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Edoxaban in Asian Patients With Atrial Fibrillation

Effectiveness and Safety

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ABSTRACT

BACKGROUND It is unclear whether edoxaban shows better risk reduction of ischemic stroke, bleeding, and all-cause mortality than warfarin in Asian patients with nonvalvular atrial fibrillation (AF).

OBJECTIVES This study compared the effectiveness and safety of edoxaban with those of warfarin in a Korean population with AF.

METHODS Using the Korean National Health Insurance Service database, we included new users of edoxaban and warfarin in patients with AF from January 2014 to December 2016 (n = 4,200 on edoxaban, and n = 31,565 on warfarin) and analyzed the risk of ischemic stroke, intracranial hemorrhage (ICH), hospitalization for gastrointestinal (GI) bleeding, hospitalization for major bleeding, and all-cause death. The propensity score matching method was used to balance covariates across edoxaban and warfarin users.

RESULTS We compared a 1:3 propensity score–matched cohort of patients with AF who were new users of edoxaban and warfarin (n = 4,061 and n = 12,183, respectively). Baseline characteristics were balanced between the 2 groups (median age 72 years; median CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female)] score 3). Edoxaban users had a significantly lower risk of ischemic stroke (hazard ratio [HR]: 0.693; 95% confidence interval [CI]: 0.487 to 0.959), ICH (HR: 0.407; 95% CI: 0.182 to 0.785), hospitalization for GI bleeding (HR: 0.597; 95% CI: 0.363 to 0.930), hospitalization for major bleeding (HR: 0.532; 95% CI: 0.352 to 0.773), and all-cause death (HR: 0.716; 95% CI: 0.549 to 0.918) than warfarin users. All subgroups (age, sex, CHA_2DS_2-VASc score, renal function, edoxaban dose) showed better clinical outcomes with edoxaban than with warfarin.

CONCLUSIONS In this real-world Asian population with AF, edoxaban might be associated with reduced risk of ischemic stroke, major bleeding, and all-cause death compared with warfarin. These benefits were consistent across various high-risk subgroups. (J Am Coll Cardiol 2018;72:838–53) © 2018 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence of AF has shown a remarkable increase in the aging population (1-4). AF increases the risk of stroke by nearly 5-fold and is related to an increase in the AF-related health care burden (5). Although stroke prevention is fundamental in the management of patients with AF, a substantial proportion of these

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patients still remain undertreated with oral anticoagulants (OACs) (6–9). Recently, direct oral anticoagulants (DOACs) have shown comparable efficacy and better safety compared with warfarin in major pivotal trials and real-world data (10–16).

Most of the patients enrolled in the major clinical trials were non-Asian, and each study was underpowered to show the risks and benefits of DOAC in Asian populations for various outcomes. Several recent publications demonstrated the greater benefits associated with real-world DOAC use in an Asian population with AF (14–16). Pooled DOACs, including dabigatran, rivaroxaban, and apixaban, demonstrated comparable effectiveness and better safety, mortality, and combined endpoints compared with warfarin in a high-risk Asian population with AF (16).

SEE PAGE 854

Edoxaban, the fourth DOAC in the market prescribed as a once-daily direct oral factor Xa inhibitor, has been rapidly prescribed in non-Asian markets (17). In the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, edoxaban treatment was noninferior to warfarin treatment for stroke prevention and was consistently associated with lower rates of all types of bleeding compared with warfarin treatment (18). However, the effectiveness and safety of edoxaban in a population-based, real-world setting have not been previously reported. Therefore, we aimed to compare the effectiveness and safety between edoxaban and warfarin in Asian patients with nonvalvular AF.

METHODS

This study used data from the national health claims database established by the National Health Insurance Service (NHIS) of Korea. The NHIS is a mandatory universal health insurance service that provides comprehensive medical care coverage for up to 97% of the Korean population (~50 million people). The remaining 3% of the Korean population with low income is covered by the Medical Aid program, which has been incorporated into a single NHIS database. The database includes each patient's demographic information, diagnoses, procedures, and prescription records in inpatient and outpatient services. Diagnoses are recorded using the International Classification of Disease-10th Revision-Clinical Modification (ICD-10-CM) codes. Although the original identification number of each patient in the NHIS is encrypted to protect the privacy of the patient using a consistent encrypting procedure, it was possible to follow all the claims belonging to the same patient continuously. This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-1704-003-840).

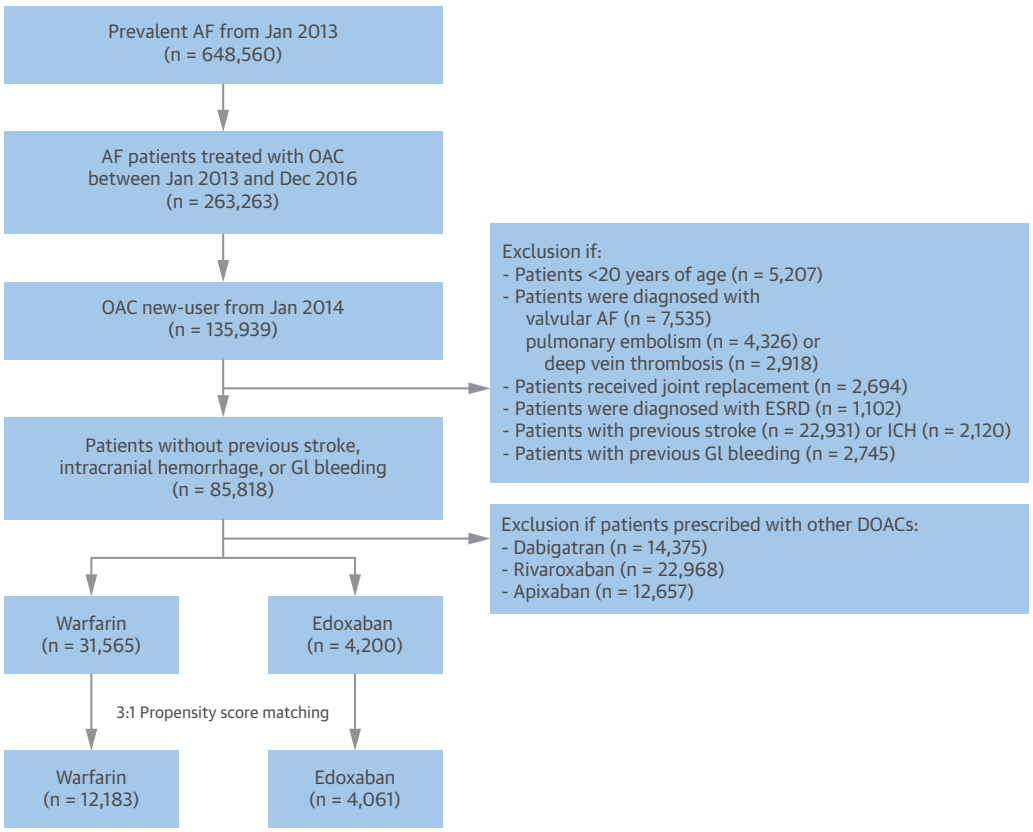
STUDY POPULATION. We identified patients who were diagnosed with AF (ICD-10-CM codes I480-484, I489) during the identification period (from January 2013 to December 2016). We excluded patients who had mitral stenosis or pre-existing mechanical heart valves. We also excluded those who had previous OAC prescriptions between January 2013 and December 2013 to analyze only those who were new warfarin and edoxaban users. We excluded patients with diagnoses of deep vein thrombosis, pulmonary embolism, or joint replacement, which could be a potential alternative indication for OAC treatment. Patients with end-stage renal disease were also excluded. In this study, patients were censored at the discontinuation of the index treatment. Therefore, all the patients in both the warfarin and edoxaban groups were prescribed the index drug from the beginning to the end of the study. Finally, we only included those who received OACs for the primary prevention of ischemic stroke during the study (from January 2014 to December 2016) and those without a history of ischemic stroke, intracranial hemorrhage (ICH), and gastrointestinal (GI) bleeding events. We focused the analysis on primary prevention; therefore, we excluded those with previous ischemic stroke, ICH, or GI bleeding events, as in our previous studies (16,19). The detailed patient enrollment flow is described in **Figure 1**. The date of the first edoxaban or warfarin prescription during the study was defined as the index date.

