced dose DOACs may increase the risk of stroke and/or mortality without reducing bleeding risk.(6, 9, 10) Notably, for apixaban, such off-label underdosing has been associated with up to a fivefold increase in stroke risk compared to the recommended dose.(9)

In Korean populations, off-label reduced dose apixaban has been associated with increased stroke risk compared to the on-label standard dose.(8, 11) Nevertheless, among patients meeting only one of the aforementioned criteria, there was no significant difference in the risk of ischemic stroke and major bleeding between those receiving the on-label standard dose and those

receiving an off-label reduced dose apixaban.(11) However, there is limited prospective data on the clinical impact of off-label reduced dose apixaban in patients at high risk for bleeding who meet the single dose reduction criterion.

This study assessed the effectiveness and safety of off-label reduced dose apixaban compared to the on-label dose apixaban in AF patients, meeting the single dose reduction criterion for apixaban in a prospective, multicenter, non-interventional cohort.

Methods

A more detailed description of the methods is presented in the **Supplemental Methods** section. The ASPIRE (Efficacy and Safety of Apixaban in Real-world Practice in Korean Frail Patients with Atrial Fibrillation) study was a prospective, multicenter, non-interventional observational investigation encompassing all geographic areas within South Korea across 32 participating centers. The study protocol was approved by each center's ethics committee and adhered to the principles of the Declaration of Helsinki (H-2108-110-1245). It was registered on ClinicalTrials.gov (NCT05773222), and informed consent was obtained from all participants.

Study population and design

Participants aged 19 years or older with non-valvular AF, who were prescribed apixaban and met the single dose reduction criterion, were screened. The criteria for apixaban dose reduction included: (i) age 80 years or older, (ii) body weight 60 kg or less, and (iii) serum creatinine level 1.5 mg/dL or higher.(5) Exclusion criteria comprised: (i) vulnerability (as defined by Korean Good Clinical Practice) or disagreement with the study, (ii) patients who experienced clinical

events, as outlined in the primary and secondary outcomes of the study, prior to enrollment while on apixaban, and (iii) meeting two or more dose reduction criteria for apixaban. The choice of apixaban dosage—5 mg twice daily (standard dose) or 2.5 mg twice daily (reduced dose)—was at the discretion of the treating physicians.

Covariates

Demographic data, anthropometric measurements, blood pressure, and heart rate were recorded. Baseline variables included comorbidities such as hypertension, diabetes mellitus, heart failure, history of stroke/transient ischemic attack (TIA), bleeding, chronic kidney disease (CKD), liver disease, and malignancy. Laboratory findings encompassed complete blood count, coagulation parameters, and renal function tests. CHA₂DS₂-VASc and HAS-BLED scores were calculated using participants' comorbidities and laboratory data.(12) AF diagnosis included type, European Heart rhythm association (EHRA) symptom classification, and rhythm control status. Baseline pharmacological treatment data and anemia status were also documented. All available data for each analysis was used without excluding entire cases.

Follow-up and outcomes

The study was prospectively followed up to 12 months after enrollment, with recommended data collection every 3 months. The primary effectiveness outcome was the first stroke/systemic embolism (SSE) during follow-up. Secondary effectiveness outcomes included TIA, myocardial infarction, cardiovascular death, all-cause death, and a composite of thromboembolic events (SSE, TIA, and myocardial infarction). The primary safety outcome was the first major bleeding (the International Society on Thrombosis and Haemostasis [ISTH] criteria), with secondary safety outcomes including a composite of major bleeding and clinically relevant non-major

bleeding [CRNMB], and a composite of major bleeding, CRNMB, and minor bleeding events.(13) Apixaban dosing status, dose changes, and 12-month laboratory tests were monitored during follow-up.

Statistical methods

Regarding baseline characteristics, continuous variables are expressed as mean $\pm$ standard deviation, while categorical variables are presented as numbers and percentages. Group comparisons were conducted using various statistical tests including the Mann-Whitney U, chi-square, Analysis of Variance, and Fisher's exact tests.

Incidence rates (IRs) were calculated as the number of events per 100 person-years (PY).

