**Effectiveness and safety of edoxaban versus warfarin in Asian patients with non-valvular atrial fibrillation**

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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:** To compare the effectiveness and safety of edoxaban with those of warfarin in Korean population with AF.

**Methods:** Using the Korean National Health Insurance Service database, we included new-users of edoxaban and warfarin among patients with AF from January 2014 through December 2016 (n=4,200 taking edoxaban and n=31,565 taking 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 one-to-three propensity score matched cohort of patients with AF who were new-users of edoxaban and warfarin (n=4,061 taking edoxaban and n=12,183 taking warfarin). Baseline characteristics were balanced between the two groups (median age 72 years; median CHA2DS2-VASc score 3). Edoxaban users had a significantly lower risk of ischemic stroke (hazard ratio (HR) 0.693, 95% confidence interval (CI) 0.487–0.959), ICH (HR 0.407, 95% CI 0.182–0.785), hospitalization for GI bleeding (HR 0.597, 95% CI 0.363-0.930), hospitalization for major bleeding (HR 0.532, 95% CI 0.352-0.773), and all-cause death (HR 0.716, 95% CI 0.549–0.918) than warfarin users. All subgroups (age, sex, CHA2DS2-VASc score, renal function, edoxaban dose) showed better clinical outcomes with edoxaban than with warfarin.

**Conclusion:** In this real-world Asian population with AF, edoxaban may be associated with reduced risk of ischemic stroke, major bleeding, and all-cause death as compared with warfarin. These benefits were consistent across various high-risk subgroups.

**Condensed Abstract**

We compared a one-to-three propensity score matched cohort of patients with AF who were new-users of edoxaban and warfarin (n=4,061 taking edoxaban and n=12,183 taking warfarin). In this real-world Asian population with AF, edoxaban was associated with reduced risk of ischemic stroke, ICH, hospitalization for GI bleeding, all-cause death, and composite outcome than warfarin. These benefits were consistent across various high-risk subgroups. To the best of our knowledge, this is the first population-based study on the effectiveness and safety of edoxaban, and the present study has the largest cohort of Asian patients with AF who have been prescribed edoxaban.

**Keywords:** Anticoagulants, Asian, atrial fibrillation, edoxaban, warfarin, stroke

**ABBREVIATIONS AND ACRONYMS**

AF = atrial fibrillation

ASD = absolute standardized difference

CI = confidence interval

COPD = chronic obstructive pulmonary disease

CrCl = creatinine clearance

GI = gastrointestinal

HR = hazard ratio

ICH = intracranial hemorrhage

NHIS = National Health Insurance System

NOAC = non-vitamin K antagonist oral anticoagulant

OAC = oral anticoagulant

PAD = peripheral artery disease

**Introduction**

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and the prevalence of AF has shown a remarkable increase with population aging (1-4). AF increases the risk of stroke by nearly five-fold and is related to an increase in AF-related healthcare burden (5). Although stroke prevention is fundamental in the management of patients with AF, a substantial proportion of these patients still remain undertreated with oral anticoagulants (OACs) (6-9). Recently, non-vitamin K antagonist oral anticoagulants (NOACs) have shown comparable efficacy and better safety compared with warfarin in major pivotal trials and real-world data (10-16).

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

Edoxaban, the fourth NOAC in the market prescribed as a once-daily direct oral factor Xa inhibitor, has been rapidly prescribed in the non-Asian markets (17). In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), edoxaban treatment was non-inferior to warfarin treatment for stroke prevention and 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 up to 97% of the Korean population (approximately 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 were recorded using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Although the original identification number of each patient in the NHIS is encrypted to protect patient’s privacy, 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 preexisting mechanical heart valves. We also excluded those who had previous OAC prescription between January 2013 to December 2013 to analyze only those who were new warfarin and edoxaban users. We excluded patients with diagnoses such as 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 censored at the discontinuation of index treatment. Therefore, all the patients in both warfarin and edoxaban groups were prescribed index drug from beginning to the end of study period. Finally, we only included in the analysis those who received OAC for the primary prevention of ischemic stroke during the study period (from January 2014 to December 2016) and had no history of ischemic stroke, intracranial hemorrhage (ICH), and gastrointestinal (GI) bleeding events. We focused the analysis on primary prevention, so 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 period 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 prior history of myocardial infarction (MI). Online Table 1 shows the definition of comorbidities in detail. We also calculated the CHA2DS2-VASc score by assigning 1 point each for age between 65 and 74 years; female sex and the presence of hypertension, diabetes, congestive heart failure, and vascular disease (prior MI or PAD) and adding 2 points each for age of ≥ 75 years or a history of stroke/transient ischemic attack/systemic thromboembolism (20). The CHADS2 score was calculated in which 2 points are assigned for history of stroke or transient ischemic attack and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure (21).