PATIENT CHARACTERISTICS. We obtained patient baseline characteristics, including age, sex, and comorbidities, such as hypertension, diabetes, dyslipidemia, congestive heart failure, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), and history of myocardial infarction (MI). Online Table 1 shows the definition of comorbidities in detail. We also calculated the CHA_2DS_2-VASc score by assigning 1 point each for age between 65 and 74 years, for female sex, for the presence of hypertension, diabetes, congestive heart failure, and vascular disease (previous MI or PAD), and adding 2 points each for age 75 years or older or a history of stroke, transient ischemic attack, or systemic thromboembolism (20). The $CHADS_2$ score was

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ASD = absolute standardized difference
CI = confidence interval
COPD = chronic obstructive pulmonary disease
CrCl = creatinine clearance
DOAC = direct oral anticoagulant
GI = gastrointestinal
HDER = high-dose edoxaban regimen
HR = hazard ratio
ICH = intracranial hemorrhage
IPW = inverse probability weighting
MI = myocardial infarction
NHIS = National Health Insurance Service
OAC = oral anticoagulant
OR = odds ratio
PAD = peripheral artery disease
TTR = therapeutic range

FIGURE 1 Study Population Enrollment Flow



From a total of 135,939 new users of direct oral anticoagulants (DOACs) from January 2013, 31,565 warfarin users and 4,200 edoxaban users were included in this study. After 3:1 propensity score matching, 12,183 warfarin users and 4,061 edoxaban users were enrolled in the final analysis. AF = atrial fibrillation; ESRD = end-stage renal disease; GI = gastrointestinal; ICH = intracranial hemorrhage.

calculated, in which 2 points were assigned for a history of stroke or transient ischemic attack and 1 point each was assigned for age 75 years or older and a history of hypertension, diabetes, or recent cardiac failure (21).

STUDY OUTCOMES. We identified 6 clinical outcomes to determine the effectiveness and safety of edoxaban and warfarin as follows: ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and ischemic stroke + ICH + all-cause death. Ischemic stroke, ICH, and hospitalization for GI bleeding were defined by ICD-10-CM codes, and detailed definitions of the outcomes are described in Online Table 1. To assess the outcomes, the patients were followed up for 1 year and censored at the outcome events or at the end of the study period. The patients were censored at 1 year to balance the follow-up period between the edoxaban and warfarin cohorts.

EDOXABAN DOSE REGIMENS. For separate analyses by edoxaban dose regimens, edoxaban 60- and 30-mg groups were identified based on the initial edoxaban prescription dose regimen. In Korea, the approved product label of edoxaban is the same as the high-dose edoxaban regimen (HDER) (i.e., 60/30 mg) in the ENGAGE AF-TIMI 48 trial (18). Dose reduction to edoxaban 30 mg was permitted if any of the following characteristics were present: estimated creatinine clearance (CrCl) of 30 to 50 ml/min, a body weight of ≤60 kg, or the concomitant use of verapamil or quinidine. The baseline characteristics of the patients who received edoxaban 30 mg were different from those who received edoxaban 60 mg. To adjust for these differences in baseline characteristics, the patients who received either 60 or 30 mg were matched 1:3 with the warfarin patients based on propensity scores. Hence, the outcomes for each edoxaban dose were compared with those in the 1:3 propensity score–matched warfarin group.

SUBGROUP ANALYSES. Subgroup analyses were conducted based on age, sex, CHA_2DS_2-VASc score, and renal function. For the age subgroup analysis, patients were categorized by age of younger than 65, 65 to 74, and 75 years or older. For the CHA_2DS_2-VASc score subgroup analysis, patients were categorized into 2 groups by scores of 0 to 2 and ≥3. For the renal function subgroup analysis, patients were classified into 2 subgroups by CrCl ≤50 ml/min and >50 ml/min. We also analyzed patients by CrCl into 4 subgroups: >30 to 50 ml/min, >50 to 80 ml/min, >80 to 95 ml/min, and >95 ml/min (22). In each subgroup analysis, the statistical significance ($p < 0.1$) of the interaction between treatment in the specific subgroups was evaluated.

STATISTICAL METHODS. For the comparison between 2 treatment groups, we performed a propensity score matching analysis (23,24). The propensity of being in the edoxaban group was estimated with a logistic regression model with all covariates in our study database as follows; age, sex, CHA_2DS_2-VASc score, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, previous MI, PAD, and COPD (Online Table 2).

Each patient in edoxaban group was matched to 3 patients in the warfarin group (1:3 matching) because there were more patients who received warfarin than edoxaban. For matching, we used the greedy, nearest-neighbor method without replacement, with a caliper of 0.01 of the propensity score (23).

The balance of baseline characteristics between the edoxaban and warfarin groups was evaluated using the absolute standardized difference (ASD). An ASD of ≤0.1 (10%) indicates a negligible difference between 2 study groups in each covariate (25). When the ASD was >0.1 (10%), the covariate was included in the Cox proportional hazards regression model.

For the clinical outcome analysis, incidence rates were estimated using the total number of clinical outcomes during the follow-up period divided by 100 person-years at risk. The risk of outcomes over time for edoxaban compared with warfarin (reference) was analyzed using survival analysis, with the Kaplan-Meier method and log-rank test for univariate analysis, and Cox proportional hazards regression for multivariate analysis. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, North Carolina).

To provide complementary analyses for balancing between the 2 treatment groups, we also performed inverse probability weighting (IPW), with and without trimming, using stabilized weights calculated from the propensity scores (26,27). In trimming IPW, stabilized weights were trimmed at the 5th and 95th percentiles of the weights to reduce the impact of extremely small and large weights. The risks for 6 study outcomes of the edoxaban and warfarin groups were obtained using weighted Cox proportional hazards regression models with IPW.

SENSITIVITY ANALYSIS. A sensitivity analysis was performed with restriction of the follow-up period to 6 months because of the short follow-up duration of the edoxaban group. We also presented the analysis without restricting the follow-up period. In this analysis, patients were not censored at 6 months or 1 year after the index date. In addition, we also performed an exploratory analysis that compared the edoxaban-treated group with warfarin patients who were only enrolled after February 2016, when edoxaban was introduced to the market. Furthermore, when we explored the relative hazards concerning clinical outcomes other than all-cause death, we performed a competing risk analysis and adjusted for the competing risks of death instead of a censoring event (28).

RESULTS

BASELINE CHARACTERISTICS. A total of 35,765 patients with AF who were newly administered edoxaban (n = 4,200) and warfarin (n = 31,565) were included in the study. Before propensity score matching, patients who used edoxaban were significantly older, had higher $CHADS_2$ scores, and had a higher likelihood of heart failure and previous MI than patients who used warfarin; use of edoxaban was also higher in women than in men (**Table 1**). After 1:3 propensity score matching, a total of 16,244 patients were included in the final analysis (4,061 for edoxaban and 12,183 for warfarin) (**Figure 1**). The mean (median) age of the matched edoxaban and warfarin cohorts was 70 (72) years, and the mean (median) CHA_2DS_2-VASc score was 3.2 (3). In the matched edoxaban cohorts, 17% (n = 690) of patients were treated with warfarin previously and 56% (n = 2,267) were prescribed edoxaban 30 mg. Overall, the 2 matched cohorts were well balanced (**Table 1** and Online Figure 1). The median follow-up duration was 0.3 years (interquartile range [IQR]: 0.1 to 0.5 years) in the edoxaban cohort and 0.9 years (interquartile range: 0.9 to 0.9 years) in the warfarin cohort ($p < 0.001$).