Survival analysis using the Kaplan-Meier method (log-rank test) and Cox proportional hazards regression assessed the risks of primary and secondary outcomes between the off-label low-dose and on-label standard-dose apixaban groups (reference). Hazard ratios (HRs) with 95%

confidence intervals (CIs) were calculated with stepwise adjustments: unadjusted, adjusted for age, sex, comorbidities, concomitant antiplatelet use and anemia. Furthermore, to compare the

clinical outcomes between the two groups after balancing the differences of baseline characteristics of the two groups, we performed an inverse probability of treatment weighting

(IPTW) analysis.(14) Propensity scores were generated using logistic regression, with matching variables including demographics, comorbidities, and medications.(14, 15) Standardized mean

differences ≤ 0.1 indicated well-balanced groups.(16) Post-matching survival analysis used log-rank tests and Cox proportional hazards regression models, accounting for calculated weights.(15)

Statistical significance was defined as $p < 0.05$. All statistical analyses were conducted utilizing SPSS version 25 (IBM Corp., Armonk, NY, USA).

Subgroup analysis

Subgroup analyses for SSE, death from any cause, and major bleeding compared on-label standard dose to off-label reduced dose apixaban across age categories, body weight, serum creatinine levels, CHA₂DS₂-VASc score, HAS-BLED score, and CKD Epidemiology Collaboration equation estimate glomerular filtrate rate (EPI eGFR). These analyses used a multivariable Cox proportional hazards regression model with adjustments.

Results

Figure 1 depicts the study flow. From March 2020 to September 2022, total 2006 patients were enrolled. After exclusions due to protocol violations, consent withdrawal, and loss to follow-up, 1944 patients were included in the analysis. Enrollment criteria were: 29.7% aged ≥ 80 years, 62.4% weighing ≤ 60 kg, and 7.9% with serum creatinine ≥ 1.5 mg/dL. Of the cohort, 48.7% received on-label standard dose apixaban (5 mg twice daily), while 51.3% received off-label reduced dose (2.5 mg twice daily) (**Figure 1**).

Baseline characteristics

Baseline characteristics of the on-label standard dose apixaban and off-label reduced dose apixaban groups are presented in **Table 1**. In comparison to the on-label standard dose group, the off-label reduced dose group exhibited older age and higher mean CHA₂DS₂-VASc and HAS-BLED scores. They had higher prevalence of hypertension, heart failure, prior stroke/TIA, prior bleeding, and CKD. This group was also more likely to receive concomitant antiplatelet therapy. Laboratory results showed greater prevalence of anemia and CKD stage 3a or greater with renal

function impairment in the off-label reduced dose group. No significant differences were observed in sex distribution or mean weight between groups. The standardized mean difference plot before and after IPTW are presented in **Supplemental Figure 1**. After IPTW, baseline characteristics of the two groups were well-balanced (standardized mean differences ≤ 0.1) (**Supplemental Table 2**).

Primary and secondary outcomes

The crude IRs, unadjusted, adjusted, and weighted HRs, and Kaplan-Meier curves with log-rank p-values of weighted IPTW population are presented in **Table 2**, **Supplemental Table 3**, and **Figure 2**. During a mean follow-up period of 1.0 ± 0.2 years, the on-label standard dose group experienced 8 SSE events compared to 7 events in the off-label reduced dose group (IR 0.9 versus 0.7 per 100 PY). Major bleeding events were observed in 5 patients in the on-label standard dose group and 10 patients in the off-label reduced dose group (IR 0.5 versus 1.0 per 100 PY). Kaplan-Meier curve of weighted IPTW population showed no statistically significant difference for both safety and effectiveness outcomes between the two dosage groups (all log-rank $p > 0.05$). Post-matching Cox proportional hazards regression models with weights the off-label reduced dose group demonstrated a comparable risk for SSE relative to the on-label standard dose group (HR 0.67, 95% CI 0.28-1.59, $p=0.370$). Regarding secondary effectiveness outcomes, no significant differences were observed between the two groups after multivariable adjustment. Post-matching Cox proportional hazards regression models with weights revealed no significant difference in the risk for major bleeding between off-label reduced dose groups and the on-label standard dose group (HR 1.38, 95% CI 0.44-4.35, $p=0.578$). For the secondary safety outcomes, no statistically significant differences were detected between the two groups

following multivariable adjustment.

