

Comparison of Acute Kidney Injury Risks Between Direct Oral Anticoagulants in Nonvalvular Atrial Fibrillation: A Propensity Score-weighted Retrospective Observational Cohort Study

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Abstract

Background

Anticoagulant use can cause anticoagulant-related nephropathy (ARN), primarily characterized by acute kidney injury (AKI). The incidence and severity of AKI associated with the use of direct oral anticoagulants (DOACs) remain unclear.

Methods

This study aimed to examine the incidence of AKI in patients with nonvalvular atrial fibrillation (NVAF) receiving DOACs. This single-center, retrospective cohort study enrolled patients with NVAF who received edoxaban, apixaban, or rivaroxaban between January 2015 and December 2023. The primary outcome was the cumulative incidence of AKI within the first year of treatment. Inverse probability of treatment weighting (IPTW) was applied to adjust for imbalances in the measured confounders between treatment groups. Additionally, outcome regression was conducted including covariates in the weighted Cox proportional hazards model.

Results

Of the 492 enrolled patients, 307, 112, and 73 received edoxaban, apixaban, and rivaroxaban, respectively. The cumulative incidence of AKI within 1 year of the administration for each of these drugs was 10.8%, 23.3%, and 25.0%, respectively (IPTW-adjusted $p < 0.001$). In multivariable Cox regression analysis with IPTW adjustment, compared with edoxaban, apixaban and rivaroxaban showed adjusted hazard ratios of 2.12 (95% confidence intervals (CI), 1.12–4.02, $p = 0.021$) and 2.92 (95% CI, 1.44–5.92, $p = 0.003$), respectively.

Conclusion

Edoxaban was associated with a lower risk of AKI than other factor Xa inhibitors.

Background

Among patients with atrial fibrillation, anticoagulants play a crucial role in preventing stroke and cerebral infarction caused by thromboembolism. Direct oral anticoagulants (DOACs) are widely prescribed for nonvalvular atrial fibrillation (NVAF) as they have demonstrated greater efficacy and safety than Vitamin K agents (VKAs) in several clinical studies [1, 2, 3, 4, 5]. Although the use of anticoagulants reduces thromboembolism events, it has been associated with anticoagulant-related nephropathy (ARN), characterized by acute kidney injury (AKI), macroscopic hematuria, glomerular hemorrhage, and red blood cell casts within the renal tubules [6, 7]. Patients with ARN have a higher mortality rate than those

without; this is particularly pronounced in cases where renal function does not improve after the onset of ARN; therefore, early prevention and detection of ARN are of utmost importance [6, 8]. Moreover, because many patients with ARN do not exhibit any signs of hematuria in clinical practice, unexplained AKI occurring during anticoagulant therapy should prompt the suspicion of ARN and appropriate management [6].

Initially, ARN was recognized as a form of kidney damage associated with warfarin; Brodsky et al. reported that the incidence rate of AKI in patients receiving warfarin therapy was 20.5% [9]. Recently, ARN has been reported not only in patients receiving warfarin but also in those receiving DOACs [10]. Some studies, including meta-analyses, have reported that DOACs are associated with a lower risk of AKI and ARN, as well as lower severity than warfarin [11, 12, 13]. These effects have been attributed to their anti-inflammatory and antioxidant properties in the kidneys [6]. While there have been several reports investigating the incidence and severity of ARN among DOACs, data remain insufficient, partly due to the heterogeneity in renal outcome definitions, including differences in the use of AKI and ARN as endpoints. Thus, the incidence and clinical features of DOAC-induced ARN remain unclear. In particular, because there have been no head-to-head comparisons between DOACs, with findings currently limited to those from network meta-analyses, determining the real differences in incidence among DOACs remains a critical challenge.

Different types of DOAC have different pharmacokinetic and pharmacodynamic profiles. Consequently, it is anticipated that the risk of AKI would vary depending on the type of DOACs used. Although several risk factors for ARN have been identified, it remains unclear whether the risk of renal injury varies among individual DOACs when these established factors are accounted for [14, 15]. Therefore, the present study aimed to examine the incidence of AKI in patients receiving edoxaban, apixaban, and rivaroxaban, all of which are factor Xa (FXa) inhibitors, and determine whether there were differences based on the type of DOACs. Compared with other DOACs, edoxaban has been evaluated less commonly in studies assessing renal outcomes [11]. This study provides data on the renal safety of edoxaban for which data are currently limited.