ISCHEMIC STROKE, ICH, HOSPITALIZATION FOR GI BLEEDING, HOSPITALIZATION FOR MAJOR BLEEDING, ALL-CAUSE DEATH, AND COMPOSITE OUTCOME. During follow-up, the incidence of ischemic stroke was 3.22 per 100 person-years and 3.89 per 100

TABLE 1 Baseline Characteristics Before and After Propensity Score Matching by Treatment Group (Edoxaban vs. Warfarin)

	Before Propensity Score Matching			After Propensity Score Matching		
	Warfarin (n = 31,565)	Edoxaban (n = 4,200)	ASD	Warfarin (n = 12,183)	Edoxaban (n = 4,061)	ASD
Age, yrs						
Mean ± SD	66.3 ± 12.9	70.8 ± 10.0	0.393	70.7 ± 10.5	70.3 ± 9.8	0.033
Median (IQR)	68 (58–76)	72 (65–78)		72 (64–78)	72 (65–77)	
<65	13,304 (42.2)	992 (23.6)		3,156 (25.9)	992 (24.4)	
65–74	8,957 (28.4)	1,606 (38.2)		4,386 (36.0)	1,602 (39.5)	
≥75	9,304 (29.5)	1,602 (38.1)		4,641 (38.1)	1,467 (36.1)	
Men	1,9385 (61.4)	2,271 (54.1)	0.149	6,889 (56.6)	2,247 (55.3)	0.024
CHA_2DS_2-VASc score						
Mean ± SD	3.27 ± 1.97	3.24 ± 1.62	0.014	3.25 ± 1.72	3.22 ± 1.63	0.017
Median (IQR)	3 (2-5)	3 (2-4)		3 (2-4)	3 (2-4)	
0–1	6,479 (20.5)	561 (13.4)		1,929 (15.8)	559 (13.8)	
2–3	11,533 (36.5)	1,885 (44.9)		5,057 (41.5)	1,828 (45.0)	
≥4	13,553 (42.9)	1,754 (41.8)		5,197 (42.7)	1,674 (41.2)	
$CHADS_2$ score						
Mean ± SD	1.82 ± 1.33	1.63 ± 1.16	0.154	1.72 ± 1.22	1.62 ± 1.17	0.079
Median (IQR)	2 (1-3)	2 (1-2)		2 (1-2)	2 (1-2)	
Hypertension	21,569 (68.3)	2,824 (67.2)	0.023	8,517 (69.9)	2,735 (67.4)	0.055
Diabetes mellitus	6,590 (20.9)	845 (20.1)	0.019	2,443 (20.1)	831 (20.5)	0.010
Dyslipidemia	11,783 (37.3)	1,660 (39.5)	0.045	4,793 (39.3)	1,602 (39.5)	0.002
Heart failure	12,246 (38.8)	948 (22.6)	0.357	2,970 (24.4)	948 (23.3)	0.024
Previous MI	1,421 (4.5)	97 (2.3)	0.121	239 (2.0)	97 (2.4)	0.029
PAD	4,923 (15.6)	710 (16.9)	0.035	1,815 (14.9)	677 (16.7)	0.049
COPD	6,590 (20.9)	748 (17.8)	0.078	2,080 (17.1)	736 (18.1)	0.028

Values are n (%), unless otherwise indicated.

ASD = absolute standardized difference; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); COPD = chronic obstructive pulmonary disease; IQR = interquartile range; MI = myocardial infarction; PAD = peripheral artery disease.

person-years for edoxaban and warfarin, respectively (Online Table 3). Patients using edoxaban had a significantly lower risk of ischemic stroke than those using warfarin (hazard ratio [HR]: 0.693; 95% confidence interval [CI]: 0.487 to 0.959; p = 0.033) (**Central Illustration**). The incidence of ICH in patients who used edoxaban and in those who used warfarin was 0.66 per 100 person-years and 1.59 per 100 person-years, respectively. The incidence rates of hospitalization for GI bleeding were 1.65 per 100 person-years and 2.02 per 100 person-years for edoxaban and warfarin, respectively, and those of hospitalization for major bleeding were 2.32 per 100 person-years and 3.56 per 100 person-years for edoxaban and warfarin, respectively. Thus, edoxaban was associated with a 60% lower risk of ICH (HR: 0.407; 95% CI: 0.182 to 0.785; p = 0.014), a 40% risk reduction in hospitalization for GI bleeding (HR: 0.597; 95% CI: 0.363 to 0.930; p = 0.030), and a 47% risk reduction in hospitalization for major bleeding compared with warfarin (HR: 0.532; 95% CI: 0.352 to 0.773; p = 0.001).

The incidence rates of all-cause death were 5.59 per 100 person-years and 6.63 per 100 person-years for edoxaban and warfarin, respectively, and the rates for the composite outcome (ischemic stroke + ICH + all-cause death) for patients who used edoxaban and warfarin were 8.9 per 100 person-years and 11.2 per 100 person-years, respectively. Edoxaban was associated with a 28% lower risk of all-cause death than warfarin (HR: 0.716; 95% CI: 0.549 to 0.918; p = 0.010). Edoxaban showed better outcomes than warfarin for the composite outcome of ischemic stroke + ICH + all-cause death (HR: 0.667; 95% CI: 0.542 to 0.812; p < 0.001). Detailed data for the number of events and incidence rates according to treatment are summarized in Online Table 3. The cumulative incidence curves for the 6 clinical outcomes are shown in **Figure 2**.

In Online Table 4, the edoxaban and warfarin groups were well balanced in all characteristics (all ASDs of <0.1) after propensity score weighting. In Online Figure 2, we summarize the HRs of the study outcomes for edoxaban in comparison with warfarin by propensity score matching and IPW, with and without trimming. Using the IPW Cox model, edoxaban was associated with better outcomes compared with warfarin, with similar HRs for all 6 outcomes as was seen in the propensity score matching analyses. In addition, trimming individuals with extreme propensity scores from IPW also showed similar results.

In addition, a sensitivity analysis was performed to adjust for the differences in the follow-up duration and period between the 2 groups; HR trends for all clinical outcomes were similar to the 1-year follow-up results (Online Table 5). The results were also consistent when they were adjusted for the competing risks of death in the total study population (Online Table 6).

OUTCOMES ACCORDING TO EDOXABAN DOSE REGIMENS. Patients on edoxaban 30 mg were older, and more were women. They had higher CHA_2DS_2-VASc scores, and more heart failure and COPD compared with those on edoxaban 60 mg (Online Table 7). We matched each edoxaban group (60 and 30 mg) with a warfarin group by propensity score. After 1:3 propensity score matching, the matched cohorts were well balanced (**Table 2**).

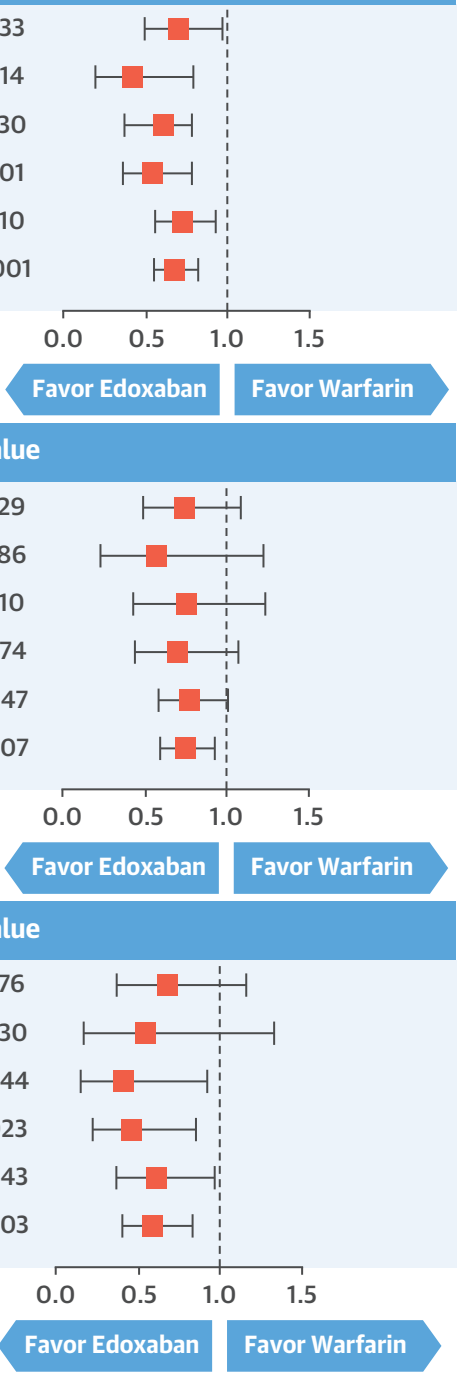
The cumulative incidence of the 6 clinical outcomes are shown in **Figures 3 and 4**. Compared with the matched warfarin group, patients on edoxaban 60 mg showed lower crude incidence rates for all 6 outcomes (Online Table 3, **Figure 3**). Patients on