*Study outcomes*

We identified six 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 the *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 or 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 mg 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 of 30 to 50ml/min, a body weight of ≤60kg, or the concomitant use of verapamil or quinidine. Necessarily, the baseline characteristics of the patients who received edoxaban 30 mg were different from those who received edoxaban 60 mg. To adjust 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, CHA2DS2-VASc score, and renal function. For the age subgroup analysis, patients were categorized by age of < 65, 65–74, and ≥ 75 years. For the CHA2DS2-VASc score subgroup analysis, patients were categorized into two groups by scores of 0–2 and ≥ 3. For the renal function subgroup analysis, patients were classified into two subgroups by creatinine clearance (CrCl) ≤ 50 mL/min and > 50 mL/min. We also analyzed patients by CrCl into four subgroups: > 30–50 mL/min, > 50–80 mL/min, > 80–95 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 two 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, CHA2DS2-VASc score, hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, prior MI, PAD, and COPD (Online Table 2).

Each patient in edoxaban group was matched to three 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 the two 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 (100 PY) at risk. The risk of outcomes over time for edoxaban as compared with warfarin (reference) was analyzed using a 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 a p value of <0.05. All statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC, USA).

To provide complementary analyses for balancing between the two treatment groups, we additionally performed inverse probability weighting (IPW) with and without trimming by using stabilized weights calculated from propensity scores (26,27). In trimming IPW, stabilized weights were trimmed at the 5th and 95th percentile of the weights to reduce the impact of extremely small and large weights. The risks for six 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 considering 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 comparison of the edoxaban treated group with warfarin patients who only enrolled after February 2016, when edoxaban was introduced into the market. Furthermore, when exploring the relative hazards concerning clinical outcomes other than all-cause death, we performed competing risk analysis adjusting for the competing risks of death instead of as a censoring event (28).

**Results**

*Baseline characteristics*

A total of 35,765 patients with AF newly administered edoxaban (n=4,200) and warfarin (n=31,565) were included. Before propensity score matching, patients using edoxaban were significantly older, and had higher CHADS2 score and had a higher likelihood of heart failure and prior myocardial infarction than patients using warfarin; use of edoxaban was 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) CHA2DS2-VASc score was 3.2 (3). In the matched edoxaban cohorts, 17% (n=690) of patients had been treated with warfarin previously and 56% (n=2,267) were prescribed edoxaban 30 mg. Overall, the two matched cohorts were well balanced (**Table 1** and Online Figure 1). The median follow-up duration was 0.3 years (interquartile range [IQR], 0.1-0.5 years) in the edoxaban cohort and 0.9 years (IQR, 0.9-0.9 years) in the warfarin cohort (p < 0.001).

*Ischemic stroke, intracranial hemorrhage, hospitalization for gastrointestinal bleeding, hospitalization for major bleeding, all-cause death, and composite outcome*

During follow-up, the incidence of ischemic stroke was 3.22 and 3.89 per 100PY 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], 0.487-0.959; p = 0.033; Central Illustration). The incidence of ICH for patients using edoxaban and those using warfarin were 0.66 and 1.59 per 100 PY, respectively. The incidence rates of hospitalization for GI bleeding were 1.65 and 2.02 per 100 PY for edoxaban and warfarin, respectively and those of hospitalization for major bleeding were 2.32 and 3.56 per 100 PY for edoxaban and warfarin, respectively. Thus, edoxaban was associated with 60% lower risk of ICH (HR, 0.407; 95% CI, 0.182-0.785; p = 0.014), a 40% risk reduction in hospitalization for GI bleeding (HR, 0.597; 95% CI, 0.363-0.930; p = 0.030), and a 47% risk reduction in hospitalization for major bleeding as compared with warfarin (HR, 0.532; 95% CI, 0.352-0.773; p = 0.001).

