Edoxaban vs. Warfarin in East Asian Patients With Atrial Fibrillation
– An ENGAGE AF-TIMI 48 Subanalysis –
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Background: In the multinational, double-blind, double-dummy ENGAGE AF-TIMI 48 phase 3 study, once-daily edoxaban was noninferior to warfarin for prevention of stroke or systemic embolism event (SEE) in patients with non-valvular atrial fibrillation (AF). Here, we evaluated the efficacy and safety of edoxaban in patients from East Asia.

Methods and Results: Patients aged ≥21 years with documented AF and CHADS score ≥2 were randomized to receive once-daily edoxaban higher-dose (60 mg) or lower-dose (30 mg) regimen or warfarin dose-adjusted to an international normalized ratio of 2.0–3.0. Patients with a creatinine clearance of 30–50 ml/min, weighing ≤60 kg, or receiving strong p-glycoprotein inhibitors at randomization or during the study received a 50% dose reduction of edoxaban or matched placebo. This prespecified subanalysis included 1,943 patients from Japan, China, Taiwan, and South Korea. The annualized rate of stroke/SEE for higher-dose edoxaban was 1.35% vs. 2.62% for warfarin (hazard ratio [HR], 0.53; 95% confidence interval [CI]: 0.31–0.90, P=0.02) and 2.52% for lower-dose edoxaban (HR, 0.98; 95% CI: 0.63–1.54, P=0.93). Compared with warfarin (4.80%), major bleeding was significantly reduced for the higher-dose (2.86%; HR, 0.61; 95% CI: 0.41–0.89, P=0.011) and lower-dose regimens (1.59%; HR, 0.34; 95% CI: 0.21–0.54, P<0.001).

Conclusions: Once-daily edoxaban provided similar efficacy to warfarin while reducing major bleeding risk in the East Asian population.

Key Words: Anticoagulant; Asian; Atrial fibrillation; Edoxaban; Factor Xa inhibitor

Atrial fibrillation (AF) is the most common arrhythmia in adults and occurs in approximately 1% of the US population <60 years of age. Among those ≥80 years of age, this rate increases to >8%.1 In Japan, the prevalence of AF is approximately 1.6% among those ≥60 years of age, increasing to 3.2% among those ≥80 years of age.2 Overall, the estimated number of people in Japan with AF is 720,000, with a prevalence of 0.56%, which is approximately two-thirds of that in the USA.2 In general, the prevalence of AF in East Asian countries is lower than that in the USA, but has been rising in recent years.2–5 Community-based studies in East Asia have reported that the prevalence of stroke among patients with AF ranges from 13% to 15%.5 Asian patients are at a greater risk for intracranial hemorrhage. In a retrospective study of patients with ischemic stroke or intracranial hemorrhage, East Asian patients had a higher prevalence of intracranial hemorrhage compared with ischemic stroke (30% and 70%, respectively) in comparison with white patients (15% and 85%, respectively).6

Editorial p ????
Until recently, warfarin was the standard of care for stroke prevention in AF7,8 and is recommended in patients with ≥2
risk factors for stroke to achieve a target international normalized ratio (INR) of 2.0–3.0 in Western countries, although the target INR is lower in elderly patients in some Asian countries, such as Japan, where the target INR is 1.5 to approximately 2.6 in AF patients ≥70 years of age. Warfarin is associated with bleeding risk, and requires frequent monitoring and dose adjustments, and may not be suitable for all patients. Direct oral anticoagulants, which include the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, developed to address concerns associated with warfarin, are now also recommended as first-line anticoagulant therapy in Japanese patients with non-valvular AF with ≥2 risk factors for stroke. Edoxaban, a direct, oral factor Xa inhibitor with predictable pharmacokinetics, is rapidly absorbed and achieves peak blood levels in 1–2 h. Approximately 50% of the edoxaban absorbed dose is excreted by the kidneys.

Methods

Study Design

This was a multinational, multi-center, randomized, double-blind, double-dummy trial comparing 2 dose regimens of edoxaban with warfarin. This was an event-driven study, with patients enrolled from 19 November 2008 to 22 November 2010. The protocol was designed and led by an executive committee in coordination with an international steering committee; all protocols and amendments were approved by the ethics committee at each institution and conform to the ethics guidelines of the 1975 Declaration of Helsinki. All participating patients provided written informed consent.

Patients

Study methods have been described previously. Briefly, patients were eligible if they were >21 years of age, had documented AF within the prior 12 months, and a CHADS2 risk score >2. Patients with a creatinine clearance (CrCl) <30 ml/min, increased risk of bleeding, need for dual antiplatelet therapy, or acute coronary syndrome or stroke in the prior 30 days were not eligible.