Methods

Study design and patients

This single-center, retrospective cohort study was conducted at Sapporo Medical University. The inclusion criteria were as follows: patients with NVAf aged ≥ 18 years who were newly initiated on DOACs (edoxaban, apixaban, or rivaroxaban) between January 2015 and December 2023. Patients for whom baseline data such as body weight and serum creatinine (SCr) were missing at the start of treatment were excluded. We used the STROBE reporting guideline to draft this manuscript [16].

Outcomes

The primary outcome was the cumulative incidence of AKI within 1 year of the initiation of anticoagulant treatment. AKI was defined according to the Kidney Disease Improving Global Outcomes criteria (i.e., SCr increase ≥ 1.5 -fold from baseline) [17]. Given the lack of systematic hematuria screening in this setting, we assessed the incidence of AKI as a surrogate marker for ARN. AKI was identified based on its first occurrence following the initiation of DOACs. For subgroup analysis, patients were categorized by baseline estimated glomerular filtration rate (eGFR) based on SCr (eGFR_{cre}) (< 60 mL/min/1.73 m² or ≥ 60 mL/min/1.73 m²) to assess whether the incidence of AKI varied according to baseline renal function. The observation period was set based on previous studies, which indicated that the incidence of AKI associated with DOACs was highest within the first year.

Data collection

The following patient data were extracted from the electronic medical records: age, sex, body mass index (BMI), eGFR_{cre}, Creatinine clearance (CrCl), concomitant conditions (congestive heart failure (CHF), hypertension (HT), diabetes mellitus (DM), stroke/transient ischemic attack (TIA), history of cancer, concomitant medications (antiplatelet drugs, proton-pump inhibitors [PPI], and non-steroidal anti-inflammatory drugs [NSAIDs]), hemoglobin, albumin, the date of initiating DOACs therapy, CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus, each given 1 point; and a history of stroke or transient ischemic attack given 2 points). The eGFR_{cre} values were recorded monthly. History of cancer included both prior and active cancers.

Statistical analysis

Continuous variables are summarized as medians (interquartile ranges) for non-normally distributed data. Categorical variables are summarized as counts and percentages. The reverse Kaplan–Meier method was applied to estimate the available follow-up time. Retrospective studies are prone to selection bias and may introduce factors that confound the associations between treatments and outcome [18]. To minimize bias, we applied inverse probability of treatment weighting to adjust for imbalances in the measured confounders between the treatment groups. The propensity scores of the three treatment groups for the baseline covariates were estimated using a multinomial logistic regression model. The model included the following potential covariates: age, sex, BMI, baseline eGFR_{cre}, concomitant disease (CHF, DM, HT, and stroke/TIA), prescription history (PPI, APT, and NSAIDs), and baseline Hb levels. Inverse probability of treatment weighting (IPTW) was subsequently applied using non-stabilized weights, which were calculated as the inverse of the probability of receiving the treatment assigned. The balance of baseline covariates was assessed using standardized mean differences (SMDs), with an SMD < 0.1 indicating a negligible imbalance. The average treatment effect (ATE) on the cumulative incidence was estimated using weighted survival functions. A weighted Cox proportional hazards model was applied to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for AKI. To account for residual confounding and improve the precision of the estimates, we performed outcome regression by including clinically important covariates (CHF, DM, HT, cancer, and

baseline eGFR_{cre}) in the weighted Cox proportional hazards model. This doubly robust approach ensures valid inferences, even if the propensity score model is slightly mis-specified [18, 19]. The E-value was calculated for the observed HR to assess the potential impact of unmeasured confounding, the E-value was calculated for the observed HR [20, 21]. For sensitivity analysis, time-varying covariates, such as the use of transfusion, contrast agents, and surgery during the observation period, were evaluated.

Furthermore, eGFR_{cre} was calculated using the Japanese eGFR formula [22]. CrCl was calculated using the Cockcroft-Gault formula [23].

Analyses were conducted using the software program JMP® student Edition version 19.0.4 (SAS Institute Inc., Cary, NC, USA), EZR version 1.70 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and R version 4.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a two-sided p-value of < 0.05.