The incidence rates of all-cause death were 5.59 and 6.63 per 100 PY for edoxaban and warfarin, respectively, and those for composite outcome (ischemic stroke + ICH + all-cause death) for patients using edoxaban and warfarin were 8.9 and 11.2 per 100 PY, respectively. Edoxaban was associated with a 28% lower risk of all-cause death than warfarin (HR, 0.716; 95% CI, 0.549-0.918; p = 0.010). Edoxaban showed better outcomes than warfarin for composite outcome of ischemic stroke + ICH + all-cause death (HR, 0.667; 95% CI, 0.542-0.812; 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 six 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. With the use of IPW Cox model, edoxaban was associated with better outcomes compared to warfarin, with similar HRs for all six 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 follow-up duration and period between the two groups: HR trends for all clinical outcomes were similar to 1 year follow-up results (Online Table 5). The results were also consistent when adjusting for the competing risks of death in the total study population (Online Table 6).

*Outcomes according to edoxaban dose regimens*

Patients with edoxaban 30 mg were older, and had more females, higher CHA2DS2-VASc score, and more heart failure and COPD compared to those with edoxaban 60 mg (Online Table 7). We had matched each edoxaban group (60 mg and 30 mg) with a warfarin group by propensity score. After 1:3 propensity score matching, matched cohort were well balanced (**Table 2**).

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

*Subgroup analyses*

The benefit of edoxaban compared with warfarin was consistent across all subgroups examined (**Figure 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 composite outcome between treatment and all subgroups except for ischemic stroke in subgroup stratified by CHA2DS2-VASc score.

*(a) Elderly patients (≥ 75 years)*

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

*(b) Patients with high CHA2DS2-VASc scores (≥ 3 points)*

There was no significant interaction between treatment and CHA2DS2-VASc score except for ischemic stroke (**Figure 5 and 6**). For ischemic stroke, the benefit of edoxaban compared with warfarin showed significant interaction between patients with CHA2DS2-VASc scores ≥ 3 (HR, 0.601; 95% CI 0.402-0.866) and <3 (HR, 1.565; 95% CI, 0.687-3.241) (p interaction = 0.042). In patients with CHA2DS2-VASc scores ≥ 3 (n=10,499, 64.6% of total population), the edoxaban group showed a lower incidence of all six outcomes than warfarin group (Online Table 8). Edoxaban significantly reduced the risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding and composite outcome of ischemic stroke + ICH + all-cause death compared with warfarin among patients with CHA2DS2-VASc scores ≥ 3, whereas edoxaban showed comparable results to warfarin in patients with CHA2DS2-VASc scores < 3 (**Figure 5 and 6**).

*(c) Patients with renal dysfunction (CrCl ≤ 50 mL/min)*

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

*(d) Patients with high normal renal function (CrCl > 95 mL/min)*

We had classified patients according to renal function into four groups with CrCl value 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 vs. 3.04 per 100 PY). Edoxaban users with high normal renal function (CrCl > 95 mL/min) showed non-significant results for ICH and composite outcome compared with warfarin users (**Figure 7**).

**Discussion**

This is 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 to those of warfarin in a population-based cohort. Our study shows that edoxaban was associated with a lower risk of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and 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, 0.83–1.19) (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 NOACs 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 in Asia-Pacific and South Africa (16.0%) in the HDER group (18). A recent meta-analysis 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 reports the largest cohort of Asian patients with AF (n=4,061) who had been prescribed edoxaban and is the first population-based study on the effectiveness and safety of edoxaban.