This subanalysis was prespecified to include patients from Japan, China, Taiwan, and South Korea. An additional posthoc analysis included patients from the Philippines and Thailand. All remaining regions were classified as non-East Asian. Patients were randomized to receive either warfarin dose-adjusted to achieve an INR 2.0–3.0 or edoxaban higher-dose regimen (60 mg) or lower-dose regimen (30 mg) once daily in a double-blind, double-dummy fashion. Patients with CrCl 30–50 ml/min, body weight <60 kg, or who were concomitantly treated with a strong p-glycoprotein inhibitor at randomization or during the study received a 50% dose reduction of edoxaban.

Outcomes

The primary efficacy outcome was time to the first stroke (ischemic or hemorrhagic) or systemic embolic event (SEE).
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The primary efficacy analysis was performed using a Cox proportional-hazards model that included treatment groups and the 2 randomization stratification factors, CHADS2 score and by factors requiring dose reduction of edoxaban. The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population. The mITT analysis included patients who underwent randomization and received ≥1 dose of the study drug. Events that occurred during the on-treatment period, which was defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of double-blind therapy (whichever came first), were counted. Events that occurred during study-drug interruptions or discontinuations that lasted >3 days were not included in the mITT analysis.

The analyses of secondary efficacy outcomes and net clinical endpoints were conducted in the intention-to-treat (ITT) population during the overall time period, defined as the period from randomization to the end of the treatment period. Thus, all events, whether on or off study drug, were counted in the ITT analyses. A two-sided 95% confidence interval (CI) for the hazard ratio (HR) was estimated using the proportional hazards model that included treatment groups and the 2 randomization stratification factors, CHADS2 score and by factors requiring dose reduction of edoxaban. The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population. The mITT analysis included patients who underwent randomization and received ≥1 dose of the study drug. Events that occurred during the on-treatment period, which was defined as the period between administration of the first dose of the study drug and either 3 days after the receipt of the last dose or the end of double-blind therapy (whichever came first), were counted. Events that occurred during study-drug interruptions or discontinuations that lasted >3 days were not included in the mITT analysis. The analyses of secondary efficacy outcomes and net clinical endpoints were conducted in the intention-to-treat (ITT) population during the overall time period, defined as the period from randomization to the end of the treatment period. Thus, all events, whether on or off study drug, were counted in the ITT analyses. A two-sided 95% confidence interval (CI) for the hazard ratio (HR) was estimated using the proportional hazards model that included treatment groups and the 2 randomization stratification factors for the primary efficacy analysis. P-values were calculated using the log-rank test. The primary safety analysis was conducted for all randomized subjects who received ≥1 dose of randomized study drug (safety analysis set). Analyses were based on randomized treatment, even if the dosage of study drug was adjusted after randomization.

Results

Patients

Of the 21,105 total patients randomized in the ENGAGE AF-

| Table 1. Demographic and Clinical Patient Characteristics |
|----------------------------------------------------------|
| **East Asian (n=1,943)** vs. **Non-East Asian (n=19,162)** | **P-value** |
| Age (years) | 70.1±5.7 | 70.7±9.5 | 0.0085 |
| Female | 545 (28.0) | 7,495 (39.1) | <0.0001 |
| Weight (kg) | 67±12.6 | 85.6±20.0 | <0.0001 |
| Dose reduction at randomization | 912 (46.9) | 4,444 (23.2) | <0.0001 |
| CrCl ≤50ml/min | 583 (30.0) | 3,491 (18.2) | <0.0001 |
| Weight ≤60kg | 594 (30.6) | 1,489 (7.8) | <0.0001 |
| Use of verapamil or quinidine | 128 (6.6) | 633 (3.3) | <0.0001 |
| CHADS2 score ≤3 | 1,487 (76.5) | 14,850 (77.5) | 0.17 |
| CHADS2 score 4–6 | 456 (23.5) | 4,312 (22.5) | 0.33 |
| Congestive heart failure | 920 (47.3) | 11,204 (58.5) | <0.0001 |
| Hypertension | 1,596 (82.1) | 18,158 (94.8) | <0.0001 |
| Age ≥75 | 729 (37.5) | 7,745 (40.4) | 0.013 |
| Diabetes mellitus | 680 (35.0) | 6,944 (36.2) | 0.28 |
| Prior stroke or TIA | 824 (42.4) | 5,149 (26.9) | <0.0001 |
| Previous use of VKA for ≥60 days | 1,153 (59.3) | 11,288 (58.9) | 0.71 |
| Paroxysmal atrial fibrillation | 373 (19.2) | 4,993 (26.1) | <0.0001 |

