Cerebrovascular Events in 21 105 Patients With Atrial Fibrillation Randomized to Edoxaban Versus Warfarin: Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48

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Background and Purpose—The once-daily oral factor Xa inhibitor, edoxaban, is as effective as warfarin in preventing stroke and systemic embolism while decreasing bleeding in a phase III trial of patients with atrial fibrillation at moderate–high stroke risk. Limited data regarding cerebrovascular events with edoxaban were reported previously.

Methods—We analyzed the subtypes of cerebrovascular events in 21 105 patients participating in Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) comparing outcomes among patients randomized to warfarin versus 2 edoxaban regimens (high dose, low dose). The primary end point for this prespecified analysis of cerebrovascular events was all stroke (ischemic plus hemorrhagic), defined as an abrupt onset of focal neurological deficit because of infarction or bleeding with symptoms lasting ≥24 hours or fatal in <24 hours. Independent stroke neurologists unaware of treatment adjudicated all cerebrovascular events.

Results—Patients randomized to high-dose edoxaban had fewer strokes on-treatment (hazard ratio, 0.80; 95% confidence interval, 0.65–0.98) than warfarin (median time-in-therapeutic range, 68.4%); patients in the low-dose edoxaban group had similar rates (hazard ratio, 1.10 versus warfarin; 95% confidence interval, 0.91–1.32). Rates of ischemic stroke or transient ischemic attack were similar with high-dose edoxaban (1.76% per year) and warfarin (1.73% per year; P=0.81), but more frequent with low-dose edoxaban (2.48% per year; P<0.001). Both edoxaban regimens significantly reduced hemorrhagic stroke and other subtypes of intracranial bleeds.

Conclusions—In patients with atrial fibrillation, once-daily edoxaban was as effective as warfarin in preventing all strokes, with significant reductions in various subtypes of intracranial bleeding. Ischemic cerebrovascular event rates were similar with high-dose edoxaban and warfarin, whereas low-dose edoxaban was less effective than warfarin.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00781391.

Key Words: anticoagulant • atrial fibrillation • cerebral hemorrhage • stroke

Atrial fibrillation (AF) increases the risk of stroke 5-fold.1 Although vitamin K antagonists reduce this risk by about two thirds compared with placebo,2 they increase the risk of serious bleeding, including intracranial hemorrhage (ICH) and fatal bleeding. In addition, vitamin K antagonists require frequent monitoring to ensure the optimal level of anticoagulation, have multiple drug–drug and food–drug interactions, and occasionally cause off-target side effects. Thus, patient acceptance and compliance is poor, with a recent US registry demonstrating treatment rates with anticoagulant of only 50% to 60% in eligible patients with AF,3 and with most patients not achieving desired levels of anticoagulation.4 Since 2009, factor-specific (factor IIa or Xa inhibitors) oral anticoagulants that do not require routine monitoring and have fewer drug–drug and no food–drug interactions have been shown to be at least as effective as warfarin in reducing stroke or systemic embolic events, while reducing ICH in patients with AF.5,6 In a meta-analysis of the 4 phase III trials comparing the...
factor-specific agents to warfarin, no significant difference in the rates of ischemic stroke were observed, but these newer anticoagulants reduced ICH by 51% and mortality by 10%.9

Edoxaban is a directly acting oral factor Xa inhibitor that is administered once daily. It is a substrate for the P-glycoprotein transport system, undergoes ≈50% renal excretion of the absorbed dose, has a rapid onset of action (1–2 hours), and a terminal half-life of ≈10 to 14 hours.10 We previously showed10 in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial of 21 105 patients with AF at moderate–high risk of stroke comparing 2 dose regimens of edoxaban to warfarin that both edoxaban regimens were noninferior in preventing stroke or systemic embolic events; superior in reducing bleeding, ICH, and cardiovascular mortality; and superior in reducing prespecified net clinical outcomes.