Results

Patient characteristics

A total of 492 patients were enrolled in the IPTW-adjusted cohort throughout the study period (Fig. 1 and Table 1). The median age of the patients was 72 years (interquartile range, 63–79), and 38% were female. The median eGFR_{cre} for those patients was 63.4 mL/min/1.73 m² (51.6–75.4). Among these, 307 (62.4%) received edoxaban, 112 (22.8%) received apixaban, and 73 (14.8%) received rivaroxaban. After weighting, the included covariates achieved a high degree of balance, with SMDs generally less than 0.1. The maximum SMD was 0.12, indicating an acceptable balance across factors (Table 1). The median follow-up duration of each drug was as follows: edoxaban, 12 (10-NE) months; apixaban, 12 (8-NE) months; and rivaroxaban, 11 (7-NE) months (NE, not estimable).

Table 1
Patient characteristics adjusted with IPTW

Age median (IQR)	All N = 492	Edoxaban N = 307	Apixaban N = 112	Rivaroxaban N = 73	SMD
	72 (63–79)	73 (62–79.5)	71 (64–78.3)	70 (61–77)	0.021
Female n (%)	187 (38.0)	128 (41.7)	39 (34.8)	20 (27.4)	0.038
BMI median (IQR)	23.3 (20.7–25.9)	23.0 (20.5–25.7)	23.4 (20.6–25.5)	24.3 (21.6–27.2)	0.023
eGFRcre median (IQR) (mL/min/1.73m ²)	63.4 (51.6–75.4)	62.8 (51.4–74.4)	66.5 (51.9–80.1)	62.9 (52.0–74.2)	0.037
eGFRcre < 60 mL/min/1.73m ² n (%)	204 (41.5)	126 (41.0)	45 (40.2)	33 (45.2)	-
CrCl	64.9 (50.4–87.2)	62.6 (49.3–83.3)	68.0 (51.4–92.3)	74.0 (53.5–94.1)	0.037
CHADS ₂ score (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	1 (1–2)	0.067
Dose appropriateness					
Appropriate dosing n (%)	402 (81.7)	258 (84.0)	87 (77.7)	57 (78.1)	-
Inappropriate dosing n (%)	90 (18.3)	49 (16.0)	25 (22.3)	16 (21.9)	-
Laboratory test					
Hemoglobin median (IQR) (g/dL)	13.5 (11.9–14.7)	13.6 (11.9–14.8)	13.4 (11.7–14.6)	13.6 (12.0–14.6)	0.093
Albumin median (IQR) (g/dL)	3.9 (3.6–4.1)	3.9 (3.6–4.1)	3.9 (3.4–4.1)	3.8 (3.7–4.2)	0.088
Concomitant					
Congestive Heart failure n (%)	169 (34.3)	104 (33.9)	39 (34.8)	26 (35.6)	0.018
Hypertension n (%)	276 (56.1)	175 (57.0)	64 (57.1)	37 (50.7)	0.056
Values are presented as median (interquartile range) number (with percentage). Abbreviations: IPTW, inverse probability of treatment weighting; IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; TIA, transient ischemic attack; APT, antiplatelet therapy; NSAIDs, non-steroidal anti-inflammatory drugs					

Age median (IQR)	All N = 492	Edoxaban N = 307	Apixaban N = 112	Rivaroxaban N = 73	SMD
	72 (63–79)	73 (62–79.5)	71 (64–78.3)	70 (61–77)	0.021
Diabetes mellitus n (%)	105 (21.3)	60 (19.5)	27 (24.1)	18 (24.7)	0.004
Stroke/TIA n (%)	50 (10.2)	29 (9.4)	15 (13.4)	6 (8.2)	0.007
Cancer, n (%)	141 (28.7)	93 (30.3)	29 (25.9)	19 (26.0)	0.120
Comedications					
APT n (%)	110 (22.4)	64 (20.8)	30 (26.8)	16 (21.9)	0.009
Proton pump inhibitor n (%)	229 (46.5)	134 (43.6)	62 (55.4)	33 (45.2)	0.049
NSAIDs n (%)	28 (5.7)	14 (4.6)	11 (9.8)	3 (4.1)	0.040
Values are presented as median (interquartile range) number (with percentage). Abbreviations: IPTW, inverse probability of treatment weighting; IQR, interquartile range; BMI, body mass index; eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; TIA, transient ischemic attack; APT, antiplatelet therapy; NSAIDs, non-steroidal anti-inflammatory drugs					