Subgroup analysis

Subgroup analyses were conducted for predefined subgroups (**Supplemental Table 4**). No significant interactions were observed in subgroup analyses.

Discussion

The key findings of this study are: (i) Patients at high risk for bleeding (older age, higher comorbidity burden, worse renal function) were more likely to receive off-label reduced-dose apixaban; and (ii) Off-label reduced-dose apixaban showed no significant differences in effectiveness or safety compared to standard-dose apixaban after multivariable adjustment and IPTW. This study is the first prospective analysis to evaluate the safety and effectiveness of off-label reduced-dose apixaban in patients meeting a single dose reduction criterion.

Off-label reduced dose prescription in Asian patients with AF has been frequently observed across several studies.(7, 9, 17) However, patient characteristics associated with this practice vary by region. In Taiwan, off-label underdosing was more common among younger patients with fewer comorbidities.(9) Conversely, the Korean COmparison study of Drugs for symptom control and complication prEvention of AF (CODE-AF) registry, found that off-label reduced dosing occurred in more than one-third of the population, particularly among older patients with lower body weight and reduced renal function.(7)

Our previous analysis of the ASPIRE cohort detailed baseline characteristics and factors linked to off-label reduced dosing(18) Patients at high risk for bleeding, especially those nearing a second dose reduction criterion, were more likely to receive reduced doses, while those with prior strokes were more often prescribed standard doses per labelling.(18) These findings highlight the complexity of DOAC dosing in clinical practice. While established criteria provide a foundation for dosing decisions, our results indicate that clinicians often consider a broader range of patient characteristics when prescribing apixaban. This practice reflects the heterogeneity of the patient population and the need for individualized approaches to anticoagulation therapy.

In this study, the outcomes between the on-label standard dose group and off-label reduced dose groups did not show any statistically significant differences when considering the baseline differences between the groups. The trend was similar to the previous study using Korean nationwide claims database, which showed higher risk of ischaemic stroke, all-cause death, and composite clinical outcomes but comparable risk of major bleeding in the off-label reduced apixaban dose group who already satisfied single dose reduction criteria.(11) Additionally, when comparing all four DOACs, underdosed patients did not show significant difference in clinical outcomes from the labeled use group whereas overdosed patients showed worse clinical outcomes in Asian AF patients.(19) In a meta-analysis on rivaroxaban dosing, J-ROCKET AF criteria of reduction showed comparable safety and effectiveness among Asian patients.(20)

These results, while differing from earlier studies reporting increased stroke risk and no major bleeding reduction in off-label dosing groups (9, 17, 21), suggest that outcomes may vary when patients are assessed based on adherence to dose reduction criteria. This underscores the importance of examining specific subgroups in off-label dosing studies. This aligns with findings

1 from the ENGAGE AF-TIMI 48 trial, where the primary net clinical outcome improved with
2 lower dosing, while secondary outcomes showed no significant differences between low and
3 high doses. (22) Considering the net clinical benefit, balancing stroke and bleeding risks may
4 require a more individualized dosing approach, potentially diverging from standard on-label
5 recommendations. Our findings further suggest that in patients at high risk for bleeding, lower
6 doses may provide comparable net clinical benefits with reduced bleeding risks rather than
7 avoiding oral anticoagulation entirely. Prospective registry data also indicate no significant
8 differences in clinical outcomes between on-label and off-label dosing.