In the current analysis, we provide detailed results on the timing, severity, and subtypes of cerebrovascular events comparing edoxaban with warfarin in the ENGAGE AF-TIMI 48 trial. We also explore the more modern definition of stroke11 that includes ischemic cerebrovascular events resolving completely <24 hours, but demonstrating evidence of infarction on brain imaging.

Methods

Study Population and Protocol

ENGAGE AF-TIMI 48 was a multinational, double-blinded, double-dummy, randomized, warfarin-controlled trial. The design12 and primary results8 have been published previously. Between November 2008 and November 2010, 21 105 patients with AF documented on an electric recording within the prior 12 months with a Cardiac Failure, Hypertension, Age, Diabetes Stroke System (CHADS2) risk score ≥2 were randomized. Patients were excluded if they had AF because of reversible causes; an estimated creatinine clearance <30 mL/min; were at increased risk for bleeding (eg, prior ICH, gastrointestinal bleeding <12 months); had other indications for anticoagulation; or required dual antiplatelet therapy.

Eligible patients were randomly allocated in a 1:1:1 ratio to warfarin, edoxaban high dose, or edoxaban low dose orally once daily. The dose of edoxaban (or matching edoxaban placebo) was 60 mg in the high-dose and 30 mg in low-dose regimens, but was reduced by 50% at randomization in ≥25% of patients who had at least 1 of the following: creatinine clearance 30 to 50 mL/min; body weight ≤60 kg, concomitant use of a strong P-glycoprotein inhibitor. The dose of edoxaban (or matching placebo) was adjusted after randomization in another 8.3% of patients. Warfarin or matching placebo was adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0 using an encrypted point-of-care device to maintain the study blind. Single antiplatelet therapy was permitted, although the recommended dose of aspirin was ≤100 mg daily.

End Points

Detailed definitions of the study end points have been published.6,12 The primary efficacy end point for this prespecified analysis of cerebrovascular events was the first stroke (either ischemic or hemorrhagic), defined as an abrupt onset of focal neurological deficit (generally in the distribution of a single artery) because of infarction or bleeding with symptoms lasting ≥24 hours or fatal in <24 hours, regardless of findings on brain imaging studies. Events that completely resolved <24 hours but met other criteria above were classified as transient ischemic attacks (TIAs).

In a prespecified sensitivity analysis, we reclassified TIAs with new infarction on a brain imaging study as an ischemic stroke. Hemorrhagic transformation of an initial ischemic stroke was classified as a primary ischemic stroke. A primary hemorrhagic stroke included bleeding that was intraparenchymal, intraventricular, or subarachnoid, and not because of trauma, surgery, tumor, or other primary process. Bleeding secondary to one of these events was classified as an ICH, but not hemorrhagic stroke. Isolated microhemorrhages (small high-intensity foci seen on MRI) were not considered strokes or ICHs.

Secondary analyses included comparisons of subtypes of ICH (hemorrhagic stroke, hemorrhagic transformation of a primary ischemic stroke, subdural, and epidural hematomas) and stroke outcomes. We used the modified Rankin Scale score13,14 at 30 to 90 days after the event as determined by the investigator to classify the severity of stroke. A nonfatal disabling event was considered one with a score 3 to 5, and a fatal stroke was assigned a score of 6. The primary net clinical outcome of interest was a composite of all nonfatal stroke, nonfatal ICH (without double counting of hemorrhagic strokes), and all-cause mortality. We also explored a variety of other net clinical outcomes combining different types of stroke, ICH, and death. All end points (other than stroke disability) were adjudicated by an independent Clinical Events Committee without knowledge of treatment allocation.