Cumulative incidence of AKI and its risk factor

The overall incidence of AKI within 1 year was 11.2% (57/492). The cumulative incidences of AKI within 1 year for edoxaban, apixaban, and rivaroxaban were 10.8%, 23.3%, and 25.0%, respectively. These differences were statistically significant (IPTW-adjusted $p < 0.001$; Fig. 2). In multivariable Cox regression analysis with IPTW adjustment, the type of DOACs was found to be significantly associated with the incidence of AKI. Compared with edoxaban, apixaban and rivaroxaban showed adjusted HRs of 2.12 (95% CI, 1.12–4.02, $p = 0.021$) and 2.92 (95% CI, 1.44–5.92, $p = 0.003$), respectively (Fig. 3).

Analyses of patients categorized by baseline eGFR_{cre} for subgroup analysis

Compared with edoxaban, rivaroxaban was significantly associated with the incidence of AKI in the group of eGFR_{cre} < 60 mL/min/1.73 m² (adjusted HR, 5.92; 95% CI, 1.82–19.2; $p < 0.001$). However, apixaban did not show a significantly different incidence of AKI compared with edoxaban (adjusted HR, 2.59; 95% CI, 0.72–9.36; $p = 0.145$) (Table 2). In the group of eGFR_{cre} ≥ 60 mL/min/1.73 m², type of DOAC (apixaban: adjusted HR, 2.09; 95% CI, 0.99–4.39; $p = 0.051$, rivaroxaban: adjusted HR, 1.64; 95% CI, 0.54–4.98; $p = 0.386$, respectively) did not show any significantly different incidence of AKI (Table 2). There were no significant interactions between the type of DOACs and baseline renal function (apixaban,

p = 0.739; rivaroxaban, p = 0.177), indicating that the effect of the drugs remained consistent across these subgroups.

Table 2

Sub-group multivariable analysis using IPTW-weighted Cox model according to baseline eGFRcre

Covariate	< 60 mL/min/1.73 m ²			≥ 60 mL/min/1.73 m ²		
	Adjusted HR	(95% CI)	P-value	Adjusted HR	(95% CI)	P-value
Drug						
Edoxaban (reference)	1.00	-	-	1.00	-	-
Apixaban	2.59	(0.72–9.36)	0.145	2.09	(0.99–4.39)	0.051
Rivaroxaban	5.92	(1.82–19.2)	0.003	1.64	(0.54–4.98)	0.386
Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.						
The estimates were derived from a weighted Cox proportional hazards model that integrated IPTW and further adjustment for potential confounders, including baseline eGFRcre, and comorbidities (CHF, HT, DM, and Cancer).						

Sensitivity analysis

In a sensitivity analysis that incorporated time-varying covariates, such as blood transfusions, contrast agent use, and surgery during the observation period, the type of DOAC was found to be significantly associated with the incidence of AKI. Compared with edoxaban, apixaban and rivaroxaban showed adjusted HRs of 2.22 (95% CI, 1.14–4.33, p = 0.019) and 2.89 (95% CI, 1.45–5.79, p = 0.003), respectively (Table 3). In the primary analysis, the E-values were 3.66 (lower limit of the 95% CI, 1.49) for apixaban and 5.29 (lower limit of the 95% CI, 2.24) for rivaroxaban, supporting the robustness to unmeasured confounding.

Table 3
Sensitivity analysis for multivariable analysis using IPTW-weighted Cox model

Covariate	Adjusted HR	(95% CI)	P-value
Drug			
Edoxaban (reference)	1.00	-	-
Apixaban	2.22	(1.14–4.33)	0.019
Rivaroxaban	2.89	(1.45–5.79)	0.003
Abbreviations: IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval.			
The estimates were derived from a weighted Cox proportional hazards model that integrated IPTW and further adjustment for potential confounders including baseline eGFR, comorbidities (CHF, HT, DM, and Cancer), and time-varying covariates.			

Discussion

Overall, this retrospective cohort study demonstrated that the incidence of AKI within 1 year differed among DOAC FXa inhibitors, with edoxaban potentially being associated with a lower incidence of AKI than the other two agents. To the best of our knowledge, no previous studies have demonstrated that edoxaban was associated with a significantly lower risk of AKI compared with other FXa inhibitors.

Brodsky et al. previously reported that the incidence of unexplained AKI following warfarin therapy was 20.5%, with a rate of 16.5% in patients without CKD and 33% in patients with CKD [9]. DOACs have been shown to reduce the risk of AKI compared to warfarin [11, 12, 13] and the incidence of AKI with DOACs is expected to be lower than that with warfarin. One prior study using VigiBase, the WHO Health Organization global database of individual case safety reports, reported that the incidences of kidney-related adverse events with DOACs were 4.6% for dabigatran, 3.5% for rivaroxaban, 2.0% for apixaban, and 1.7% for edoxaban [24]. Another study using the Japanese Adverse Drug Event Report (JADER) database also reported rates of 3.5% for dabigatran, 2.4% for rivaroxaban, 3.0% for apixaban, and 2.2% for edoxaban [15], which were comparable. The incidence of AKI in this study was higher than that reported previously. This discrepancy is likely due to the fact that the outcomes were evaluated based on laboratory test results.

Although different DOACs show distinct pharmacokinetic and pharmacodynamic profiles, there are currently no randomized controlled trials directly comparing the risk of AKI or its incidence among individual DOACs. In a network meta-analysis, no difference was observed in the risk of AKI between the apixaban and rivaroxaban groups. Because data on edoxaban were limited, the assessment of AKI risk was restricted [11]. Our findings indicated that edoxaban was associated with a significantly lower risk of AKI compared to apixaban and rivaroxaban, even after adjusting for IPTW. Renal impairment induced by DOACs is dose-dependent [25], and it is believed that differences in the renal clearance rates of each

drug influence the incidence of AKI. The renal clearance rates of each DOACs were as follows: edoxaban, 50%; apixaban, 27%; and rivaroxaban, 36% [26]. The fact that the incidence of AKI in the present study did not correlate with the renal clearance rate of each DOAC suggests the involvement of mechanisms that cannot be explained by drug accumulation. Bleeding-related mechanisms may contribute to the development of AKI. Indeed, the observed tendency toward a higher risk of AKI with rivaroxaban, which has been reported to carry a higher bleeding risk than other FXa inhibitors, is consistent with a mechanism involving bleeding-mediated renal injury [6]. However, the fact that the risk of AKI with edoxaban is lower than that with apixaban cannot be fully explained by the drug characteristics alone, and we cannot rule out the possibility that this was influenced by differences in dose adjustment or unmeasured confounders. In this study, the rates of appropriate dosing for each DOACs were generally similar. Prior experimental studies have suggested that FXa inhibitors may exert pleiotropic effects beyond anticoagulation, including the modulation of inflammation and fibrosis through protease-activated receptor (PAR)-mediated signaling pathways [27]. Several other studies have suggested that edoxaban may exhibit anti-inflammatory effects, with differences among DOACs observed in certain experimental animal models. However, these findings have not been validated in human populations, and their clinical significance remains unclear [28].

In summary, the present study demonstrated that the incidence of AKI differs between patients treated with FXa inhibitors. We further found that edoxaban was associated with a lower incidence of AKI than the other two agents.

Limitations

This study has some limitations. First, the single-center retrospective and small sample size indicate that the results may have been affected by selection bias and should therefore be interpreted with caution. Although all DOACs were managed under similar clinical conditions in our tertiary care setting, bias due to differential losses to follow-up cannot be entirely excluded. Furthermore, as this study used prescription data exclusively from our hospital, medications prescribed at other institutions were not captured. We further reviewed the prescription records from our institution's electronic medical system as comprehensively as possible. However, the possibility of unrecorded prescriptions could not be completely ruled out. Second, although we employed IPTW and calculated the E-values to mitigate the impact, the possibility of unmeasured confounding factors remains. Third, we could not account for urine output in the AKI definition, which may have led to an underestimation of the incidence. However, as the present study included outpatients, it was difficult to assess urine output. Fourth, we used the CHADS₂ score to assess the risk of ischemic stroke, following guidelines in Japan [29]. Although international guidelines [30] have shifted toward the CHA₂DS₂-VA score, both scoring systems share core risk factors. Given that the part of our study cohort is derived from a Japanese population during a era when the CHADS₂ score was the primary risk stratification tool, using the CHADS₂ score accurately represents the clinical background of the participants. Finally, this study focused on safety and did not

evaluate the efficacy of DOACs. However, the relationship between the incidence of AKI and efficacy requires further investigation.