9 The ARISTOTLE trial established apixaban's official dosing protocol, using a standard dose of 5
10 mg twice daily and a reduced dose of 2.5 mg twice daily for patients meeting at least two
11 specific criteria, which demonstrated superior stroke prevention and reduced bleeding compared
12 to warfarin.(5) In the ARISTOTLE trial, patients with single dose reduction criterion accounted
13 for 22.8% of the total study population. These patients generally had a higher risk of bleeding
14 and thromboembolic events compared to those with no dose reduction criteria. However, even in
15 this subgroup, apixaban 5 mg twice daily demonstrated similar benefits to the main ARISTOTLE
16 results, showing superiority over warfarin in reducing stroke, major bleeding, and intracranial
17 hemorrhage.(23) In the ARISTOTLE trial, patients in this subgroup were not included in the 2.5
18 mg twice daily regimen, making it impossible to infer its clinical outcomes. Unlike ARISTOTLE,
19 our study evaluated the clinical outcomes of patients meeting a single dose reduction criterion
20 who were prescribed either apixaban 5 mg or 2.5 mg twice daily at the physician's discretion.
21 Our findings indicate no significant difference in ischemic or bleeding outcomes compared to the
22 on-label dose in these single dose reduction criterion patients, suggesting that some individuals
23 may tolerate a lower dose without compromising efficacy or safety. Although this study is not a

1 randomized controlled trial and cannot conclusively recommend dose reduction for patients
2 meeting the single dose reduction criterion, it highlights the need for individualized assessment
3 in specific populations without overriding existing guidelines.

4 Monitoring NOAC plasma concentrations may help determine appropriate individualized dosing
5 strategies for patients at high risk for bleeding. While off-label reduced doses typically result in
6 lower plasma concentrations, the relationship between drug levels and clinical outcomes is
7 complex.(24, 25) The ENGAGE AF-TIMI 48 trial showed that Asian patients, often with lower
8 body weight, had reduced edoxaban concentrations and anti-factor Xa activity but a higher
9 bleeding risk.(25) Another study found that some patients on off-label underdosed apixaban or
10 rivaroxaban still achieved acceptable peak plasma concentrations.(26) These findings highlight
11 the intricate relationship between drug levels and therapeutic outcomes, supporting the need for
12 individualized DOAC dosing, potentially with pharmacokinetic monitoring.

14 *Limitations*

15 This study has certain limitations that should be acknowledged. First, our study was conducted at
16 a single tertiary medical center in Korea with a predominantly Asian patient population, which
17 may limit the generalizability of our findings to other racial or ethnic groups and different
18 healthcare systems. Previous research has shown that there can be racial differences in both
19 stroke and bleeding outcomes, highlighting the need for caution when extrapolating these results
20 to more diverse or non-Asian populations. (27, 28) Second, the relatively short mean follow-up
21 period may not fully capture long-term outcomes or rare events in this chronic condition,
22 limiting the generalizability of the findings to long-term anticoagulation management. To address
23 this limitation, we are planning an extended cohort analysis with a longer follow-up duration,

1 providing more comprehensive insights into the long-term effectiveness and safety of different
2 apixaban dosing strategies. Third, despite the use of IPTW and multivariable adjustments,
3 unmeasured confounders may still influence the results due to the study's observational design.
4 Our dataset did not capture the duration of apixaban use prior to enrollment, including potential
5 dose adjustments made for clinical reasons before study initiation. Additionally, changes in
6 apixaban dose or other medications, including antiplatelet therapy during follow-up, may have
7 also impacted the findings. Such data were not collected or included in this study and, therefore,
8 could not be adjusted for. This should be considered when interpreting the results. Fourth, the
9 small number of events, particularly for primary outcomes, may have reduced the statistical
10 power to detect significant differences. During the follow-up period, we observed only 15 SSE (8
11 in the on-label group and 7 in the off-label group) and 15 major bleeding events (5 in the on-
12 label group and 10 in the off-label group). The confidence intervals in our results suggest some
13 degree of uncertainty, which is not uncommon in studies with a limited number of events. Fifth,
14 data on patient adherence to the prescribed apixaban regimen was unavailable, potentially
15 affecting the interpretation of effectiveness and safety outcomes. Sixth, the findings are specific
16 to apixaban and may not be generalizable to other direct oral anticoagulants. Lastly, the lack of
17 pharmacokinetic data limits the interpretation of the relationship between dosing, drug levels,
18 and clinical outcomes.