CENTRAL ILLUSTRATION **Edoxaban Versus Warfarin: Hazard Ratios of 6 Study Outcomes**

Edoxaban, Total vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.693 (0.487-0.959)	0.033
Intracranial hemorrhage (ICH)	0.407 (0.182-0.785)	0.014
Hospitalization for GI bleeding	0.597 (0.363-0.930)	0.030
Hospitalization for major bleeding	0.532 (0.352-0.773)	0.001
All-cause death	0.716 (0.549-0.918)	0.010
Ischemic stroke + ICH + all-cause death	0.667 (0.542-0.812)	<0.001

Edoxaban 30 mg vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.733 (0.481-1.076)	0.129
ICH	0.565 (0.217-1.215)	0.186
Hospitalization for GI bleeding	0.744 (0.421-1.228)	0.110
Hospitalization for major bleeding	0.693 (0.430-1.062)	0.274
All-cause death	0.764 (0.575-0.997)	0.047
Ischemic stroke + ICH + all-cause death	0.737 (0.585-0.917)	0.007

Edoxaban 60 mg vs. Warfarin	HR (95% CI)	p Value
Ischemic stroke	0.669 (0.356-1.153)	0.176
ICH	0.532 (0.159-1.326)	0.230
Hospitalization for GI bleeding	0.402 (0.140-0.913)	0.044
Hospitalization for major bleeding	0.452 (0.211-0.847)	0.023
All-cause death	0.603 (0.356-0.959)	0.043
Ischemic stroke + ICH + all-cause death	0.580 (0.394-0.825)	0.003



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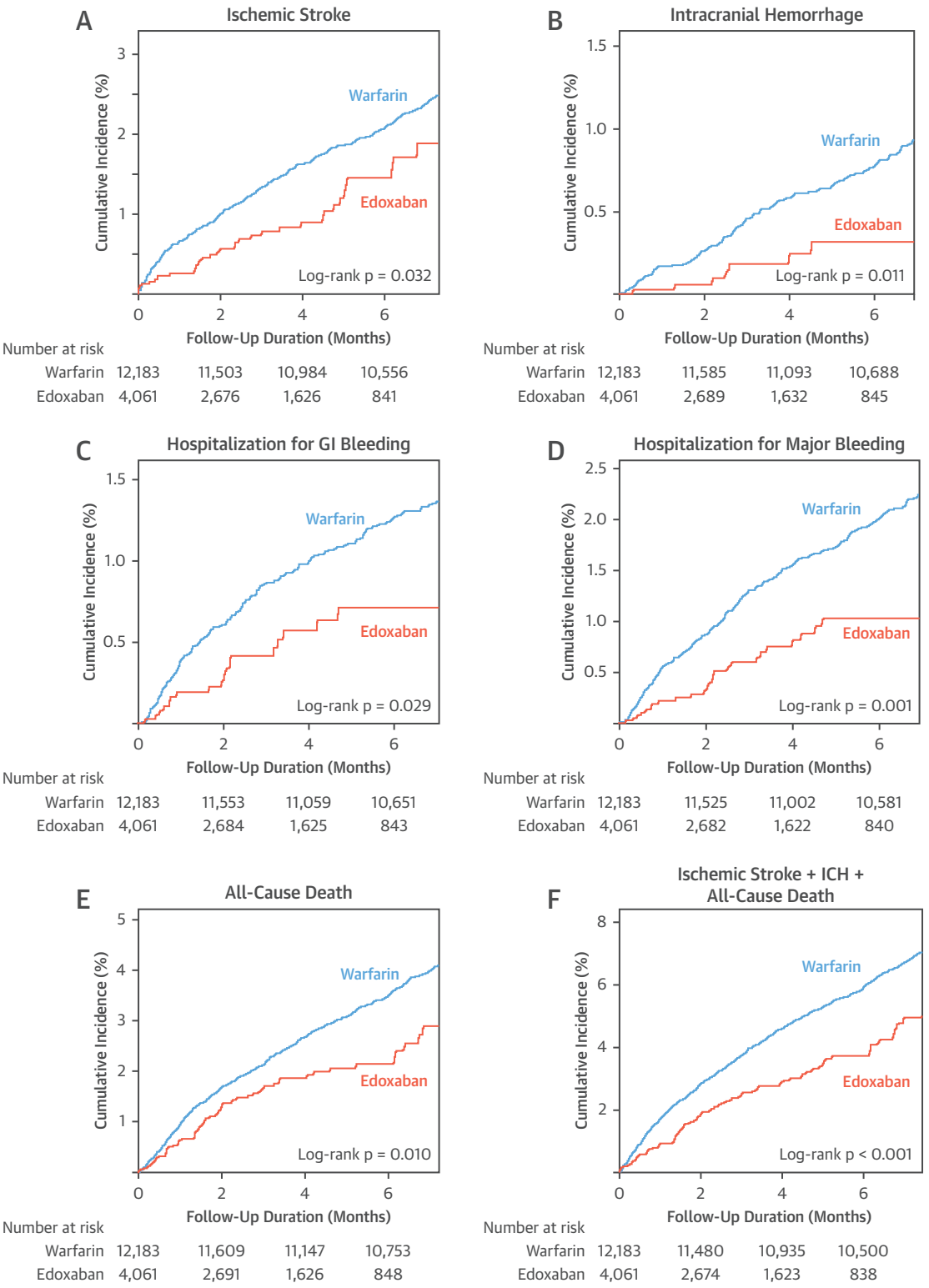
Compared with warfarin user as the reference, edoxaban was associated with a 31%, 59%, and 28% risk reduction in ischemic stroke, intracranial hemorrhage (ICH), and all-cause death, respectively. Edoxaban users had a significantly lower risk of composite outcome of ischemic stroke + ICH + all-cause death (hazard ratio [HR]: 0.667; 95% confidence interval [CI]: 0.542 to 0.812; $p < 0.001$). Edoxaban was associated with a 40% and 47% risk reduction in hospitalization for gastrointestinal (GI) bleeding and hospitalization for major bleeding, respectively. The benefit of edoxaban compared with that of warfarin was consistent across both dose regimens.

FIGURE 2 Cumulative Incidence of 6 Study Outcomes in Edoxaban and Warfarin Groups



Compared with warfarin, edoxaban carried a significantly lower risk for ischemic stroke **(A)**, ICH **(B)**, hospitalization for GI bleeding **(C)**, hospitalization for major bleeding **(D)**, all-cause death **(E)**, and composite outcome of ischemic stroke + ICH + all-cause death **(F)**. Abbreviations as in Figure 1.

edoxaban 60 mg tended to be associated with a lower risk of ischemic stroke and ICH, but this was nonstatistically significant (**Central Illustration**). The edoxaban group had a significantly lower risk of hospitalization for GI bleeding (HR: 0.402; 95% CI: 0.140 to 0.913; p = 0.044), hospitalization for major bleeding (HR: 0.452; 95% CI: 0.211 to 0.847; p = 0.023), all-cause death (HR: 0.603; 95% CI: 0.356 to 0.959; p = 0.043), and the composite outcome of ischemic stroke + ICH + all-cause death (HR: 0.580; 95% CI: 0.394 to 0.825; p = 0.003) (**Central Illustration**). Compared with matched warfarin, edoxaban 30 mg users showed consistently lower incidence rates for all 6 outcomes (Online Table 3, **Figure 4**) and tended to be have a lower risk for all 6 outcomes, but this was nonstatistically significant except for all-cause death and composite outcome (**Central Illustration**).

SUBGROUP ANALYSES. The benefit of edoxaban compared with warfarin was consistent across all of the examined subgroups (**Figures 5 and 6**). There were no significant interactions with respect to ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome between treatment and all subgroups, except for ischemic stroke in the subgroup stratified by CHA_2DS_2-VASc score.

Older adult patients (75 years or older). The results for all 6 outcomes of these were consistent across the 3 age groups. Among 6,108 (37.6% of the total) patients aged 75 years or older (4,641 warfarin users and 1,467 edoxaban users), the edoxaban group showed a consistently lower crude incidence rate in ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome of ischemic stroke + ICH + all-cause death than the warfarin group (Online Table 8). Older adult edoxaban users showed better outcomes for ICH, hospitalization for major bleeding, all-cause death, and the composite outcome of ischemic stroke + ICH + all-cause death, with a trend for lower risks for ischemic stroke and hospitalization for GI bleeding (**Figures 5 and 6**, Online Table 8).

Patients with high CHA_2DS_2-VASc scores (≥3 points). There was no significant interaction between treatment and CHA_2DS_2-VASc score, except for ischemic stroke (**Figures 5 and 6**). For ischemic stroke, the benefit of edoxaban compared with warfarin showed significant interaction between patients with CHA_2DS_2-VASc scores ≥3 (HR: 0.601; 95% CI: 0.402 to 0.866) and <3 (HR: 1.565; 95% CI: 0.687 to 3.241) (p interaction = 0.042). In patients with CHA_2DS_2-VASc scores ≥3 (n = 10,499; 64.6% of total population), the edoxaban group showed a lower incidence of all 6 outcomes than the warfarin group (Online Table 8). Edoxaban significantly reduced the risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, and the composite outcome of ischemic stroke + ICH + all-cause death compared with warfarin among patients with CHA_2DS_2-VASc scores ≥3, whereas edoxaban showed comparable results to warfarin in patients with CHA_2DS_2-VASc scores <3 (**Figures 5 and 6**).

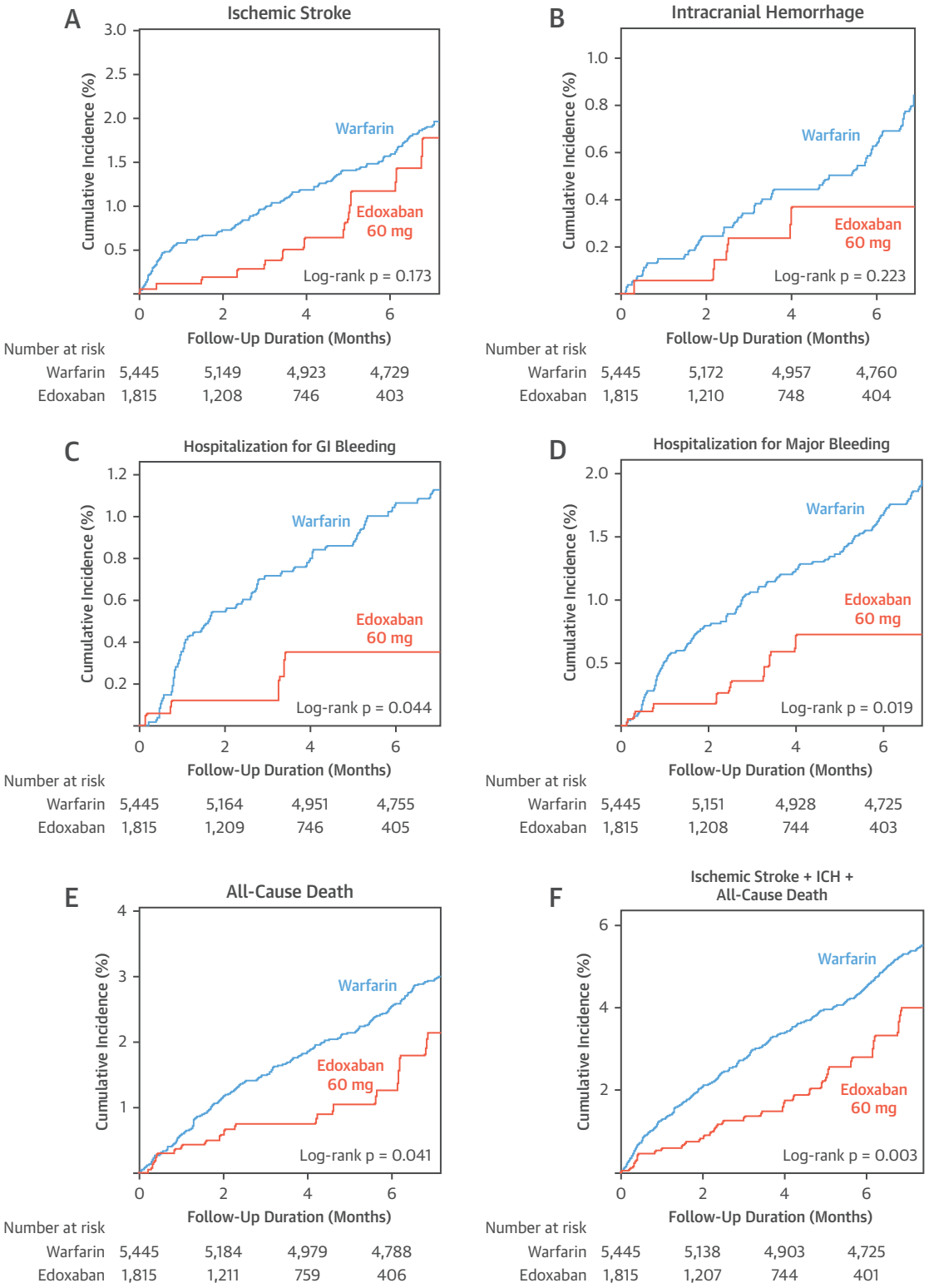
Patients with renal dysfunction (CrCl ≤50 ml/min). Among patients with available CrCl values (75% of the total population), 684 (5.6%) patients had moderate renal dysfunction (CrCl ≤ 50 ml/min). Edoxaban users with renal dysfunction (CrCl ≤50 ml/min) showed nonsignificant results for ischemic stroke (HR: 0.918; 95% CI: 0.141 to 3.430), hospitalization for GI bleeding (HR: 0.960; 95% CI: 0.148 to 3.566), all-cause death (HR: 0.707; 95% CI: 0.209 to 1.798), and the composite outcome (HR: 0.611; 95% CI: 0.211 to 1.409) compared with warfarin users, although point estimates suggested trends toward better outcomes (**Figures 5 and 6**).

TABLE 2 Baseline Characteristics of Propensity Matched Population by Each Edoxaban Dose Regimens

	Edoxaban 30 mg vs. Warfarin			Edoxaban 60 mg vs. Warfarin		
	Warfarin (n = 7,113)	Edoxaban 30 mg (n = 2,371)	ASD	Warfarin (n = 5,505)	Edoxaban 60 mg (n = 1,835)	ASD
Age, yrs						
Mean ± SD	74.1 ± 9.8	73.8 ± 9.1	0.031	66.8 ± 10.6	66.7 ± 9.6	0.009
Median (IQR)	75 (68–81)	75 (69–80)		68 (61–74)	68 (61–74)	
<65	1,021 (14.5)	317 (13.4)		2,100 (38.2)	681 (37.1)	
65–74	2,363 (33.2)	843 (35.2)		2,136 (38.8)	779 (42.5)	
≥75	3,718 (52.3)	1,220 (51.5)		1,269 (23.1)	375 (20.4)	
Men	3,233 (45.5)	1,076 (45.4)	0.001	3,607 (65.5)	1,210 (65.9)	0.009
CHA_2DS_2-VASc score						
Mean ± SD	3.66 ± 1.69	3.61 ± 1.60	0.033	2.77 ± 1.61	2.76 ± 1.52	0.014
Median (IQR)	4 (2-5)	4 (2-5)		3 (2-4)	3 (2-4)	
0–1	678 (9.5)	203 (8.6)		1,149 (20.9)	360 (19.6)	
2–3	2,665 (37.5)	942 (39.7)		2,705 (49.1)	947 (51.6)	
≥4	3,770 (53.0)	1,226 (51.7)		1,651 (30.0)	528 (28.8)	
$CHADS_2$ score						
Mean ± SD	1.87 ± 1.24	1.79 ± 1.2	0.065	1.55 ± 1.17	1.42 ± 1.08	0.117
Median (IQR)	2 (1-3)	2 (1-2)		1 (1-2)	1 (1-2)	
Hypertension	4,798 (67.5)	1,569 (66.2)	0.027	3,944 (71.6)	1,264 (68.9)	0.060
Diabetes mellitus	1,429 (20.1)	465 (19.6)	0.012	1,125 (20.4)	385 (21.0)	0.013
Dyslipidemia	2,562 (36.0)	878 (37.0)	0.021	2,337 (42.5)	786 (42.8)	0.008
Heart failure	1,839 (25.8)	590 (24.9)	0.022	1,113 (20.2)	365 (19.9)	0.008
Previous MI	167 (2.4)	60 (2.5)	0.012	106 (1.9)	37 (2.0)	0.007
PAD	1,200 (16.9)	426 (17.9)	0.029	692 (12.6)	283 (15.4)	0.082
COPD	1,420 (20.1)	485 (20.5)	0.009	706 (12.8)	266 (14.5)	0.049

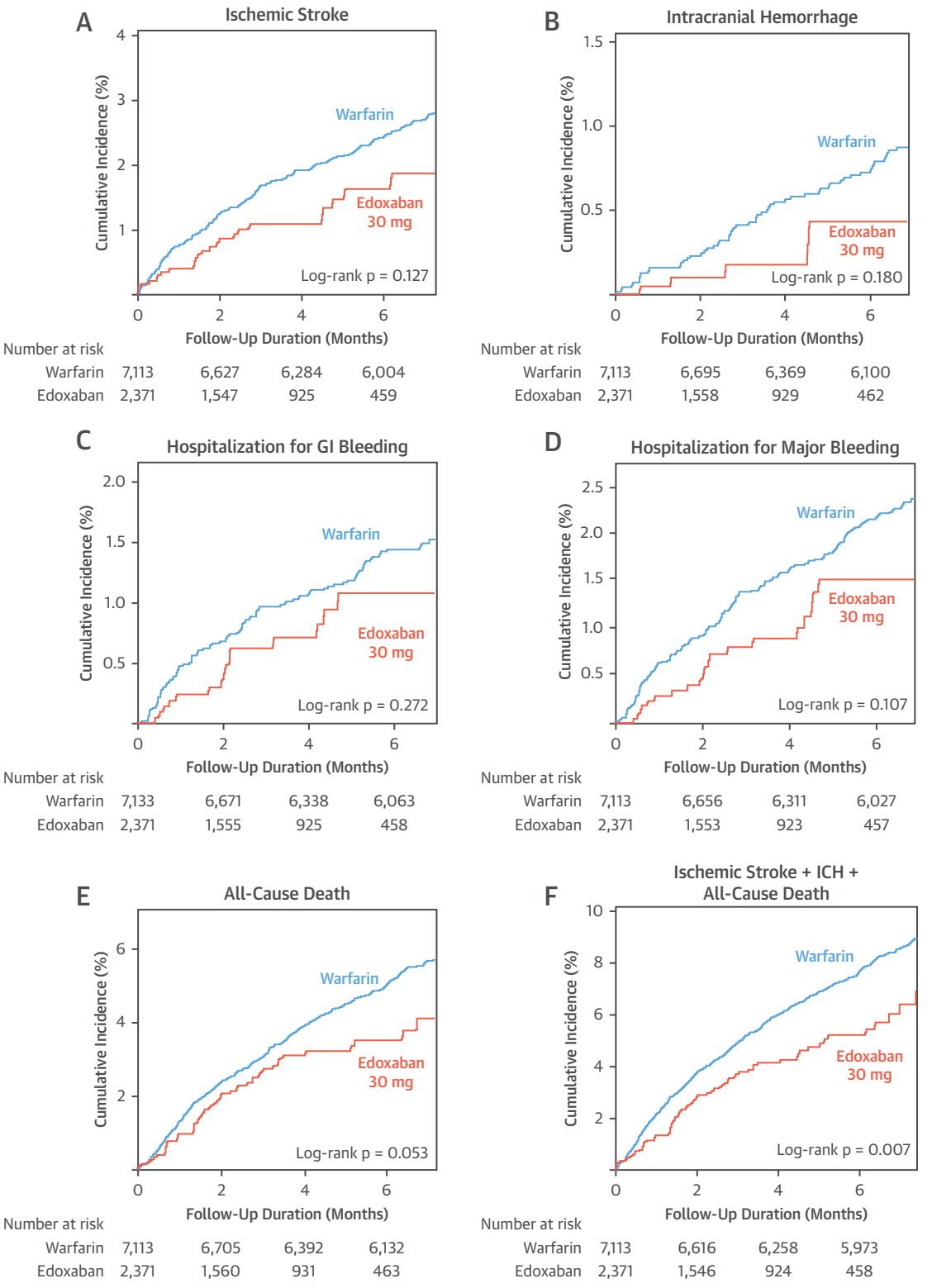
Values as n (%), unless otherwise indicated.
Abbreviations as in Table 1.

FIGURE 3 Cumulative Incidence of 6 Study Outcomes in Edoxaban 60 mg and Matched Warfarin Groups



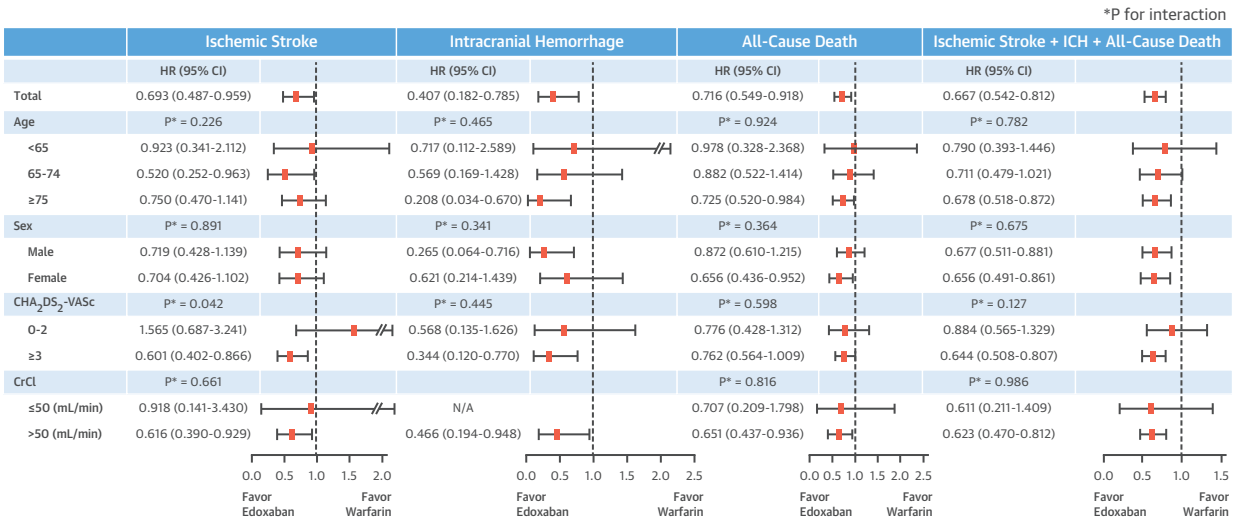
Cumulative incidence of 6 study outcomes in edoxaban 60 mg and matched warfarin groups. **(A)** Ischemic stroke, **(B)** ICH, **(C)** hospitalization for GI bleeding, **(D)** hospitalization for major bleeding, **(E)** all-cause death, and **(F)** composite outcome of ischemic stroke + ICH + all-cause death. Abbreviations as in Figure 1.

FIGURE 4 **Cumulative Incidence of 6 Study Outcomes in Edoxaban 30 mg and Matched Warfarin Groups**



Cumulative incidence of 6 study outcomes in edoxaban 30 mg and matched warfarin groups. **(A)** Ischemic stroke, **(B)** ICH, **(C)** hospitalization for GI bleeding, **(D)** hospitalization for major bleeding, **(E)** all-cause death, and **(F)** composite outcome of ischemic stroke + ICH + all-cause death. Abbreviations as in Figure 1.

FIGURE 5 HR of Ischemic Stroke, ICH, All-Cause Death, and Composite Outcome According to Subgroups in Edoxaban and Warfarin Groups



The benefit of edoxaban compared with that of warfarin was consistent across almost all subgroups examined, especially in high-risk patients such older adults (75 years or older) and those with higher CHA_2DS_2-VASc scores (≥3). *p for interaction. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism, vascular disease, age 65–74 years, sex category (female); CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; other abbreviation as in Figure 1.