Statistical Consideration

The primary efficacy analysis compared both edoxaban dose regimens to warfarin in the prevention of all stroke and was performed as reported for the main study analysis6 initially in the modified intention-to-treat population during the on-treatment period, with interval censoring of events while off study drug for >3 days. A second analysis was conducted in the intention-to-treat (all patients randomized) population1 during the overall study period (from randomization to final treatment period visit) without interval censoring of events while off study drug. All other efficacy and net clinical outcome analyses were performed in the intention-to-treat population counting all events. ICH analyses were conducted in the population that received at least 1 dose of study drug by the actual treatment received, during the on-treatment period. All analyses were performed independently by the TIMI study group, who take responsibility for and decided to submit this article. Data were analyzed using Stata v12.1 and SAS v9.2.

Results

Baseline Characteristics and Stroke Outcomes

The trial enrolled 21 105 patients with median age 72 years and median CHADS2 score 2.8, of whom 38% were women and 28% had a prior stroke or TIA before randomization. After randomization, a total of 794 (1.4% per year) patients had an ischemic stroke, 164 (0.29% per year) a hemorrhagic stroke, and 20 147 no stroke during the 2.8 years (median) of follow-up. Patients with ischemic stroke were more likely to be women, older, from Eastern Europe, with more stroke risk factors, whereas patients with hemorrhagic stroke were more likely to be naive to vitamin K antagonists, receiving concomitant aspirin, from Asia, and had higher blood pressure at randomization (see the online-only Data Supplement).

Primary Efficacy Analyses

As previously reported,3 the median time in therapeutic range (TTR) for the warfarin-treated patients was 68.4% (interquartile range, 56.5–77.4%), and during the on-treatment period in the modified intention-to-treat population, stroke occurred in 219 patients receiving warfarin (1.41% per year) compared with 174 patients receiving high-dose edoxaban (1.13% per year) and 243 receiving low-dose edoxaban (1.55% per year). Patients randomized to high-dose edoxaban had significantly fewer first strokes as compared with warfarin (high-dose edoxaban versus warfarin hazard ratio [HR], 0.80; 95%
confidence interval, 0.65–0.98; \( P=0.027 \) in the analysis during the on-treatment period in the modified intention-to-treat population, whereas the corresponding HR for the low-dose edoxaban group versus warfarin was 1.10 (95% confidence interval, 0.91–1.32; \( P=0.33 \); Figure 1A). The upper bound for both edoxaban regimens was below the 1.38 boundary recommended by the US Food and Drug Administration for the assessment of noninferiority of the primary study end point of the main trial.

As previously described, in the intention-to-treat cohort counting all events between randomization and the final study visit, all stroke tended to occur less frequently with high-dose edoxaban (1.49% per year) as compared with warfarin (1.69% per year), but tended to occur more frequently with low-dose edoxaban (1.91%; Figure 1B). Rates of fatal and disabling ischemic strokes were similar between high-dose edoxaban and warfarin, but generally more frequent with low-dose edoxaban than warfarin (Table 1).

### Secondary Analyses

Both doses of edoxaban markedly reduced hemorrhagic stroke as compared with warfarin (HR, 0.54 and 0.33 for high-dose and low-dose edoxaban groups; both \( P<0.001 \); Table 1). The risk of hemorrhagic stroke in the warfarin group seemed higher early after randomization (0.39% at 6 months), whereas the risk of hemorrhagic stroke in the edoxaban arms was nearly linear throughout 3.5 years of follow-up (Figure 2A).

The rates of ischemic cerebrovascular events (stroke or TIA) were similar in the warfarin (1.73% per year) and high-dose edoxaban (1.76% per year; HR, 1.02; 95% confidence interval, 0.87–1.19; \( P=0.81 \)) groups, but was significantly increased with low-dose edoxaban (2.48%; HR, 1.43; 95% confidence interval, 1.24–1.65; \( P<0.001 \); Table 1). Of note, there was no excess in early ischemic stroke in the first weeks after initiation of warfarin as compared with either edoxaban regimen (Figure 2B, inset), despite the faster onset of action of edoxaban as compared with warfarin.