Data given as mean±SD or n (%). †Quantitative data, t-test; qualitative data, χ² test. CHADS2, congestive heart failure, hypertension, age, diabetes, prior stroke or TIA; CrCl, creatinine clearance; SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist.
TIMI 48 trial, 1,943 patients were from East Asia (Figure 1). Of these patients, 1,010 were from Japan, 469 were from China, 234 were from Taiwan, and 230 were from South Korea. A total of 644 patients were randomized to warfarin, 646 to the edoxaban higher-dose regimen, and 653 to the edoxaban lower-dose regimen, with 592, 609, and 612 patients completing the end of study visit from the warfarin, edoxaban higher-dose, and edoxaban lower-dose regimens, respectively.

Demographic and baseline clinical characteristics were well balanced between the warfarin and edoxaban groups (Table 1). Compared with patients outside of East Asia, the East Asian population was twice as likely to require dose reduction at randomization, had a lower number of females, and weighed nearly 20 kg less on average.

For patients receiving warfarin therapy, the median time in therapeutic range was not significantly different (P ≥ 0.05) between East Asian (INR 2.0–3.0, 67.1%; INR 1.8–3.2, 82.6%) and non-East Asian patients (INR 2.0–3.0, 68.6%; INR 1.8–3.2, 83.1%).

Efficacy

During the treatment period, stroke or SEE occurred at a rate of 2.62% per year in the East Asian mITT population for warfarin as compared with 1.34% per year for patients in the edoxaban higher-dose regimen (HR vs. warfarin, 0.53; 95% CI: 0.31–0.90; P=0.02; interaction for higher-dose regimen, P=0.64) and 2.52% per year for the edoxaban lower-dose regimen (HR vs. warfarin, 0.98; 95% CI: 0.63–1.54; P=0.93; interaction for lower-dose regimen, P=0.11; Figure 2; Table 2). Consistent results were observed in the non-East Asian population, with rates of stroke or SEE of 1.16% per year for the higher-dose regimen (HR, 0.84; 95% CI: 0.68–1.04; P=0.10) and 1.51% per year for the edoxaban lower-dose regimen (HR, 1.09; 95% CI: 0.90–1.33; P=0.38), compared with a rate of 1.38% for warfarin in the non-East Asian population. Results did not differ significantly between the East Asian and non-East Asian populations. There were no gender-based differences in efficacy between the East Asian and non-East Asian populations. Similar results were observed when patients from the Philippines and Thailand were included in the East Asian cohort in a post-hoc analysis (Tables S1, S2).

Compared with warfarin, higher-dose edoxaban reduced the rate of stroke or SEE by 45%, while rates were similar in the lower-dose edoxaban group.

In the East Asian population, the overall rate of stroke was decreased with the edoxaban higher-dose regimen compared with warfarin (1.20% vs. 2.48%; P=0.02), whereas the stroke rate with the edoxaban lower-dose regimen (2.52%) was similar to warfarin. The decrease in overall stroke rate was primarily due to significant decreases in hemorrhagic stroke, with a rate of 0.46% for the edoxaban higher-dose regimen (P=0.03) and 0.26% for the lower-dose regimen (P=0.01) compared with a rate of 1.23% for warfarin. Patients receiving the edoxaban higher-dose regimen also had a numerically lower but not significantly different rate of ischemic stroke relative to warfarin (0.80% vs. 1.30%). Rate of ischemic stroke was increased in patients receiving the edoxaban lower-dose regimen (2.26% vs. 1.31%; Table 2). As in the East Asian population, hemorrhagic stroke rate in the non-East Asian population was significantly reduced by the edoxaban higher-dose (0.24%, P=0.01) and lower-dose regimens (0.10%, P<0.001) relative to warfarin (0.41%; Table 2). Ischemic stroke was increased in patients receiving the edoxaban lower-dose regimen in the non-East Asian population (1.35% vs. 0.89%).