19 20 **Conclusion**

21 In this prospective cohort of Korean AF patients meeting a single dose reduction criterion, off-
22 label reduced-dose apixaban was not associated with a higher risk of stroke/systemic embolism

or major bleeding compared to on-label standard dosing. These findings suggest the potential value of individualized anticoagulation strategies (e.g., reduced dose apixaban), particularly for patients at high risk for bleeding. Further research, including randomized controlled trials, is warranted to investigate alternative apixaban dosing strategies for patients at high risk of bleeding, which may be particularly relevant for East Asian populations.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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- 20 Ecological Epidemiological Study Comparing Korea and United Kingdom Subjects. *Thromb Haemost*.
- 21 2024;124(9):842-51.

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1 Table 1. Baseline characteristics of the whole study population according to apixaban dose.

	Total (n=1944)	Apixaban dose		p- value
		On-label standard dose (n=947)	Off-label reduced dose (n=997)	
Single dose reduction criteria				
Age ≥80 years	578 (29.7%)	242 (25.6%)	336 (33.6%)	<0.001
Body weight ≤60 kg	1213 (62.4%)	654 (69.1%)	559 (62.4%)	<0.001
Creatinine ≥1.5 mg/dL	153 (7.9%)	51 (5.4%)	102 (10.2%)	<0.001
Age, years	74.3 ± 7.9	72.5 ± 8.2	76.0 ± 7.1	<0.001
<65	221 (11.4%)	150 (15.8%)	71 (7.1%)	<0.001
65–74	669 (34.4%)	397 (41.9%)	272 (27.3%)	<0.001
75–79	476 (24.5%)	158 (16.7%)	318 (31.9%)	<0.001
Sex (female)	1084 (55.8%)	533 (56.3%)	551 (55.3%)	0.652
Bodyweight (kg)	60.1 ±10.0	59.8 ± 9.7	60.4 ± 10.3	0.073
≤50	247 (12.7%)	105 (11.1%)	142 (14.2%)	0.037
51–60	966 (49.7%)	549 (58.0%)	417 (41.8%)	<0.001
>60	731 (37.6%)	293 (30.9%)	438 (43.9%)	<0.001
CHA ₂ DS ₂ –VASc score	3.5 ± 1.4	3.4 ± 1.4	3.7 ± 1.3	<0.001
≥3	1494 (76.9%)	679 (71.7%)	815 (81.7%)	<0.001
HAS–BLED score *	1.6 ± 0.9	1.6 ± 0.9	1.7 ± 0.9	0.015
≥3	248 (12.8%)	113 (11.9%)	135 (13.5%)	0.209
Comorbidities				
Hypertension	1381 (71.0%)	652 (68.8%)	729 (73.1%)	0.038
Diabetes Mellitus	608 (31.3%)	284 (30.0%)	324 (32.5%)	0.233
Heart failure	464 (23.9%)	201 (21.2%)	263 (26.4%)	0.008
Prior stroke/TIA	207 (10.6%)	125 (13.2%)	82 (8.2%)	<0.001
Prior bleeding	138 (7.1%)	50 (5.3%)	88 (8.8%)	0.002
CKD	213 (11.0%)	64 (6.8%)	149 (14.9%)	<0.001
Not on dialysis	173 (8.9%)	54 (5.7%)	119 (11.9%)	<0.001
On dialysis	25 (1.3%)	8 (0.8%)	17 (1.7%)	0.092
Previous kidney transplantation	14 (0.7%)	2 (0.2%)	12 (1.2%)	0.010
Liver disease	74 (3.8%)	33 (3.5%)	41 (4.1%)	0.470
Malignancy	265 (13.6%)	120 (12.7%)	145 (14.5%)	0.229
Antiplatelet use**	125 (6.6%)	44 (4.8%)	81 (8.4%)	0.002
SAPT	105 (5.6%)	36 (1.9%)	69 (3.7%)	0.624
DAPT	7 (0.4%)	4 (0.2%)	3 (0.2%)	0.211
Prior OAC	1444 (74.3%)	707 (74.7%)	737 (73.9%)	0.249
Prior VKA	54 (2.8%)	23 (2.4%)	31 (3.1%)	0.361
Prior DOAC	1390 (71.5%)	684 (72.2%)	706 (70.8%)	0.139
Apixaban	829 (42.6%)	437 (46.1%)	392 (39.3%)	0.001
Dabigatran	99 (5.1%)	51 (5.4%)	48 (4.8%)	0.561
Edoxaban	315 (16.2%)	131 (13.8%)	184 (18.5%)	0.005
Rivaroxaban	147 (7.6%)	65 (6.9%)	82 (8.2%)	0.253
Atrial fibrillation type				
Not determined	84 (4.3%)	31 (3.3%)	53 (5.3%)	0.027
Paroxysmal	1010 (52.0%)	499 (52.7%)	511 (51.3%)	0.526
Non paroxysmal	850 (43.7%)	417 (44.0%)	433 (43.4%)	
Persistent	685 (35.2%)	325 (34.3%)	360 (36.1%)	0.055