Conclusions

Overall, the present study examined the association between the type of DOACs and the risk of AKI within the first year of treatment. We first demonstrated that edoxaban was associated with a lower risk of AKI than other DOACs.

Abbreviations

DOACs: direct oral anticoagulants

NVAF: nonvalvular atrial fibrillation

VKAs: vitamin K agents

ARN: anticoagulant-related nephropathy

AKI: acute kidney injury

FXa: factor Xa

SCr: serum creatinine

eGFR: estimated glomerular filtration rate

BMI: body mass index

CrCl: Creatinine clearance

CHF: congestive heart failure

HT: hypertension

DM: diabetes mellitus

TIA: transient ischemic attack

PPI: proton-pump inhibitors

NSAIDs: non-steroidal anti-inflammatory drugs

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of Sapporo Medical University (approval number: 362-23), who waived the requirement for informed consent due to the retrospective nature of the study. Patient consent was obtained using the opt-out methodology.

Consent for publication: Not applicable

Data availability statement: The deidentified data of participants will not be shared.

Competing interests: The authors declare no conflicts of interest.

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Authors' contributions: T.A. and T.I. conceived and designed the study. T.A. and T.I. collected data. T.A. analyzed the data and wrote the manuscript. Y.I., S.F., M. F. and T.T. critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Figures

Figure 1

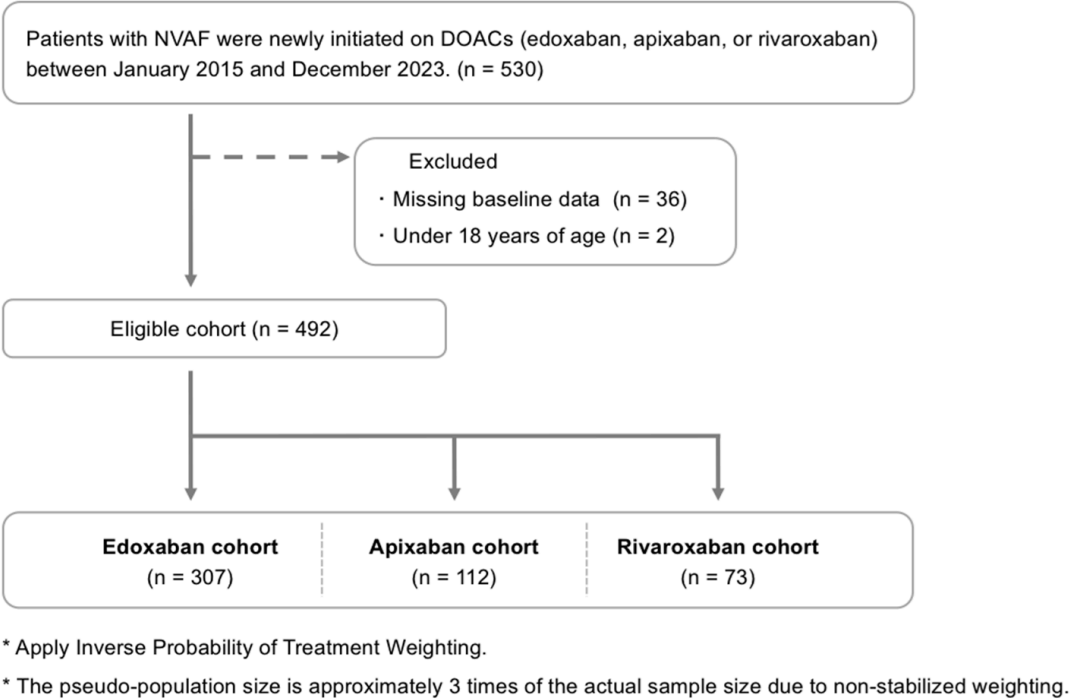


Figure 1

Flow chart of the inclusion of the study participants.
Abbreviations: DOACs, direct oral anticoagulants; NVAf, nonvalvular atrial fibrillation.