Among East Asian patients who received a 50% dose reduction, the annualized rate of stroke or SEE in the warfarin group was higher than in the edoxaban higher-dose regimen and similar to that in the lower-dose regimen (Table 3). Annu-
Table 2. Efficacy Endpoints

| Primary endpoint | Warfarin (n=644 (mITT) n=641 (ITT)) | East Asian Edoxaban (n=653 (mITT)) | Lower-dose warfarin (n=6371) | Warfarin (n=6392 (mITT) n=6389 (ITT)) | East Asian Edoxaban (n=6360 (mITT)) | Lower-dose warfarin (n=6381) |
|------------------|-------------------------------------|-----------------------------------|-----------------------------|-------------------------------------|-----------------------------------|-----------------------------|
|                  | n (% patients/year) | HR† (95% CI), P-value | n (% patients/year) | HR† (95% CI), P-value | n (% patients/year) | HR† (95% CI), P-value |
| mITT, on treatment period | 38 (2.62) | 0.53 (0.31–0.90), 0.02 | 38 (2.52) | 0.98 (0.63–1.54), 0.93 | 194 (1.36) | 0.84 (0.68–1.04), 0.10 |
| ITT, overall study period | 47 (2.71) | 0.70 (0.45–1.09), 0.11 | 52 (2.94) | 1.09 (0.73–1.62), 0.67 | 290 (1.71) | 0.90 (0.76–1.06), 0.20 |
| Stroke (mITT) | 36 (2.48) | 0.50 (0.28–0.88), 0.02 | 38 (2.52) | 1.04 (0.66–1.64), 0.87 | 183 (1.30) | 0.86 (0.69–1.06), 0.16 |
| Hemorrhagic | 18 (1.23) | 0.37 (0.16–0.89), 0.03 | 4 (0.26) | 0.22 (0.07–0.64), <0.01 | 58 (0.41) | 0.33 (0.24–0.48, 0.01) |
| Ischemic | 19 (1.31) | 0.64 (0.31–1.32), 0.23 | 34 (2.26) | 1.77 (1.01–3.10), 0.05 | 123 (0.89) | 0.99 (0.77–1.27, 0.94) |
| Fatal | 4 (0.27) | 0.48 (0.09–2.63), 0.40 | 2 (0.13) | 0.48 (0.09–2.67), 0.40 | 39 (0.28) | 1.11 (0.72–1.71), 0.63 |
| SEE (mITT) | 2 (0.14) | 0.87 (0.16–7.51), 0.93 | 0 – | – | 11 (0.08) | 0.55 (0.20–1.49), 0.24 |
| Key secondary endpoints (ITT, overall study period) | 70 (4.02) | 0.61 (0.42–0.89), 0.01 | 66 (3.72) | 0.93 (0.66–1.30), 0.57 | 761 (4.47) | 0.89 (0.80–0.99), 0.03 |
| Stroke, SEE, or death from CV causes | 44 (2.44) | 0.61 (0.42–0.89), 0.01 | 66 (3.72) | 0.93 (0.66–1.30), 0.57 | 761 (4.47) | 0.89 (0.80–0.99), 0.03 |
| MACE | 76 (4.38) | 0.61 (0.43–0.88), 0.01 | 71 (0.92) | 0.92 (0.67–1.27), 0.16 | 850 (5.04) | 0.91 (0.82–1.00), 0.05 |
| Stroke, SEE, or death | 88 (5.05) | 0.64 (0.46–0.90), 0.01 | 78 (4.40) | 0.87 (0.64–1.18), 0.87 | 958 (5.63) | 0.92 (0.84–1.01), 0.08 |
| Other endpoints (ITT, overall study period) | 50 (2.77) | 0.63 (0.40–0.98), 0.04 | 34 (1.84) | 0.66 (0.42–1.02), 0.06 | 789 (4.51) | 0.93 (0.85–1.03), 0.19 |
| Death, any cause | 32 (1.77) | 0.63 (0.40–0.98), 0.04 | 34 (1.84) | 0.66 (0.42–1.02), 0.06 | 789 (4.51) | 0.93 (0.85–1.03), 0.19 |
| Death, CV causes | 32 (1.77) | 0.63 (0.40–0.98), 0.04 | 34 (1.84) | 0.66 (0.42–1.02), 0.06 | 789 (4.51) | 0.93 (0.85–1.03), 0.19 |
| MI | 8 (0.45) | 0.83 (0.30–2.30), 0.72 | 6 (0.33) | 0.74 (0.26–2.12), 0.57 | 133 (0.78) | 0.94 (0.74–1.20), 0.09 |

1Edoxaban dose vs. warfarin. 2For higher-dose edoxaban, interaction between East Asian and non-East Asian, P=0.64; for lower-dose edoxaban, interaction between East Asian and non-East Asian, P=0.11. 3HR, 95% CI derived from a Cox model that included only patients who received the assigned treatment; P-value calculated using log-rank test. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ITT, intention-to-treat; MACE, major adverse cardiac event; MI, myocardial infarction; mITT, modified ITT; SEE, systemic embolic event.

Alized rates of stroke or SEE in the non-East Asian patients who received a 50% dose reduction were similar across the treatment regimens (interaction for higher-dose regimen, P=0.93; interaction for lower-dose regimen, P=0.17).

Safety

Among East Asian patients, both regimens of edoxaban led to significant reductions in major bleeding compared with warfarin. The annualized rate of major bleeding in the warfarin group was 4.80% compared with 2.86% in the edoxaban higher-dose regimen (HR vs. warfarin, 0.61; 95% CI: 0.41–0.89; P=0.011; P=0.12 for interaction) and 1.59% in the edoxaban lower-dose regimen (HR vs. warfarin 2034; 95% CI: 0.21–0.54; P<0.001; P=0.12 for interaction; Figure 3). Similar to East Asian patients, the rate of major bleeding for edoxaban was significantly reduced in non-East Asian patients, with a rate of 2.74% for the edoxaban higher-dose regimen (HR, 0.83; 95% CI: 0.73–0.96; P=0.009) and 1.62% for the edoxa-
East Asian patients receiving edoxaban also had a significantly reduced rate of intracranial bleeding: 0.60% for the edoxaban higher-dose regimen (HR vs. warfarin, 0.31; 95% CI: 0.15–0.66; P=0.002) and 0.46% for the lower-dose regimen (HR vs. warfarin, 0.24; 95% CI: 0.11–0.56; P<0.001), vs. warfarin lower dose regimen (HR, 0.49; 95% CI: 0.42–0.58; P<0.001), vs. 3.29% for warfarin (Table 4). Similar results were observed when patients from the Philippines and Thailand were included in the East Asian cohort in a post-hoc analysis (Tables S1,S2).

| Primary endpoint (stroke or SEE) | Warfarin (dose reduced) | Edoxaban (dose reduced) | Warfarin (dose reduced) | Edoxaban (dose reduced) |
|----------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| mITT, on treatment period | n=296 (ITT) | n=294 (mITT) | n=315 (ITT) | n=315 (mITT) |
| n (% patients/year/ year) | 19 (2.92) | 9 (1.41) | 22 (3.16) | 1.10 (0.60–2.04), 0.75 |
| HR† (95% CI), P-value | 0.50 (0.23–1.11), 0.09 | 1.07 (0.62–1.83), 0.81 | 1.07 (0.62–1.83), 0.81 |
| Stroke (mITT) | n=1488 (ITT) | n=1482 (mITT) | n=1470 (ITT) | n=1459 (mITT) |
| n (% patients/ year) | 25 (3.11) | 17 (2.09) | 28 (3.31) | 1.07 (0.62–1.83), 0.81 |
| HR† (95% CI), P-value | 0.68 (0.37–1.27), 0.23 | 0.68 (0.37–1.27), 0.23 | 0.68 (0.37–1.27), 0.23 |
| SEE (mITT) | 2 (0.31) | 2 (0.31) | NC (0.00) | NC (0.00) |
| n (% patients/ year) | 95 (2.59) | 89 (2.37) | 95 (2.59) | 89 (2.37) |
| HR† (95% CI), P-value | 0.81 (0.62–1.83), 0.81 | 0.81 (0.62–1.83), 0.81 | 0.81 (0.62–1.83), 0.81 |

†Edoxaban dose vs. warfarin. ‡For higher-dose edoxaban, interaction between East Asian and non-East Asian population, P=0.93; for lower-dose edoxaban, interaction between East Asian and non-East Asian, P=0.17. †HR and 95% CI were derived from a Cox model that included only patients who received the randomly assigned treatment; P-value calculated using log-rank test. NC, not calculated. Other abbreviations as in Table 2.

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Figure 3. Rate of major bleeding in East Asian patients treated with warfarin or edoxaban. CI, confidence interval; HR, hazard ratio.
1.92% for warfarin. There were no significant differences between warfarin and either dose regimen of edoxaban in rates of fatal, fatal intracranial, or gastrointestinal bleeding in East Asian patients (Table 4). Both regimens of edoxaban significantly reduced life-threatening bleeding, CRNM bleeding, major or CRNM bleeding, and any overt bleeding in comparison with warfarin. Unlike the East Asian population, both regimens of edoxaban significantly decreased the rates of fatal bleeding, and the edoxaban higher-dose regimen significantly increased gastrointestinal bleeding compared with warfarin in the non-East Asian patients (Table 4).

In East Asian and non-East Asian patients who received a 50% dose reduction, both edoxaban dose regimens significantly reduced the annualized rates of major bleeding compared with warfarin (P=0.99 for higher-dose regimen interaction; P=0.09 for lower-dose regimen interaction; Table 5).

The annualized rate of the primary net clinical outcome (death from any cause, stroke, SEE, or major bleeding) was significantly lower for both regimens of edoxaban as compared with warfarin in the East Asian population. The annualized rate was 8.80% for warfarin and 5.60% for the edoxaban higher-dose regimen (HR vs. warfarin, 0.64; 95% CI: 0.50–0.83; P=0.001), and 5.96% for the edoxaban lower-dose regimen (HR vs. warfarin, 0.68; 95% CI: 0.53–0.87; P=0.003). Compared with warfarin, both edoxaban regimens were associated with a significantly lower rate of the secondary net clinical outcome. For the non-East Asian population, rates for both the primary and secondary net clinical outcomes were significantly lower for both regimens of edoxaban compared with warfarin, except for the secondary net clinical outcome for the higher-dose edoxaban regimen (Table 4).

AE Analyses of adverse effects by treatment group showed that there were no differences between the East Asian and non-East Asian populations in AE, serious AE (SAE) including

| Table 4. Safety and Net Clinical Endpoints |
|--------------------------------------------|
| **Endpoint** | **Warfarin** | **East Asian** | **Warfarin** | **Non-East Asian** |
| | (n=641) | Higher-dose (n=642) | Lower-dose (n=652) | Higher-dose (n=6,371) | Lower-dose (n=6,350) |
| | n (% patients/ year) | n (% patients/ year) | HR† (95% CI), P-value | n (% patients/ year) | n (% patients/ year) | HR† (95% CI), P-value |
| Major bleeding‡ | 68 (4.80) | 42 (2.86) (0.41–0.89), 0.011 | 24 (1.59) (0.21–0.54), <0.001 | 456 (3.29) (2.74–3.73), 0.009 | 230 (0.49) (1.62–0.42), <0.001 |
| Fatal CRNM bleeding | 28 (1.92) | 9 (0.60) (0.03–0.20), 0.029 | 7 (0.46) (0.09–0.26), 0.408 | 104 (0.74) (0.37–0.70), 0.212 | 34 (0.22–0.47), <0.001 |
| Fatal intracranial bleeding | 4 (0.27) | 1 (0.07) (0.03–0.20), 0.029 | 1 (0.07) (0.03–0.21), 0.221 | 38 (0.27) (0.16–0.31), 0.062 | 11 (0.15–0.56), <0.001 |
| Gastrointestinal bleeding | 16 (1.11) | 15 (1.01) (0.45–1.15), 0.802 | 11 (0.72) (0.31–1.35), 0.312 | 174 (1.24) (1.04–1.54), 0.021 | 118 (0.67) (0.83–0.84), <0.001 |
| Life-threatening bleeding | 28 (1.93) | 10 (0.66) (0.17–0.71), 0.004 | 6 (0.39) (0.09–0.50), <0.001 | 94 (0.67) (0.37–0.78), 0.001 | 34 (0.24–0.37), <0.001 |
| CRNM bleeding | 203 (17.07) | 170 (13.33) (0.64–0.97), 0.024 | 138 (10.10) (0.49–0.75), <0.001 | 1,193 (9.50) (8.21–9.80), 0.001 | 831 (6.24–6.71), <0.001 |
| Major or CRNM bleeding | 248 (21.38) | 202 (16.15) (0.64–0.92), 0.005 | 155 (11.50) (0.45–0.67), <0.001 | 1,513 (12.23) (1.00–1.40), 0.001 | 1,006 (0.58–0.88), <0.001 |
| Any overt bleeding | 281 (25.49) | 231 (19.35) (0.65–0.92), 0.004 | 187 (14.36) (0.48–0.69), <0.001 | 1,833 (15.55) (13.64–0.82), 0.001 | 1,312 (10.31) (0.63–0.72), <0.001 |
| Net clinical outcome | | | | | |
| Primary§ | 145 (8.80) | 97 (5.60) (0.50–0.83), <0.001 | 103 (5.96) (0.53–0.87), <0.001 | 1,317 (8.04) (7.43–8.10), <0.001 | 1,145 (6.87) (7.92–0.92), <0.001 |
| Secondary§ | 86 (4.94) | 46 (2.52) (0.36–0.73), 0.001 | 53 (2.91) (0.42–0.83), 0.002 | 901 (5.26) (4.86–1.01), 0.083 | 784 (4.54) (0.78–0.95), 0.002 |

Data are from the safety cohort during the treatment period (from first dose of study drug), with interval censoring of events during study-drug interruptions lasting >3 days, except for net clinical outcomes, which are presented for the overall treatment period (which began at the time of randomization). ‡Edoxaban dose vs. warfarin. †For higher-dose edoxaban, interaction between East Asian and non-East Asian population, P=0.12; for lower-dose edoxaban, interaction between East Asian and non-East Asian, P=0.12. §Composite of stroke, systemic embolic event, major bleeding, or death from any cause. ¶Composite of disabling stroke, life-threatening bleeding, or death from any cause. CRNM, clinically relevant non-major bleeding. Other abbreviations as in Table 2.
fatal AE, or drug-related SAE either in the overall or on-treatment period (Table S3). There were no differences in AE leading to drug interruptions during the on-treatment period.

**Discussion**

In East Asian patients, both the edoxaban higher-dose and lower-dose regimens were at least as effective as warfarin in preventing stroke and SEE, with significantly lower rates observed with higher-dose edoxaban as compared with warfarin for the on-treatment analysis. Hemorrhagic stroke rates were reduced for both edoxaban dosage regimens compared with warfarin while the lower-dose edoxaban regimen was not as effective in preventing ischemic stroke. Rates of major bleeding and intracranial bleeding were significantly reduced for both regimens of edoxaban. Overall, results in the East Asian population were consistent with those in the non-East Asian population, despite some significant differences in population demographics. Of note, a significantly greater proportion of East Asian patients than non-East Asian patients qualified for a 50% dose reduction. There was a greater reduction in bleeding with no apparent differences in the rate of stroke and SEE between the dose-reduced and non-reduced patients in both the East Asian and non-East Asian populations.

Rate of hemorrhagic stroke was higher in each treatment group of East Asian patients compared with that observed in the non-East Asian patients. Higher-dose edoxaban, however, may provide a greater reduction for East Asian patients than for non-East Asian patients in the risk for hemorrhagic stroke compared with warfarin; compared with warfarin, higher-dose edoxaban reduced the risk for hemorrhagic stroke by 63% in East Asian patients and by 43% in non-East Asian patients. The efficacy of low-dose edoxaban vs. warfarin for the prevention of hemorrhagic stroke was similar between the 2 patient populations. Similarly, while rates for intracranial bleeding were higher across the treatment groups for East Asian patients compared with non-East Asian patients, higher-dose and lower-dose edoxaban reduced the risk for intracranial bleeding in East Asian patients by 69% and 76%, respectively, vs. warfarin and by 49% and 68%, respectively, in non-East Asian patients.

A limited number of studies have addressed the safety and efficacy of non-vitamin K antagonist oral anticoagulants in East Asian patients. The efficacy of dabigatran 110 mg and 150 mg twice daily and rivaroxaban 15 mg or 20 mg once daily have been shown to be at least similar to warfarin in Asian patients of varying composition and non-East Asian patients with non-valvular AF. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, a trend toward greater bleeding in a broad population of Asian patients (China, Hong Kong, Japan, South Korea, Taiwan, India, Malaysia, Philippines, Singapore, and Thailand) vs. non-Asian patients was noted, with statistically greater rates of total bleeding and hemorrhagic stroke following warfarin treatment compared with dabigatran. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), East Asian patients (China, Korea, Taiwan, Hong Kong) also had higher rates of major or CRNM bleeding, regardless of treatment, compared with patients from other geographical regions. In the J-ROCKET AF trial, which specifically evaluated in Japanese patients with non-valvular AF the safety and efficacy of rivaroxaban 15 mg once daily compared with dose-adjusted warfarin, rivaroxaban was non-inferior to warfarin for the prevention of stroke and SEE and for rates of major or CRNM bleeding, and these results were consistent with those observed in the global ROCKET AF trial. Consistent with these findings, numerically higher numbers of life-threatening bleeding, CRNM bleeding, major or CRNM bleeding, and overt bleeding in the East Asian population were also noted in the current analysis.
although it was not designed for direct comparisons between the East Asian and non-East Asian populations. These data suggest a greater propensity for bleeding in Asian patients. In fact, Asian patients receiving vitamin K antagonist therapy had a higher rate of intracranial hemorrhage compared with other ethnic groups. The risk of bleeding is exacerbated in elderly patients, and maintenance of an INR 1.6–2.6 in Japanese patients has been proposed to reduce the risk of hemorrhagic events, although it may be less effective in reducing stroke occurrence. Data from the J-RHYTHM Registry, a prospective, observational, nationwide study, demonstrated that maintaining warfarin at an INR 1.6–2.6 provided similar efficacy and greater reductions in major bleeding rates compared with other INR ranges for Japanese patients ≥70 years of age and this benefit is evident even in those ≥85 years of age. Intracerebral or subarachnoid hemorrhages comprise 15%–20% of all strokes in Caucasian patients, and the percentage may be 1.5–2-fold higher in Asian patients. Thus, the significant reduction in both the rates of intracranial hemorrhage and hemorrhagic stroke with either regimen of edoxaban may be of particular importance in this patient population.