Rates of TIA and the combination of all strokes or TIA were similar with warfarin and high-dose edoxaban, whereas these end points were significantly more frequent with low-dose edoxaban (Table 1). The sensitivity analysis, which reclassified nonfatal ischemic cerebrovascular events with complete resolution of symptoms <24 hours but with brain imaging demonstrating a new cerebral infarction from TIA (protocol definition) to ischemic stroke, identified 37 additional ischemic strokes (14 in the warfarin group, 9 in the high-dose edoxaban group, 14 in the low-dose edoxaban group). Inclusion of these 37 events in the comparison of stroke by treatment group did not alter the results qualitatively (Table 1).

Both edoxaban dose regimens reduced ICH, with substantial reductions observed in fatal ICH in both edoxaban arms as compared with warfarin (HR, 0.58; \( P=0.031 \), and HR, 0.28; \( P=0.001 \), respectively, for high-dose and low-dose edoxaban versus warfarin; Table 1). Both edoxaban dose regimens reduced a variety of subtypes of ICH, including parenchymal, subarachnoid, and subdural or epidural bleeds (Table 2). There were 8 patients in the warfarin group who had hemorrhagic transformation of an ischemic stroke as compared with 12 in the high-dose edoxaban group (\( P=0.38 \)) and 20 in the low-dose edoxaban group (\( P=0.03 \) versus warfarin). Only 5 patients had microhemorrhages observed on MRI scans that were unassociated with a stroke (2 warfarin, 3 high-dose edoxaban groups, respectively; Table 2).

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** All stroke by treatment group. The on-treatment analysis (A) was conducted in the modified intention-to-treat (mITT) population (all patients who took at least 1 dose of study drug) counting events that occurred while on-treatment plus 3 d after discontinuation. Interval censoring was implemented for time during interruptions lasting \( \geq 4 \) days. The upper bound of the confidence intervals (CIs) of the hazard ratios for both the high-dose and low-dose edoxaban regimens as compared with warfarin did not cross \( <1.38 \), the prespecified boundary for noninferiority to warfarin. The ITT analysis (B) was conducted in all randomized patients counting all events between randomization and the last visit. TTR indicates time in therapeutic range.
Composite End Points

Both edoxaban dose groups reduced the composite of death, nonfatal stroke, or ICH, as compared with warfarin (HR, 0.88; \( P = 0.003 \), and HR, 0.90; \( P = 0.021 \) for the high-dose and low-dose edoxaban groups, respectively). In comparisons of a variety of other combinations of death, nonfatal stroke, and nonfatal ICH shown in Table 3, both dose regimens of edoxaban tended to have fewer events than warfarin with the exception of the composite of death or nonfatal ischemic stroke, which was similar in the warfarin and low-dose edoxaban groups (HR, 0.96; \( P = 0.35 \); Table 3).

Relationship Between INR and Stroke Events in the Warfarin Arm

Among 6587 patients randomized to warfarin who did not have a stroke, the INR was between 2.0 and 3.0 for a mean of 65.2% (SD, 18.6%) of the time as compared with 57.5% (SD, 22.6%) and 61.9% (SD, 17.6%) of the time in patients with an ischemic stroke (n=222) and patients with an ICH (n=88), respectively (3-way \( P < 0.001 \)). Patients who had experienced an ischemic stroke had a greater proportion of time below an INR 1.5 (10.4% versus 6.0% for those without stroke; \( P < 0.001 \); see the online-only Data Supplement). An INR \( \geq 4.0 \) was present 3.2% of the time in patients with hemorrhagic stroke versus 1.8% for those without a stroke (\( P = 0.45 \)).

Discussion

The principal findings of this detailed analysis of cerebrovascular events in the ENGAGE AF-TIMI 48 trial comparing 2 dose regimens of edoxaban with warfarin in patients with AF at moderate to high risk of stroke are:

1. During the on-treatment period, high-dose edoxaban achieved lower rates, and low-dose edoxaban similar rates, of stroke (hemorrhagic plus ischemic) as compared with warfarin.
2. Both dose regimens of edoxaban were associated with reduced rates of various subtypes of ICH, with marked reductions of hemorrhagic stroke, particularly in the first 6 months after randomization as compared with warfarin.
3. High-dose edoxaban and warfarin achieved similar rates of ischemic stroke, TIA, and their composite, regardless of whether the protocol or newer definition of stroke that incorporates brain imaging was used; patients in the low-dose edoxaban group experienced higher rates of ischemic cerebrovascular events compared with patients in the warfarin group.
4. A variety of composite outcomes combining death, nonfatal stroke, and nonfatal ICH favored edoxaban compared with warfarin.

We previously showed\(^{6} \) that the primary clinical benefit of edoxaban compared with warfarin is the marked reduction in hemorrhagic stroke and other intracranial bleeds, an observation that is similar to those reported in the individual studies with other factor-specific oral anticoagulants\(^{5,7,8} \) and a comprehensive meta-analysis of all 4 new agents.\(^{9} \) The high-dose edoxaban regimen offers similar protection from ischemic stroke as warfarin, which itself is highly effective (67% reduction compared with placebo).\(^{3} \) Although the low-dose regimen of edoxaban had a higher risk of ischemic stroke than warfarin (excess of 5.2 per 1000 patient-years of treatment), the primary finding in the current on-treatment analysis for noninferiority to warfarin in overall stroke means that low-dose edoxaban preserves (with 97.5% certainty) at least half
of the benefit of warfarin as compared with placebo to reduce all stroke. The low-dose regimen of edoxaban was also shown to have other benefits, including marked reduction in bleeding (including ICH, gastrointestinal, and fatal bleeding) and significantly lower all-cause mortality compared with warfarin. Nonetheless, high-dose edoxaban provides a more consistent profile of benefit across a variety of types of cerebrovascular and cardiovascular events and seems to be the preferred regimen for the majority of patients. In patients who are at increased risk of ICH (eg, older patients, Asian race, on concomitant aspirin), low-dose edoxaban may represent a safer option. In addition, it is noteworthy that low-dose edoxaban significantly reduced the composite of death or nonfatal disabling stroke—2 of the most serious consequences of AF—by 10% as compared with warfarin.

Because of important differences in patient populations, quality of warfarin management, use of concomitant therapies, and other trial features, comparisons across the 4 large studies of factor-specific oral anticoagulants versus warfarin should be discouraged. For example, the median TTR among the centers participating in ENGAGE AF-TIMI 48 was 68.4%, the highest rate in the 4 trials. Indeed, the top quartile achieved a TTR >77.4%, a rate that slightly exceeds the TTR of 76.2% reported in specialty best practice centers in Sweden. Because prior research suggests that each 7% increase in TTR translates into a 1% per year reduction in major bleeding and an ≈0.6% per year reduction in thromboembolic events, the relatively high median TTR (68.4%) achieved in ENGAGE AF-TIMI 48 would be expected to have led to lower rates of both ischemic stroke and major bleeding in the warfarin arm compared with the warfarin-treated patients of similar risk 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) (median TTR, 58%) and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) (median TTR, 64%) trials. Furthermore, our data support a relationship between the amount of time the INR is out of range and poor outcomes, because patients randomized to warfarin who had an ischemic stroke spent more time with an INR <1.5 than those with hemorrhagic stroke or no stroke, whereas patients with hemorrhagic stroke spent nearly twice as much time with an INR ≥4.0. Nevertheless, despite the generally good
management of warfarin in this trial overall, both edoxaban regimens markedly reduced ICH as compared with warfarin.

The precise reason for the halving of ICH reported with factor-specific anticoagulants as compared with warfarin is unknown and is likely multifactorial. Although supratherapeutic INRs are associated with increased rates of ICH, particularly in the elderly,18 most of the ICHs in patients on warfarin occur when the INR is in the therapeutic range.19,20 Furthermore, our prior observations that the high-dose edoxaban regimen was associated with significantly more gastrointestinal bleeding but fewer ICHs compared with warfarin, whereas low-dose edoxaban reduced both types of bleeding compared with warfarin,4 suggests that the relationship between bleeding and anticoagulant therapy is complex, involving interactions between the intensity of anticoagulation, patient risk, and site of bleeding.

Some have hypothesized that the suppression of factor VIIa and tissue factor–VIIa complexes by vitamin K antagonists impairs the protective hemostatic milieu in the brain that protects elderly patients against the risk of ICH.21 In contrast, the newer oral anticoagulants that inhibit clotting factors more distal in the cascade do not interfere with the formation of the tissue factor–VIIa complex. However, because the subdural, epidural, and subarachnoid spaces are not as rich in tissue factor as the brain, the reduction in bleeding observed with edoxaban and other factor-specific agents in these extraparenchymal locations raises the possibility of other mechanism(s). It will be interesting to compare the rates of ICH with newer anticoagulants in development that inhibit more proximal targets in the cascade, such as inhibitors of tissue factor,22 factor VIIa,23 factor IXa,24 and factor Va.25

### Conclusions

In a randomized, double-blind trial in 21,105 patients with AF at moderate to high risk of stroke, once-daily edoxaban was as effective as well-managed warfarin in the prevention of all strokes. Both dose regimens of edoxaban reduced the subtypes of ICH. High-dose edoxaban and warfarin achieved similar rates of ischemic stroke and TIA, whereas low-dose edoxaban seems less effective than warfarin in the prevention of ischemic cerebrovascular events. Both edoxaban regimens

### Table 2. Intracranial Hemorrhagic Events by Treatment Group (On-Treatment)

<table>
<thead>
<tr>
<th>Events, %/y</th>
<th>Warfarin (n=7036)</th>
<th>Edoxaban High Dose (n=7035)</th>
<th>Edoxaban High Dose vs Warfarin</th>
<th>Edoxaban Low Dose (n=7034)</th>
<th>Edoxaban Low Dose vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All intracranial hemorrhages</td>
<td>0.85%</td>
<td>0.39%</td>
<td>0.47 &lt;0.001</td>
<td>0.26%</td>
<td>0.30 &lt;0.001</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.47%</td>
<td>0.26%</td>
<td>0.54 &lt;0.001</td>
<td>0.16%</td>
<td>0.33 &lt;0.001</td>
</tr>
<tr>
<td>Parenchymal</td>
<td>0.42%</td>
<td>0.24%</td>
<td>0.57 0.002</td>
<td>0.14%</td>
<td>0.33 &lt;0.001</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>0.06%</td>
<td>0.02%</td>
<td>0.36 0.081</td>
<td>0.02%</td>
<td>0.36 0.079</td>
</tr>
<tr>
<td>Subdural or epidural</td>
<td>0.30%</td>
<td>0.10%</td>
<td>0.35 &lt;0.001</td>
<td>0.08%</td>
<td>0.26 &lt;0.001</td>
</tr>
<tr>
<td>Fatal intracranial hemorrhages</td>
<td>0.27%</td>
<td>0.15%</td>
<td>0.58 0.031</td>
<td>0.08%</td>
<td>0.28 &lt;0.001</td>
</tr>
<tr>
<td>Fatal subdural or epidural bleed</td>
<td>0.07%</td>
<td>0.01%</td>
<td>0.15 0.013</td>
<td>0.01%</td>
<td>0.15 0.013</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>n=8</td>
<td>n=12</td>
<td>1.49 0.38</td>
<td>n=20</td>
<td>2.48 0.03</td>
</tr>
<tr>
<td>Microhemorrhage (without stroke)</td>
<td>n=2</td>
<td>n=3</td>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage.

*Excluding primary hemorrhagic stroke.
†Includes Rankin score 3 to 5.