Long-standing persistent	91 (4.7%)	48 (5.1%)	43 (4.3%)	0.456
Permanent	73 (3.8%)	43 (4.5%)	30 (3.0%)	0.078
EHRA classification				
I	460 (23.7%)	218 (23.0%)	242 (24.3%)	0.516
IIa	774 (39.8%)	379 (40.0%)	395 (39.6%)	0.856
IIb	236 (12.1%)	98 (10.3%)	138 (13.8%)	0.018
III	56 (2.9%)	20 (2.1%)	36 (3.6%)	0.048
IV	2 (0.1%)	1 (0.1%)	1 (0.1%)	0.971
Unknown	416 (21.4%)	231 (24.4%)	185 (18.6%)	0.002
Lab				
Haemoglobin (g/dL) ***	13.0 ± 1.8	13.2 ± 1.8	12.8 ± 1.7	<0.001
Anemia (men ≤13 g/dL, female ≤12g/dL)	523 (26.9%)	222 (23.4%)	301 (30.2%)	<0.001
Platelet (x10 ³ /μl)	207.2 ± 69.0	209.1 ± 65.0	205.4 ± 72.6	0.175
PT INR ****	1.2 ± 0.5	1.2 ± 0.3	1.2 ± 0.7	0.822
Creatinine (mg/dL)	1.0 ± 0.7	0.9 ± 0.6	1.1 ± 0.8	<0.001
CrCl (ml/min)	56.2 ± 17.5	60.1 ± 17.0	52.5 ± 17.1	<0.001
CrCl <50 (ml/min)	716 (36.8%)	271 (28.6%)	445 (44.6%)	<0.001
eGFR (MDRD) (mL/min/1.73m ²)	72.3 ± 23.1	76.2 ± 21.5	68.6 ± 24.0	<0.001
eGFR (CKD-EPI) (mL/min/1.73m ²)	71.0 ± 20.0	75.1 ± 18.3	67.0 ± 20.8	<0.001
Stage 1 (eGFR ≥90)	269 (13.8%)	180 (19.0%)	89 (8.9%)	<0.001
Stage 2 (60 ≤eGFR <90)	1086 (55.9%)	559 (59.0%)	527 (52.9%)	0.030
Stage 3a (45 ≤eGFR <60)	337 (17.3%)	135 (14.3%)	202 (20.3%)	<0.001
Stage 3b (30 ≤eGFR <45)	151 (7.8%)	54 (5.7%)	97 (9.7%)	0.001
Stage 4 (15 ≤eGFR <30)	42 (2.2%)	6 (0.6%)	36 (3.6%)	<0.001
Stage 5 (eGFR <15)	15 (0.8%)	3 (0.3%)	12 (1.2%)	0.023

* n= 1881

** n=1886

*** n=1726

**** n=520

Categorical variables were presented as a percentage and continuous variables were presented as mean and standard deviation.

Abbreviation: CKD, chronic kidney disease; CrCl, Creatinine clearance; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; EPI, Epidemiology Collaboration equation; MDRD, modification of diet in renal disease;; PT INR, prothrombin time international normalized ratio; SAPT, single antiplatelet therapy; TIA, transient ischemic attack; VKA, Vitamin K antagonist.