In HDER group in ENGAGE AF-TIMI 48 trial, edoxaban showed a reduction in major bleeding (HR, 0.80; 95% CI 0.71-0.92) as compared with warfarin, mainly driven by a reduction in intracranial bleeding (HR, 0.47; 95% CI, 0.34-0.63) (18). This better safety result was consistently observed in our study. Although the HDER group in ENGAGE AF-TIMI 48 trial increased the risk of GI bleeding compared with warfarin (HR, 1.23; 95% CI 1.02-1.50), the risk of hospitalization for GI bleeding was significantly lower in the edoxaban group than warfarin group in present study. In subgroup meta-analysis of pivotal NOAC clinical trials, standard-dose NOACs were associated with the increased risk of GI bleeding in non-Asian patients but not amongst Asian patients (OR, 1.44; 95% CI, 1.12-1.85 for non-Asian; OR, 0.79; 95% CI, 0.48-1.32 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 to that with warfarin in patients with CrCl > 95ml/min (HR, 1.47; 95% CI, 0.91–2.39, p = 0.12) (22). There was a significant inverse relationship between median trough edoxaban concentration and CrCl with the most apparent decreased in concentrations occurring in the CrCl range of 90–110 mL/min (22). Based on these findings, the current US Food and Drug Administration labeling for edoxaban restricts its use in patients with a CrCl > 95mL/min (30). However, we found that the risk of ischemic stroke did not increase in patients with high normal CrCl (≥ 95 mL/min) and there was no significant interaction between the renal function and treatment. There might be several explanations for our results. First, this study included only Asian patients with AF; therefore, there may 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. Edoxaban plasma concentrations are 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 predict effective stroke prevention have not been defined. Third, warfarin control in Asian population with AF is usually poorer than that in the Western population with AF (33-35). The median time in 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 has been consistently reported in Asian population than that in 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 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial has reported a TTR of 55%, which is lower than that of patients in Western countries (36).We speculate that TTR in the real-world data would be lower than that in major clinical trials.

In the present study, 56% of patients with edoxaban were prescribed edoxaban 30 mg. Both patients received edoxaban 60 mg and 30 mg showed trends towards better outcomes for most clinical events compared to warfarin. Our results demonstrated the effectiveness and safety of edoxaban 60 mg, and this was consistent with previous meta-analysis that reported that regular dose of NOACs 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, low dose edoxaban regimen (LDER, 30/15mg) was associated with an unfavorable trend in the risk for ischemic stroke or systemic embolism compared with warfarin (HR, 1.14; 95% CI, 1.19-1.67; p < 0.001) (18). Based on these results, only the HDER has been 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 one dose reduction criteria according to drug label, i.e., renal impairment (CrCl 30–50 mL/min), body weight of ≤ 60 kg, or concomitant use of a potent phosphorylated glycoprotein inhibitor (18,30,37).

Reclassifying the study patients prescribed 30 mg edoxaban enrolled in the ENGAGE AF-TIMI 48 trial according to this current drug label, 74.6% of patients prescribed off-labeled 30 mg edoxaban and, in this population, both non-Asian and Asian patients showed 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 is unclear whether 30 mg edoxaban had enough potency to reduce the risk of ischemic stroke in the Asian population.

*Study Limitations*

There were several limitations for this study. 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 warfarin group is the inherent limitation of many real-world studies comparing NOACs and warfarin using claims databases. Previous large real-world studies have 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 is 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 NOAC in reducing the risk of ICH compared with warfarin. Again, poor TTR control is 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, hence we have not provided the HRs of cardiovascular and non-cardiovascular death. Indeed, the inherent limitation of the claims database would make it difficult to analyze the cause of death. In accordance with many studies based on real-world databases, we only report the results of all-cause death as one of the relevant ‘hard’ end points (11,15,40,41). However, the substantial treatment benefit of edoxaban on all-cause death might include both CV and non-CV death and the benefit on non-CV 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, given 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 two treatments are additional limitations of this study. Finally, concomitant use of P-glycoprotein inducers/inhibitors or antiplatelet agents which 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 were not enough to make definite conclusion for each dose; however, the trends for each dose were consistent with the overall edoxaban results, and the p values for interaction were non-significant. Besides edoxaban dose, the numbers of edoxaban patients was insufficient to obtain statistical significance in some subgroups, although favorable point estimates are evident. However, to the best of our knowledge, this is the first study and the largest Asian study reporting the real-world safety and effectiveness of edoxaban.

**Conclusion**

In real-world practice among Asian population with AF, edoxaban may 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).

**Perspectives**

**Competency in Medical Knowledge 1:** This was the first population-based study to investigate the effectiveness and safety of edoxaban compared with warfarin in Asians patients with nonvalvular AF.