Interestingly, despite a trend toward increased rates of bleeding in the East Asian population, the rates of gastrointestinal bleeding with edoxaban were similar to warfarin, but higher with the edoxaban higher-dose regimen (1.57%) compared with non-East Asian patients. Similarly, in a subanalysis of RE-LY, Asian patients had numerically lower rates of major gastrointestinal bleeding compared with non-Asian patients receiving dabigatran 150mg, and a significant interaction between treatment and region. In a study of rivaroxaban in Japanese patients, major gastrointestinal bleeding rates were also lower in patients receiving rivaroxaban compared with warfarin. The reasons for this are not understood.

A limitation of this subanalysis was that the number of patients in the East Asian group was relatively small compared with the non-East Asian group and did not provide sufficient power for statistical comparisons. This study also was not designed to directly compare the East Asian population to the non-East Asian population. Another limitation of this subanalysis was our definition of “East Asian,” which was prespecified in the ENGAGE AF-TIMI 48 statistical analysis plan to include patients from China, South Korea, Taiwan, and Japan. Other countries that may be considered part of this geographical region, such as Thailand and the Philippines, were not included, which could suggest a bias in the definition of “East Asian”. This was addressed, however, in post-hoc analysis. When patients from the Philippines and Thailand who participated in the ENGAGE AF trial were included in the analysis of the primary efficacy and safety endpoints, there was no difference in results compared with the original East Asian cohort, indicating a lack of bias in the definition of the study cohort.

Conclusions

Both regimens of edoxaban were at least as effective as warfarin in preventing stroke and SEE in East Asian patients with non-valvular AF while significantly reducing the rate of major bleeding and intracranial hemorrhage. The results in the East Asian population were consistent with those outside East Asia.

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Conflicts of Interest

T.Y. has received honoraria from Daiichi Sankyo, Boehringer Ingelheim, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Eisai, Tanabe-Mitsubishi, and Otsuka Pharmaceutical; and has received research funding from Daiichi Sankyo, Boehringer Ingelheim, and Tanabe-Mitsubishi. Y.K. has received lecture fees from Daiichi Sankyo, Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, and Pfizer, and research funding from Daiichi Sankyo and Boehringer Ingelheim. R.P.G. has served as a consultant and has received honoraria from Bristol-Myers Squibb, Janssen, Portola, Pfizer, Daiichi Sankyo, Merck & Co, and Sanofi-Aventis; and has received research funding through his institution from Daiichi Sankyo, Merck & Co, Johnson & Johnson, Sanofi-Aventis, and AstaZeneeca T.K., K.M., and K.A. are employees of and have stock options in Daiichi Sankyo Co, Ltd, Tokyo, Japan. M.M. is an employee of and has stock options in Daiichi Sankyo Pharma Development, Edison, NJ, USA. C.T.R. has served as a consultant and has received honoraria from Daiichi Sankyo, Boehringer Ingelheim, Bayer, and Portola. N.C. has received consultation fees from Daiichi Sankyo as a steering committee member. Y.J.S. has received consultant fees from Daiichi Sankyo. Y.Y. and S.-A.C. declare no conflicts of interest.

Author Contributions

R.P.G., M.M., and C.T.R. were involved in the concept and design of the study and in the analysis and interpretation of the data. T.Y., Y.K., Y.Y., S.-A.C., N.C., Y.J.S., T.K., K.M., and K.A. were involved in the analysis and interpretation of the data. Each author critically reviewed the manuscript and provided final approval to submit this manuscript for publication.

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**Supplementary Files**

**Supplementary File 1**

**Table S1.** Primary endpoint (East Asian vs. East Asian including the Philippines and Thailand)

**Table S2.** Primary endpoint (East Asian including the Philippines and Thailand vs. Non-East Asian)

**Table S3.** Non-bleeding AE

Please find supplementary file(s):

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