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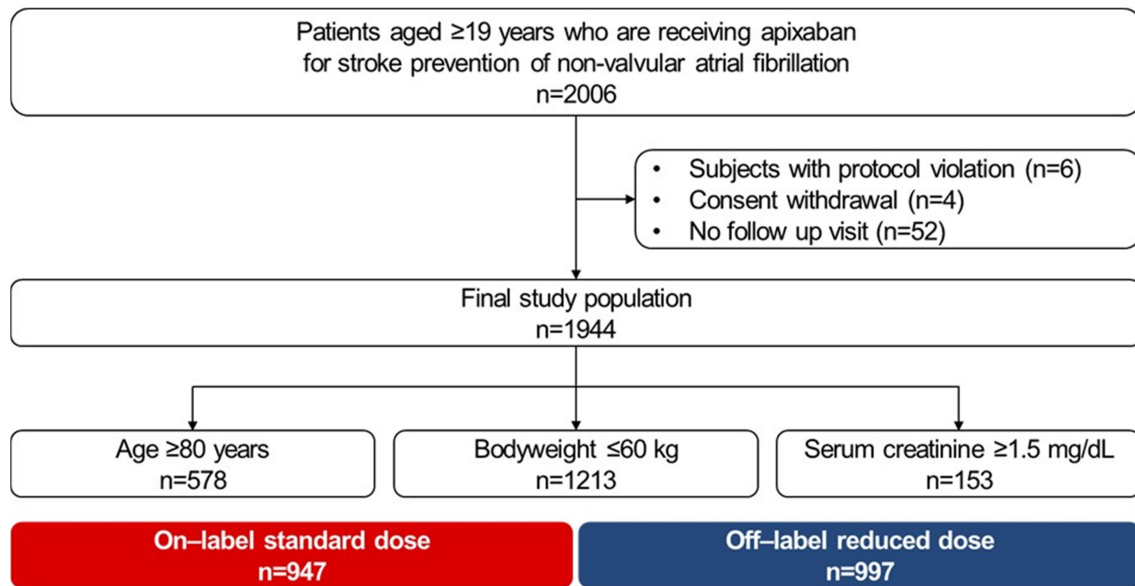
1 **Table 2. Incident rate and hazard ratios of clinical outcomes**

		Events	IR per 100 PY	Unadjusted HR (95% CI)	Weighted HR (95% CI)
Effectiveness	Primary outcome: Stroke/systemic embolism				
	On-label standard dose	8	0.9	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	7	0.7	0.84 (0.30–2.31)	0.67 (0.28-1.59)
	p-value			0.731	0.370
	Secondary outcomes				
	TIA				
	On-label standard dose	3	0.3	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	1	0.1	0.32 (0.03–3.06)	0.42 (0.04-4.08)
	p-value			0.322	0.455
	MI				
	On-label standard dose	2	0.2	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	2	0.2	1.04 (0.15–7.40)	1.31 (0.11-14.56)
	p-value			0.967	0.822
	Death from cardiovascular cause				
	On-label standard dose	2	0.2	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	2	0.2	0.96 (0.14–6.82)	0.69 (0.09-5.01)
	p-value			0.967	0.714
	Death from any cause				
	On-label standard dose	5	0.5	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	17	1.8	3.26 (1.20–8.84)	2.63 (0.93-7.45)
	p-value			0.020	0.068
	Composite of stroke/systemic embolism/TIA/MI				
	On-label standard dose	13	1.4	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	10	1.1	0.73 (0.32–1.67)	0.67 (0.28-1.59)
	p-value			0.463	0.370
Safety	Secondary outcomes: Major bleeding				
	On-label standard dose	5	0.5	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	10	1.0	1.91 (0.65–5.58)	1.38 (0.44-4.35)
	p-value			0.238	0.578
	Secondary outcomes				
	Major bleeding and clinically relevant nonmajor bleeding				
	On-label standard dose	12	1.3	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	21	2.2	1.67 (0.82–3.40)	1.55 (0.70-3.42)
	p-value			0.154	0.278
	Composite of major, clinically relevant nonmajor bleeding, and minor bleeding				
	On-label standard dose	57	6.4	1.00 (reference)	1.00 (reference)
	Off-label reduced dose	59	6.4	1.00 (0.69–1.43)	0.83 (0.52-1.33)
	p-value			0.966	0.451

2 Abbreviation: CI, confidence interval; HR, hazard ratio; IR, incidence rate; MI, myocardial infarction; PY,
3 person-years; TIA, transient ischemic attack.

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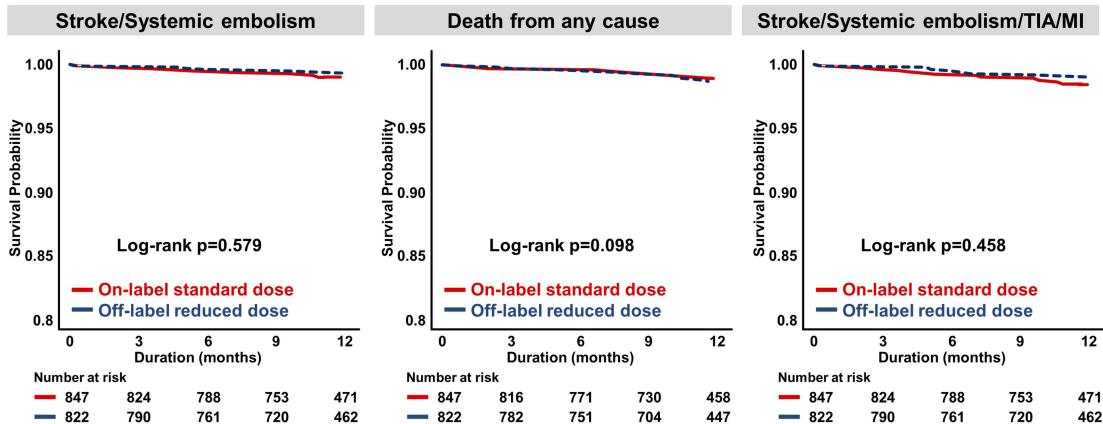
2 **Figure 1. Study Flow.** The overall enrollment flow is presented.

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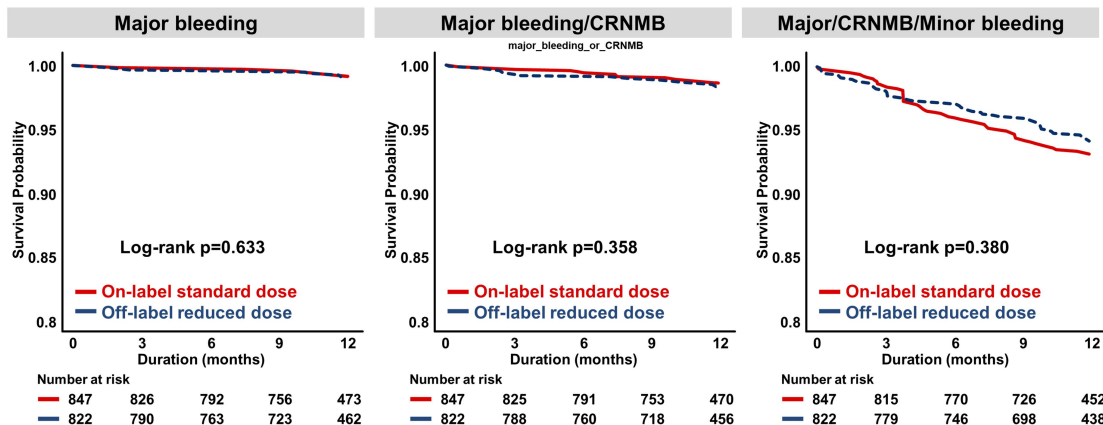
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1 **Figure 2. Kaplan-Meier curves of clinical outcomes after inverse probability of**
 2 **treatment weighting.** After IPTW, Kaplan-Meier curves showed comparable risks for most
 3 outcomes, except for stroke/systemic embolism.

(a) Effectiveness



(b) Safety



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 5 Abbreviations: CRNMB, clinically relevant non major bleeding; IPTW, inverse probability of
 6 treatment weighting; MI, myocardial infarction; TIA, transient ischemic attack.