Patients with high normal renal function (CrCl >95 ml/min). We classified patients according to renal function into 4 groups with CrCl values of 30 to 50, >50 to 80, >80 to 95, and >95 ml/min. There was no significant interaction of ischemic stroke with edoxaban versus warfarin across renal subgroups by CrCl strata. The incidence of ischemic stroke of edoxaban with high normal renal function was lower than that of warfarin without statistical significance (2.20 per 100 person-years vs. 3.04 per 100 person-years). Edoxaban users with high normal renal function (CrCl >95 ml/min) showed nonsignificant results for ICH and the composite outcome compared with warfarin users (Figure 7).

The results of the subgroup analyses for edoxaban 60 mg and 30 mg are presented in Online Tables 9 to 12.

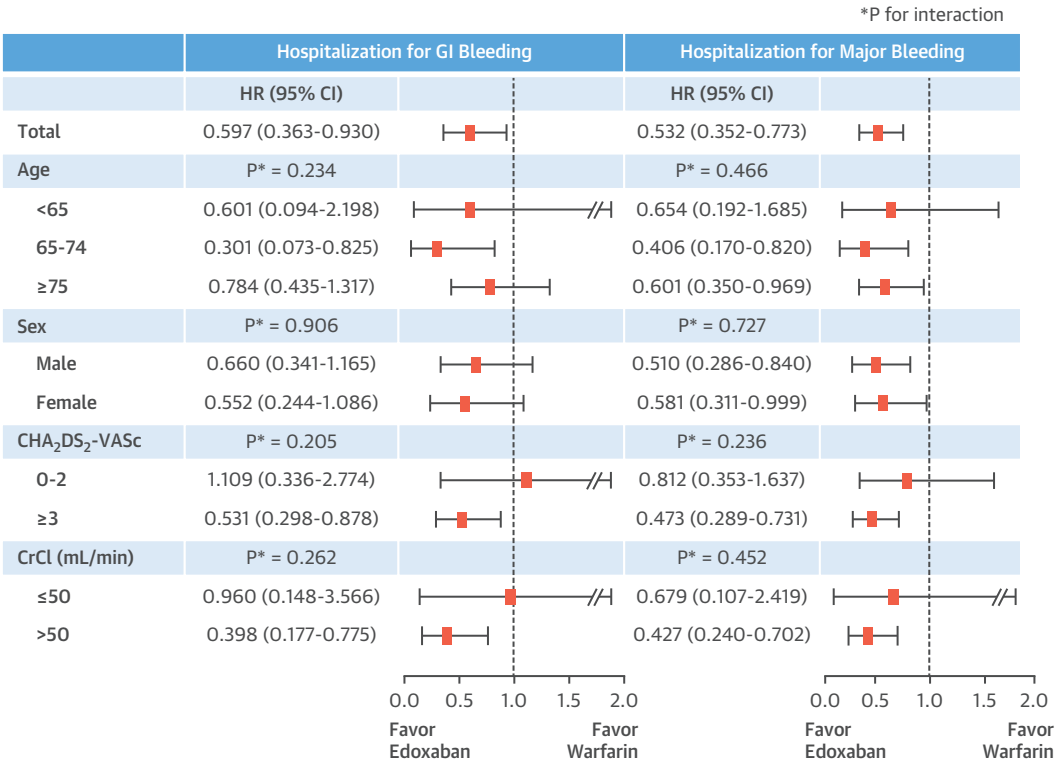
DISCUSSION

This was the first real-world, population-based study to investigate the effectiveness and safety of edoxaban with a specific focus on Asian patients with nonvalvular AF. No study has previously reported the effectiveness and safety of edoxaban compared with those of warfarin in a population-based cohort. Our study showed that edoxaban was associated with a lower risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome of ischemic stroke + ICH + all-cause death than warfarin.

In the ENGAGE AF-TIMI 48 trial, HDER (60-/30-mg arm) showed better outcomes for stroke or systemic embolism events than the well-managed warfarin group, whereas HDER showed almost a neutral risk compared with warfarin with respect to ischemic stroke only (HR: 1.00; 95% CI: 0.83 to 1.19) (18). In this study, we found that edoxaban showed better outcomes for ischemic stroke and all-cause death than warfarin in Asian patients with AF.

Recently, a Taiwanese nationwide population-based study demonstrated that rivaroxaban and dabigatran were associated with reduced risk for ischemic stroke, ICH, and all-cause death compared with warfarin (15). The Korean nationwide population-based study also showed the benefit of pooled DOACs, including rivaroxaban, dabigatran, and apixaban compared with that of warfarin in patients with AF (16). In the ENGAGE AF-TIMI 48 trial, there were only 1,128 patients from the Asian Pacific and South Africa (16.0%) in the HDER group (18). A recent metaanalysis evaluated a total of 646 Asian patients prescribed edoxaban 60 mg and 653 Asian patients prescribed edoxaban 30 mg (29). To the best of our knowledge, the present study reported the largest cohort of Asian patients with AF (n = 4,061) who were prescribed edoxaban and was

FIGURE 6 **HRs of Hospitalization for GI Bleeding and Hospitalization for Major Bleeding According to Subgroups in Edoxaban and Warfarin Groups**



The benefit of edoxaban compared with that of warfarin was consistent across all subgroups examined. *p for interaction. Abbreviations as in Figures 1 and 5.

the first population-based study on the effectiveness and safety of edoxaban.

In the HDER group in the ENGAGE AF-TIMI 48 trial, edoxaban showed a reduction in major bleeding (HR: 0.80; 95% CI: 0.71 to 0.92) compared with warfarin, which was mainly driven by a reduction in intracranial bleeding (HR: 0.47; 95% CI: 0.34 to 0.63) (18). This better safety result was consistently observed in our study. Although the HDER group in the ENGAGE AF-TIMI 48 trial increased the risk of GI bleeding compared with warfarin (HR: 1.23; 95% CI: 1.02 to 1.50), the risk of hospitalization for GI bleeding was significantly lower in the edoxaban group than the warfarin group in present study. In a subgroup metaanalysis of pivotal DOAC clinical trials, standard dose DOACs were associated with an increased risk of GI bleeding in non-Asian patients but not among Asian patients (odds ratio: 1.44; 95% CI: 1.12 to 1.85 for non-Asian; odds ratio: 0.79; 95% CI: 0.48 to 1.32 for Asian patients; p interaction = 0.041) (29).

In the ENGAGE AF-TIMI 48 trial, the risk of ischemic stroke tended to increase with edoxaban treatment compared with that of warfarin in patients with CrCl >95 ml/min (HR: 1.47; 95% CI: 0.91 to 2.39; p = 0.12) (22). There was a significant inverse relationship between the median trough edoxaban concentration and CrCl, with the most apparent decrease in concentrations that occurred in the CrCl range of 90 to 110 ml/min (22). Based on these findings, the current U.S. Food and Drug Administration labeling for edoxaban restricts its use in patients with a CrCl >95 ml/min (30). However, we found that the risk of ischemic stroke did not increase in patients with a high normal CrCl (≥95 ml/min), and there was no significant interaction between renal function and treatment.