Figure 2

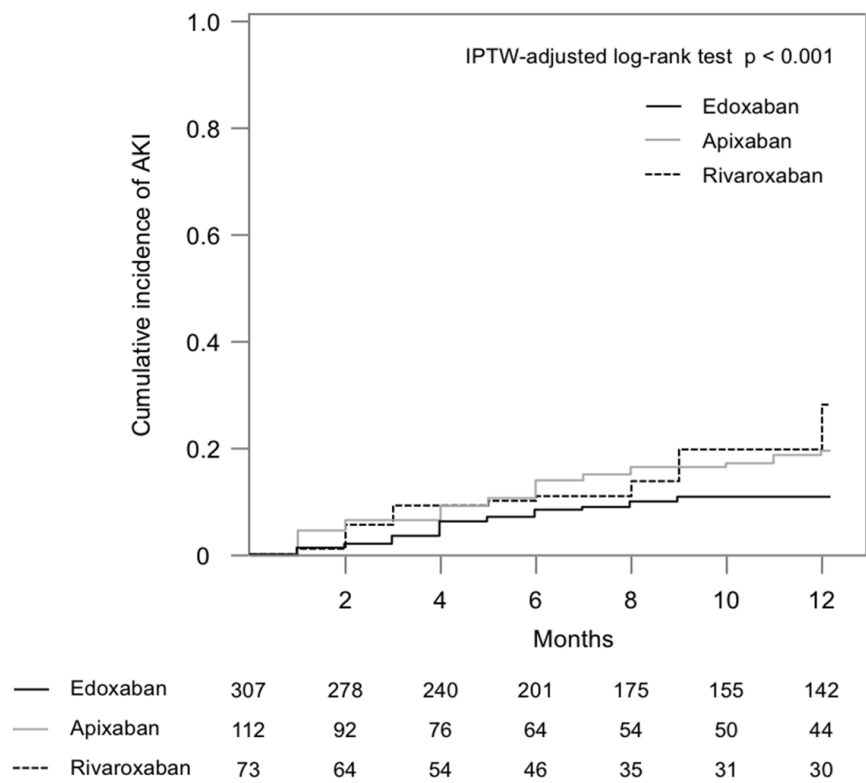


Figure 2

Cumulative incidence probability of AKI after inverse probability of treatment weighting. P-values were calculated using the IPTW-adjusted log-rank test.

Abbreviations: AKI, acute kidney injury; IPTW, inverse probability of treatment weighting.

Figure 3

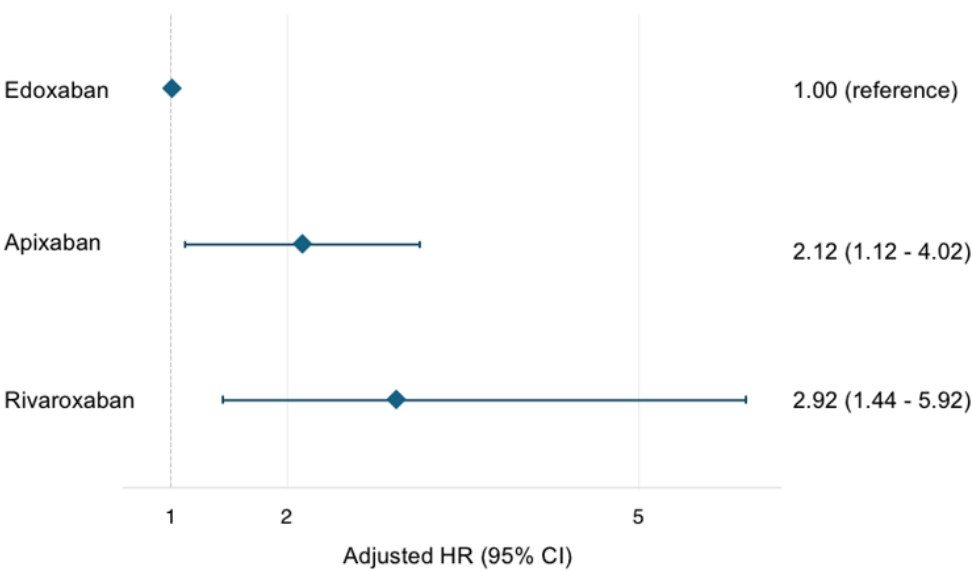


Figure 3

Multivariable analysis of factors associated with AKI risk. The forest plot displays the adjusted hazard ratios (HR) and 95% confidence interval (CI). The estimates were derived from a weighted Cox proportional hazards model that incorporated inverse probability of treatment weighting and further adjustment for potential confounders, including baseline eGFRcre, and comorbidities (CHF, HT, DM, and Cancer).

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