### Table 3. Composite Outcomes of Death, Stroke, and ICH (Intention-to-Treat Population, Overall Time Period)

<table>
<thead>
<tr>
<th>Events, %/y</th>
<th>Warfarin (n=7036)</th>
<th>Edoxaban High Dose (n=7035)</th>
<th>Edoxaban High Dose vs Warfarin</th>
<th>Edoxaban Low Dose (n=7034)</th>
<th>Edoxaban Low Dose vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, nonfatal stroke, ICH*</td>
<td>5.74%</td>
<td>5.04%</td>
<td>0.88 0.003</td>
<td>5.20%</td>
<td>0.90 0.021</td>
</tr>
<tr>
<td>Death or nonfatal stroke</td>
<td>5.49%</td>
<td>4.94%</td>
<td>0.90 0.017</td>
<td>5.15%</td>
<td>0.93 0.13</td>
</tr>
<tr>
<td>Death or nonfatal ICH</td>
<td>4.88%</td>
<td>4.27%</td>
<td>0.87 0.004</td>
<td>4.03%</td>
<td>0.82 &lt;0.001</td>
</tr>
<tr>
<td>Death or nonfatal ischemic stroke</td>
<td>5.27%</td>
<td>4.85%</td>
<td>0.92 0.064</td>
<td>5.06%</td>
<td>0.96 0.35</td>
</tr>
<tr>
<td>Death or nonfatal hemorrhagic stroke</td>
<td>4.62%</td>
<td>4.13%</td>
<td>0.89 0.019</td>
<td>3.91%</td>
<td>0.84 &lt;0.001</td>
</tr>
<tr>
<td>Death or nonfatal disabling stroke†</td>
<td>4.61%</td>
<td>4.24%</td>
<td>0.92 0.078</td>
<td>4.15%</td>
<td>0.90 0.024</td>
</tr>
</tbody>
</table>

ICH indicates intracranial hemorrhage.

*Excluding primary hemorrhagic stroke.
†Includes Rankin score 3 to 5.
were associated with a reduction in a variety of net outcomes as compared with warfarin that included various composites of death, nonfatal stroke, and nonfatal ICH.

Acknowledgments

We acknowledge Andrea Crompton for her assistance in preparing the electronic submission of this article. The work was supported by Daiichi Sankyo Pharma Development.

Disclosures

Dr Giugliano has served as a consultant and had received honoraria from Bristol-Myers Squibb, Janssen, Daiichi Sankyo, Merck, and Sanofi, and reports grants (through the Brigham and Women’s Hospital) from Daiichi Sankyo, Merck, Johnson & Johnson, Sanofi, and AstraZeneca. Dr Ruff has served as a consultant and received honoraria from Daiichi Sankyo, Boehringer Ingelheim, and Bristol-Myers Squibb, and reports grants (through the Brigham and Women’s Hospital) from Daiichi Sankyo. Drs Rost and Silverman were members of the Clinical Endpoint Committee for the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial and received honoraria for their work. Dr Wiviott was the Chairman of the ENGAGE AF-TIMI 48 trial Clinical Endpoint Committee and reports receiving consulting fees from AstraZeneca, Bristol-Myers Squibb, Eisai, Arena Pharmaceuticals, Eli Lilly, Daiichi Sankyo, Aegerion, AngelMed, Janssen Pharmaceuticals, Xoma, ICON Clinical Research, and Boston Clinical Research Institute and grant support through his institution from AstraZeneca, Bristol-Myers Squibb, Eisai, Arena Pharmaceuticals, Merck, Eli Lilly, Daiichi Sankyo, and Sanofi. N. Deenadayalu, C. Lowe, S.A. Murphy, and L.T. Grib report grant support through their institution from Daiichi Sankyo. Dr Boucher reports no conflicts. Dr Patel, J. Dave, Dr Shi, and Dr Mercuri are employees of Daiichi Sankyo and report owning Stock Appreciation Rights and Restricted Stock Units. Dr Mercuri reports holding a patent related to the clinical properties of edoxaban. Dr Antman reports receiving grant support through his institution from Daiichi Sankyo. Dr Braunwald reports grants (through the Brigham and Women’s Hospital) and personal fees from lectures from Daiichi Sankyo. For outside the submitted work, Dr Braunwald received grants (through the Brigham and Women’s Hospital) and personal fees for lectures from Daiichi Sankyo for the effective anticoagulation with factor Xa next generation in atrial fibrillation: blending of nonvalvular atrial fibrillation: implications for clinical practice. Am J Cardiovasc Drugs. 2014;14:111–127.


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Stroke. 2014;45:2372-2378; originally published online June 19, 2014;
doi: 10.1161/STROKEAHA.114.006025

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/45/8/2372

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

I. Supplemental Table - Baseline Characteristics by Stroke Outcome (Intention-To-Treat Population, Overall Time Period)

II. Supplemental Figure - Percent of time with INR <1.5 and >4.0 by Stroke Event in the Patients Randomized to Warfarin.
### Supplement I – Baseline Characteristics by Stroke Outcome (Intention-To-Treat Population, Overall Time Period)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Stroke (N = 20,147)</th>
<th>Ischemic Stroke (N = 794)</th>
<th>Hemorrhagic Stroke (N = 164)</th>
<th>3-way P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [interquartile range]</td>
<td>72 [64, 77]</td>
<td>74 [67, 79]</td>
<td>73 [68, 79]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>38</td>
<td>45</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td>0.062</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>26</td>
<td>21</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>23</td>
<td>23</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>51</td>
<td>56</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>CHADS$_2$ score, mean (SD)</td>
<td>2.8 (1.0)</td>
<td>3.2 (1.1)</td>
<td>2.9 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS$_2$ score ≥ 3</td>
<td>53</td>
<td>66</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHADS$_2$ score ≥ 4</td>
<td>22</td>
<td>37</td>
<td>24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>58</td>
<td>57</td>
<td>51</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>94</td>
<td>92</td>
<td>92</td>
<td>0.040</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>40</td>
<td>48</td>
<td>45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>36</td>
<td>32</td>
<td>35</td>
<td>0.043</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>28</td>
<td>45</td>
<td>34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dose reduced at randomization</td>
<td>25</td>
<td>37</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior VKA experience</td>
<td>59</td>
<td>58</td>
<td>52</td>
<td>0.22</td>
</tr>
<tr>
<td>Aspirin at randomization</td>
<td>29</td>
<td>29</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mean, SD) at entry</td>
<td>130 (15.3)</td>
<td>132.6 (14.9)</td>
<td>133.8 (15.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region</td>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>SD</td>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------</td>
<td>----</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>North America (N=4681)</td>
<td>22</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Latin America (N=2661)</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Western Europe (N=3236)</td>
<td>15</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Eastern Europe (N=7144)</td>
<td>34</td>
<td>37</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Asia, Japan, S Africa (N=3383)</td>
<td>16</td>
<td>18</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
<th>SD</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>White (N=17,067)</td>
<td>81</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>Asian (N=2909)</td>
<td>14</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Black (N=278)</td>
<td>1.3</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>All Others (N=850)</td>
<td>4.1</td>
<td>3.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Data in tables are % of patients unless otherwise specified

CHADS<sub>2</sub> stands for congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or TIA. The score is calculated by counting 1 point for all factors except stroke or TIA which is assigned 2 points.

SBP = systolic blood pressure, SD = standard deviation, TIA = transient ischemic attack, VKA = Vitamin K antagonist
Supplement II - Percent of time with INR <1.5 and ≥4.0 by Stroke Event in the Patients Randomized to Warfarin.

No Stroke (N=6587)
- Mean % time INR > 4.0: 6.0%
- Mean % time INR < 1.5: 1.8%

Ischemic Stroke (N=222)
- Mean % time INR > 4.0: 10.4%
- Mean % time INR < 1.5: 2.4%

Hemorrhagic Stroke (N=88)
- Mean % time INR > 4.0: 5.8%
- Mean % time INR < 1.5: 3.2%