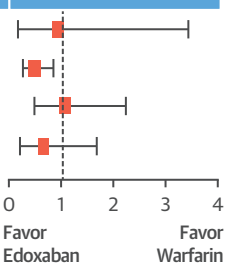
There might be several explanations for our results. First, this study included only Asian patients with AF; therefore, there might be racial differences with the ENGAGE AF-TIMI 48 trial population. Second, Asian patients with AF have a smaller body size than Western patients with AF; thus, the plasma concentrations of edoxaban might not decrease in those with high CrCl levels. Edoxaban plasma

FIGURE 7 HRs of Ischemic Stroke, ICH, and Composite Outcome According to CrCl Subgroups

*P for interaction

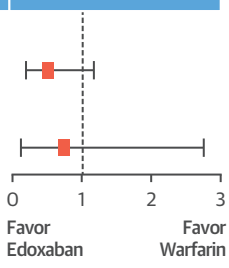
A

Ischemic Stroke				
	No. of events (IR, %/year)		HR (95% CI)	P*
CrCl (mL/min)	Edoxaban	Warfarin		
30-50	2 (5.39)	21 (4.85)	0.918 (0.141-3.430)	0.457
>50-80	12 (2.25)	143 (3.77)	0.474 (0.246-0.830)	
>80-95	8 (3.69)	49 (2.96)	1.065 (0.454-2.217)	
>95	4 (2.20)	40 (3.04)	0.644 (0.189-1.668)	



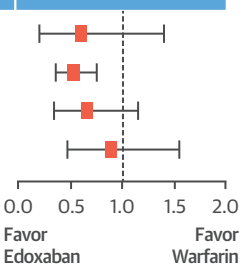
B

Intracranial Hemorrhage				
	No. of events (IR, %/year)		HR (95% CI)	P*
CrCl (mL/min)	Edoxaban	Warfarin		
30-50	0 (0.0)	11 (2.50)	N/A	N/A
>50-80	5 (0.94)	67 (1.75)	0.502 (0.173-1.156)	
>80-95	0 (0.0)	21 (1.26)	N/A	
>95	2 (1.09)	16 (1.21)	0.730 (0.112-2.745)	



C

Ischemic Stroke + ICH + All-Cause Death				
	No. of events (IR, %/year)		HR (95% CI)	P*
CrCl (mL/min)	Edoxaban	Warfarin		
30-50	5 (13.4)	73 (16.9)	0.611 (0.211-1.409)	0.531
>50-80	33 (6.19)	359 (9.52)	0.537 (0.366-0.762)	
>80-95	13 (5.99)	122 (7.39)	0.669 (0.355-1.161)	
>95	14 (7.71)	97 (7.40)	0.900 (0.483-1.560)	



There was no significant interaction in ischemic stroke **(A)** with edoxaban versus warfarin across renal subgroups by CrCl strata. Edoxaban users with high normal renal function (CrCl >95 ml/min) showed nonsignificant results for ICH **(B)** and composite outcome **(C)** compared with warfarin users. *p for interaction. IR = incidence rate; other abbreviations as in Figures 1 and 5.

concentrations were associated with anti-factor Xa activity and outcomes, including stroke and bleeding, and pharmacokinetic studies demonstrated lower drug concentrations in patients with higher CrCl (>80 ml/min) (31,32). However, these studies were not based on Asian patients as the majority of the study population, and absolute edoxaban concentration thresholds that predicted effective stroke prevention were not defined. Third, warfarin control in the Asian population with AF was usually poorer than that in the Western population with AF (33–35). The median time in the therapeutic range (TTR) was 68.4% in the warfarin group of the ENGAGE AF-TIMI 48 trial, and warfarin was also well-

managed with a median TTR of 68.2% in patients with CrCl >95 ml/min. Although we could not evaluate TTR of our warfarin group because of the major limitations of the national claim database, lower TTR was consistently reported in the Asian population than that in the non-Asian population in clinical trials and a recent global AF registry (33-35). A recent analysis of Korean patients with AF enrolled in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial reported a TTR of 55%, which was lower than that of patients in Western countries (36). We speculated that TTR in the real-world data would be lower than that in major clinical trials.

In the present study, 56% of patients on edoxaban were prescribed the 30-mg dose. Patients received both edoxaban 60 and 30 mg showed trends toward better outcomes for most clinical events compared with warfarin. Our results demonstrated the effectiveness and safety of edoxaban 60 mg, and this was consistent with a previous meta-analysis that reported that regular doses of DOACs were effective and safe enough in Asian patients, perhaps even more than among the non-Asian population (29). In the ENGAGE AF-TIMI 48 trial, the low-dose edoxaban regimen (30/15 mg) was associated with an unfavorable trend in the risk for ischemic stroke or systemic embolism compared with warfarin (HR: 1.14; 95% CI: 1.19 to 1.67; $p < 0.001$) (18). Based on these results, only the HDER was approved for stroke prevention in patients with nonvalvular AF (30,37-39). Therefore, edoxaban 30 mg use is only recommended in patients who have at least 1 dose reduction criteria according to the drug label, that is, renal impairment (CrCl 30 to 50 ml/min), body weight of ≤60 kg, or concomitant use of a potent phosphorylated glycoprotein inhibitor (18,30,37).

By reclassifying the study patients prescribed 30-mg edoxaban enrolled in the ENGAGE AF-TIMI 48 trial according to the current drug label, 74.6% of patients were prescribed off-labeled 30 mg edoxaban. In this population, both non-Asian and Asian patients showed an unfavorable outcome for ischemic stroke (29). In our study, 44% of patients prescribed 30-mg edoxaban did not meet the dose reduction criteria, which might have affected the outcomes of our study. However, it was unclear whether 30 mg edoxaban had enough potency to reduce the risk of ischemic stroke in the Asian population.

STUDY LIMITATIONS. First, although patients with edoxaban and warfarin seem to be matched well by the propensity score model, there might be residual confounding factors. We could not adjust for measurable data not accessible in the NHIS database, as well as some unmeasurable confounding factors such as physician's decision, which could not be propensity matched in this study. Second, we could not evaluate TTR in the warfarin group. The lack of data regarding TTR in the warfarin group was the inherent limitation of many real-world studies comparing DOACs and warfarin claims databases. Previous large real-world studies also described this as a limitation, as in our study (15,16). Poor TTR control in the warfarin group was observed in previous Asian studies, and it was possible that more favorable results of edoxaban with regard to ischemic stroke were partially caused by inadequate anticoagulation of warfarin (33-35). However, this could not explain the benefit of DOACs in reducing the risk of ICH compared with warfarin. Again, poor TTR control was closer to the real-world clinical practice in Asian patients with AF. Third, patients who had a history of ischemic stroke, ICH, or GI bleeding were excluded in this study. Therefore, the results of our study could not be extrapolated to those with previous stroke, ICH, or GI bleeding. Fourth, the cause of death could not be verified in this study; therefore, we could we not provide the HRs of cardiovascular and noncardiovascular death. The inherent limitation of the claims database would make it difficult to precisely analyze the cause of death. In accordance with many studies based on real-world databases, we only reported the results of all-cause death as 1 of the relevant hard endpoints (11,15,40,41). However, the substantial treatment benefit of edoxaban on all-cause death might include both cardiovascular and noncardiovascular death, and the benefit on noncardiovascular death could be interpreted as a signal of residual confounding in the propensity score–matched populations. Fifth, the follow-up period for edoxaban administration in our study was short because of the more recent introduction of the drug. The shorter follow-up duration of the edoxaban group than the warfarin group and the different enrollment periods of the 2 treatments were additional limitations of this study. Finally, concomitant use of P-glycoprotein inducers and/or inhibitors or antiplatelet agents that could affect effectiveness and safety of edoxaban were not analyzed in this study. A detailed drug–drug interaction analysis would be needed in future studies.

Although the consistent benefits of edoxaban were shown in the sensitivity analyses, cautious interpretation is needed. The numbers of edoxaban-treated patients, when subdivided into smaller dose subgroups and propensity matched, were not sufficient to make definite conclusions for each dose; however, the trends for each dose subgroup were consistent with the overall edoxaban results, and the p values

for interaction were nonsignificant. Besides the edoxaban dose, the numbers of edoxaban patients was insufficient to obtain statistical significance in some subgroups, although favorable point estimates were evident. However, to the best of our knowledge, this was the first study and the largest Asian study that has reported the real-world safety and effectiveness of edoxaban.

CONCLUSIONS

In real-world practice among an Asian population with AF, edoxaban might be associated with reduced risk of ischemic stroke, major bleeding, and all-cause death than warfarin. These benefits were consistent across various high-risk subgroups, including patients with high CrCl (>95 ml/min).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared with warfarin in Asian patients with atrial fibrillation, edoxaban was associated with reduced risk of ischemic stroke, major bleeding, and all-cause death.

TRANSLATIONAL OUTLOOK: Additional studies are necessary to assess the effectiveness and safety of various edoxaban dose regimens in subgroups of Asian patients defined by age, sex, renal function, and frequently encountered comorbidities.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.