**Competency in Medical Knowledge 2:** In this real-world Asian population with AF, edoxaban was associated with reduced risk of ischemic stroke, major bleeding, and all-cause death compared with warfarin.

**Competency in Patient Care:** Considering that the risk of ischemic stroke was not increased in patients with high normal CrCl (≥ 95 mL/min), edoxaban can be safely used in Asian patients with nonvalvular AF.

**Translational Outlook:** Further studies including more Asian patients will be needed to confirm the findings of this study regarding the effectiveness and safety of edoxaban dose regimen across the subgroups.

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**Figure legends**

**Central Illustration. Hazard ratios of 6 study outcomes in edoxaban versus warfarin.** Compared with warfarin user as the reference, edoxaban was associated with a 31%, 59%, and 28% of risk reduction in ischemic stroke, ICH, and all-cause death, respectively. Edoxaban users had a significantly lower risk of composite outcome of ischemic stroke + ICH + all-cause death (HR, 0.667; 95% CI 0.542-0.812; p < 0.001). Edoxaban was associated with a 40% and 47% of risk reduction in hospitalization for GI bleeding and hospitalization for major bleeding, respectively. The benefit of edoxaban compared with that of warfarin was consistent across both dose regimens. CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage

**Figure 1.** **Study population enrollment flow.** From a total of 135,939 new users of OAC 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; OAC = oral anticoagulation.

**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, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and composite outcome of ischemic stroke + ICH + all-cause death. GI = gastrointestinal; ICH = intracranial hemorrhage

**Figure 3. Cumulative incidence of 6 study outcomes in edoxaban 60 mg and matched warfarin groups.** GI = gastrointestinal; ICH = intracranial hemorrhage

**Figure 4. Cumulative incidence of 6 study outcomes in edoxaban 30 mg and matched warfarin groups.** GI = gastrointestinal; ICH = intracranial hemorrhage

**Figure 5. Hazard ratios of ischemic stroke, intracranial hemorrhage, 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 subgroups examined, especially in high risk patients such as elderly (≥ 75 years) and with higher CHA2DS2-VASc scores (≥ 3). \*P for interaction. CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; ICH = intracranial hemorrhage

**Figure 6. Hazard ratios of hospitalization for gastrointestinal 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. CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio

**Figure 7. Hazard ratios of ischemic stroke, intracranial hemorrhage, and composite outcome according to creatinine clearance subgroups.** There was no significant interaction in ischemic stroke with edoxaban versus warfarin across renal subgroups by CrCl strata. Edoxaban users with high normal renal function (CrCl > 95 mL/min) showed non-significant results for ICH and mortality compared with warfarin users. \*P for interaction.CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; ICH = intracranial hemorrhage.

**Table 1. Baseline characteristics before and after propensity score matching by treatment group (edoxaban versus 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, years |  |  |  |  |  |  |  |
| 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 |
| CHA2DS2-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) |
| CHADS2 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 |
| Prior 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 |

Categorical variables, n (%)

Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation.

**Table 2. Baseline characteristics of propensity matched population by each edoxaban dose regimens**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Edoxaban 30mg versus warfarin | | |  | Edoxaban 60mg versus warfarin | | |
|  | Warfarin  (n=7,113) | Edoxaban 30 mg  (n=2,371) | ASD |  | Warfarin  (n=5,505) | Edoxaban 60 mg  (n=1,835) | ASD |
| Age, years |  |  |  |  |  |  |  |
| 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 |
| CHA2DS2-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) |
| CHADS2 score |  |  |  |  |  |  |  |
| Mean ± SD | 1.87±1.24 | 1.79±1.2 | 0.065 |  |  |  |  |
| Median (IQR) | 2 (1-3) | 2 (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 |  | 1125 (20.4) | 385 (21.0) | 0.013 |
| Dyslipidemia | 2,562 (36.0) | 878 (37.0) | 0.021 |  | 2337 (42.5) | 786 (42.8) | 0.008 |
| Heart failure | 1,839 (25.8) | 590 (24.9) | 0.022 |  | 1113 (20.2) | 365 (19.9) | 0.008 |
| Prior 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 |

Categorical variables, n (%)

Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation