Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation

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Summary
The primary objective of this study was to compare the safety of four fixed-dose regimens of edoxaban with warfarin in patients with non-valvular atrial fibrillation (AF). In this 12-week, parallel-group, multicentre, multinational study, 1,146 patients with AF and risk of stroke were randomised to edoxaban 30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid or warfarin dose-adjusted to a target international normalised ratio of 2.0–3.0. The study was double-blind to edoxaban dose, but open-label to warfarin. Primary outcomes were occurrence of major and/or clinically relevant non-major bleeding and elevated hepatic enzymes and/or bilirubin. Mean age was 65 ± 8.7 years and 64.4% were warfarin-naive. Whereas major plus clinically relevant non-major bleeding occurred in 3.2% of patients randomised to warfarin, the incidence of bleeding was significantly higher with the edoxaban 60 mg bid (10.6%; p=0.002) and 30 mg bid regimens (7.8%; p=0.029), but not with the edoxaban 60 mg qd (3.8%) or 30 mg qd regimens (3.0%). For the same total daily dose of 60 mg, both bleeding frequency and trough edoxaban concentrations were higher in the 30-mg bid group than in the 60-mg qd group. There were no significant differences in hepatic enzyme elevations or bilirubin values among the groups. The safety profiles of edoxaban 30 and 60 mg qd in patients with AF were similar to warfarin. In contrast, the edoxaban bid regimens were associated with more bleeding than warfarin. These results suggest that in this three-month study, edoxaban 30 or 60 mg qd are safe and well-tolerated.

Keywords
Anticoagulant, atrial fibrillation, DU-176b, edoxaban, factor Xa inhibitor

Introduction
Atrial fibrillation (AF) is the most common cardiac rhythm abnormality, affecting over 3 million people in the United States and 4.5 million in the European Union (1, 2). Vitamin K antagonists (VKAs), such as warfarin, reduce the risk of stroke and death in patients with AF (3). Consequently, current guidelines recommend anticoagulant therapy for patients with non-valvular AF who are at risk for stroke (2).

Although effective, VKAs have numerous limitations, which result in their underuse in eligible patients with AF (4). Frequent monitoring of the international normalised ratio (INR) and dose adjustments are necessary to ensure that a therapeutic anticoagulant effect is maintained (5), which is burdensome for patients and their physicians and costly for the healthcare system. Even with monitoring, the INR is often above or below the therapeutic range, which places patients at risk of bleeding or stroke, respectively (6).

These limitations have prompted the development of new oral anticoagulants that can be given in fixed doses and produce such a predictable anticoagulant response that little or no coagulation monitoring is needed. Most of these new agents target either factor Xa (FXa) or thrombin, key enzymes in the coagulation pathway (7).

Edoxaban, the free base of DU-176b, is a new, direct oral FXa inhibitor. Evaluation of its pharmacokinetics (PK) reveals that peak plasma concentrations of edoxaban are achieved 1–2 hours (h) after dosing and that elimination follows a biphasic pattern with a terminal elimination half-life of approximately 8–10 h (8). Edoxaban demonstrates linear PK with both area under the curve (AUC) and maximum plasma concentrations (Cmax) increasing in a dose-proportional fashion after administration of single doses up to 150 mg (8). The estimated oral bioavailability of edoxaban is at least 50%, and approximately 35% of the total administered oral dose is excreted via the kidneys (8). Pharmacodynamic (PD)
measures such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and anti-Xa levels are linearly correlated with edoxaban plasma concentrations, indicating that edoxaban produces a rapid and predictable anticoagulant effect (8).

In phase II dose-finding studies in patients undergoing elective hip or knee arthroplasty, once-daily (qd) edoxaban reduced the risk of postoperative venous thromboembolism in a dose-dependent fashion, while the rates of bleeding were similar across doses (9, 10). Building on this information and the PK results from phase I studies, we conducted a phase II dose-finding study to compare the safety of four fixed-dose regimens of edoxaban with that of warfarin (dose-adjusted to achieve a target INR between 2.0 and 3.0) in patients with non-valvular AF with at least two risk factors for stroke. In addition, the PK and PD of edoxaban were also determined.

Materials and methods

Study design

This was a multicentre, multinational study that used a randomised, parallel-group, multidose, active-controlled design. Patients between 18 and 85 years of age with persistent non-valvular AF with at least two risk factors for postoperative venous thromboembolism were randomised. W omen must have been postmenopausal and/or have undergone bilateral oophorectomy. Patients were excluded if they had mitral valve disease, endocarditis, or a mechanical valve; contraindications to anticoagulation therapy, including a known bleeding disorder, recent major bleeding, uncontrolled hypertension, a haemoglobin less than 10.0 g/dl, a platelet count less than 100,000/μl or a white blood cell count less than 3,000/μl; a requirement for ongoing treatment with a thienopyridine; AF secondary to reversible disorders (e.g., thyrotoxicosis); left ventricular aneurysm or atrial myxoma; an estimated life expectancy <12 months; planned surgery or intervention within the study period; a history of hepatitis B or C or HIV infection; serum transaminase and/or alkaline phosphatase ≥1.5 times the upper limit of normal (ULN) reference range or bilirubin ≥1.0 times ULN; creatinine clearance <30 ml/minute (min); a cardiac pacemaker or implantable cardioverter-defibrillator; investigational drug treatment (including edoxaban) or device implantation in the last three months, or plan to receive such therapy during the study period.

Using a central, interactive, automated telephone system, eligible patients who provided written informed consent were randomly allocated to receive one of four fixed-dose once daily (qd) or twice-daily (bid) edoxaban regimens (30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid) or warfarin in a 1:1:1:1 ratio. The randomisation schedule was generated by an independent biostatistician who was not part of the study team. The study was double-blind with respect to edoxaban dose, but open-label for randomisation between edoxaban and warfarin. Placebo edoxaban tablets were provided to patients randomised to edoxaban to maintain the blind for the edoxaban dose and dosing regimen. Patients taking warfarin who were randomised to edoxaban were instructed to stop warfarin and were started on study drug when their INR was less than or equal to 2.2. All patients received study drug for three months, with clinical and laboratory assessments scheduled for days 1 (randomisation), 7, 14, 21, 28, 42, 56, 70, and day 84 (end of treatment). Open-label warfarin was dose-adjusted to achieve a target INR of 2.0 to 3.0 and warfarin was started at a dose of ≤55 mg/day in those who were warfarin-naive or at their pre-study dose if they had been on warfarin prior to study entry. The study was approved by the Institutional Review Board of each participating study centre and carried out in accordance with the Declaration of Helsinki.

Endpoints

The primary outcome measures were related to safety and included bleeding and abnormalities of hepatic function. Suspected bleeding events were assessed by an independent blinded adjudication committee and were classified according to International Society on Thrombosis and Haemostasis guidelines (12) with minor modifications. Major bleeding was defined as bleeding that was fatal or in a critical site (intracranial, intraocular, intraspinal, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) or overt and associated with a decline in haemoglobin of ≥2 g/dl or requiring transfusion of ≥2 units of blood. Clinically relevant non-major bleeding was defined as bleeding that did not meet the definition of major bleeding, but was considered clinically significant (including spontaneous gastrointestinal bleeding or rectal bleeding; macroscopic haematuria or urethral bleeding requiring medical attention; skin haematoma ≥25 cm²; and gingival bleeding or spontaneous ear-nose-throat bleeding lasting ≥5 min) and/or resulted in discontinuation of study medication. Minor bleeding was defined as any bleeding that did not meet the criteria for a major or clinically relevant non-major bleeding event.

The incidence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) over three times ULN and/or bilirubin over two times ULN was also recorded.

Secondary endpoints included the incidence of major adverse cardiovascular events; a composite of stroke (ischaemic or haemorrhagic), systemic embolic event (SEE), myocardial infarction, cardiovascular death, and hospitalisation for any cardiac condition; and evaluation of edoxaban PK and PD markers.

PK and PD evaluations

Samples for PK measurements were collected prior to and 1–3 h after the day 28 morning dose in all patients randomised to edoxaban. Plasma concentrations of edoxaban were determined using
liquid chromatography and tandem mass spectrometry; an assay with a lower limit of detection of 0.76 ng/ml. The intra-day and inter-day precision of the assay was < 11% with a range of -6.9% to 5.8%. Using population PK methodology, post-hoc Bayesian estimates of steady-state plasma exposure parameters, including steady-state $C_{\text{max}}$ ($C_{\text{maxss}}$), minimum steady-state concentration ($C_{\text{minss}}$), and AUC from 0 to 24 h at steady-state ($AUC_{\text{ss}}$), were calculated for each subject (15). Details of the PK analysis will be presented separately elsewhere. Blood samples were collected at each visit for PD variables, including D-dimer and prothrombin fragment (F1+2), which were measured using the VIDAS® D-dimer Exclusion™ (Biomnis; Seine, France), and Enzygnost® (monoclonal) F1+2 (Dade Behring; Marberg, Germany) assays, respectively.

**Statistical methods**

The sample size was determined based on the precision of the estimate of the incidence of major plus clinically relevant non-major bleeding events or abnormalities in hepatic function. If the true incidence of either of these is 3%, a sample size of 200 patients per group provides an estimate of incidence with precision of 2.36% (95% confidence interval [CI], 0.64%–5.36%). The safety population and PK/PD population included all patients who received at least one dose of study drug and had at least one post-dose safety assessment or PK and/or PD assessment, respectively. The plasma edoxaban exposure metrics were summarised statistically as median values with upper and lower quartiles. Relationships between bleeding events and edoxaban exposure metrics were explored using linear logistic regression. The proportion of subjects with major plus clinically relevant non-major bleeding events during treatment (from the time of first dose to next day of last dose) and abnormalities in hepatic function post initial study dose were estimated for each treatment along with the 95% CI. Fisher’s exact test was used to test the hypothesis of equal proportion between each edoxaban dose regimen and warfarin. Change from baseline in D-dimer and F1+2 were summarised, and differences between treatment groups were estimated with 95% CI.
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Results

Study population

A total of 1,784 patients were screened; 1,146 patients were randomised and 889 patients completed the study. Disposition of patients is provided in Figure 1. The mean age of the safety population was 65 ± 8.7 years, 724/1,146 patients (63.3%) had a CHADS₂ score of 2, and 736/1,143 (64.4%) were warfarin-naïve. The edoxaban 60 mg bid treatment arm was prematurely terminated after 180 total patients were enrolled based on the recommendation of the independent Data Safety Monitoring Committee because of an excess of bleeding. Baseline characteristics of the safety population by treatment regimen are provided in Table 1.

Warfarin doses were adjusted based on INR values obtained by individual investigators at their local laboratories. The percentage

| Table 1: Baseline characteristics of the safety population. |
|----------------------------------|-------------------------------|-------------------------------|
|                                | Edoxaban                      | Warfarin                     |
|                                | 30 mg qd N = 235              | 30 mg bid N = 244             |
|                                | 60 mg qd N = 234              | 60 mg bid N = 180             |
| Age, mean ± SD (years)         | 65.2 ± 8.3                    | 64.8 ± 8.8                   |
| Male, n (%)                    | 140 (59.6)                    | 150 (61.5)                   |
| Race, n (%)                    |                               |                              |
| White                          | 230 (97.9)                    | 239 (98.0)                   |
| Black                          | 1 (0.4)                       | 0 (0.0)                      |
| Asian                          | 0 (0.0)                       | 1 (0.4)                      |
| Other                          | 4 (1.7)                       | 4 (1.6)                      |
| Geographic location, n (%)     |                               |                              |
| America                        | 20 (8.5)                      | 23 (9.4)                     |
| Eastern Europe                 | 215 (91.5)                    | 221 (90.6)                   |
| Warfarin-naïve, n (%)          | 159 (67.7)                    | 140 (57.4)                   |
| Aspirin on admission, n (%)    | 123 (52.3)                    | 121 (49.6)                   |
| Weight (kg), mean ± SD         | 89.0 ± 17.6                   | 87.8 ± 18.0                  |
| BMI (kg/m²), mean ± SD         | 30.5 ± 5.0                    | 30.4 ± 5.6                   |
| SBP, n (%)*                    |                               |                              |
| < 160 mm Hg                    | 203 (86.4)                    | 229 (93.9)                   |
| ≥ 160 mm Hg                    | 32 (13.6)                     | 15 (6.1)                     |
| Creatinine clearance (ml/min), | 88.38 ± 28.89                 | 86.59 ± 30.13                |
| mean ± SD                      | 24 (10.3)                     | 20 (10.3)                    |
| CHADS₂ index, n (%)            |                               |                              |
| 2                              | 148 (63.0)                    | 156 (63.9)                   |
| 3                              | 49 (20.9)                     | 50 (20.5)                    |
| 4–6                            | 38 (16.2)                     | 38 (15.6)                    |

*p = 0.033 across groups. bid, twice daily; BMI, body mass index; N, number; qd, once daily; SBP, systolic blood pressure; SD, standard deviation.

<table>
<thead>
<tr>
<th>INR range</th>
<th>Number (%) of subjects in the warfarin group</th>
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<tbody>
<tr>
<td>&lt; 2.0</td>
<td>226 (93.0) 174 (74.4) 129 (56.8) 122 (53.5) 106 (46.3) 93 (40.8) 93 (41.5) 93 (41.5) 87 (40.5)</td>
</tr>
<tr>
<td>≥ 2.0 to ≤ 3.0</td>
<td>16 (6.6) 50 (21.4) 74 (32.6) 81 (35.5) 98 (42.8) 115 (50.4) 114 (50.9) 110 (49.1) 108 (50.2)</td>
</tr>
<tr>
<td>≥ 1.8 to ≤ 3.2</td>
<td>29 (11.9) 68 (29.1) 97 (42.7) 110 (48.3) 130 (56.8) 136 (59.7) 143 (63.8) 134 (59.8) 139 (64.5)</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>1 (0.4) 10 (4.3) 24 (10.6) 25 (11.0) 25 (10.9) 20 (8.8) 17 (7.6) 21 (9.4) 20 (9.3)</td>
</tr>
<tr>
<td>&gt; 3.2</td>
<td>1 (0.41) 8 (3.4) 17 (7.5) 18 (7.9) 18 (7.9) 17 (7.5) 12 (5.4) 16 (7.1) 16 (7.4)</td>
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INR, international normalised ratio; N, number.
of subjects with INR values within the target range of 2.0 to 3.0 steadily increased from baseline. Based on local laboratory INR values (Table 2), the majority (almost 60%) of subjects had INR values ≥ 2.0, approximately 50% had INR values in the 2.0 to 3.0 range, and 60% had INR values within the range of 1.8 to 3.2 by week 6. The time in therapeutic range, calculated using the method of Rosendaal (16) and excluding INR values in the first six weeks of therapy, was 49.7% for an INR range of 2.0 to 3.0 and 63.9% for an extended therapeutic INR range of 1.8 to 3.2.

**Bleeding events**

Major plus clinically relevant non-major bleeding events were observed in 3.0%, 7.8%, 3.8%, 10.6%, and 3.2% of patients in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively (Table 3). Compared with warfarin, the incidence of major plus clinically relevant non-major bleeding was significantly higher with edoxaban doses of 30 mg bid or 60 mg bid. With the 30 mg or 60 mg qd edoxaban regimens, the incidence of major plus clinically relevant non-major bleeding was similar to that in patients randomised to warfarin. For the same total daily dose of 60 mg, the 30 mg bid edoxaban regimen was associated with a trend (p = 0.08) toward increased major plus clinically relevant non-major bleeding with the 60 mg qd edoxaban regimen.

**Other outcomes**

Overall, 95/235 (40.4%), 97/244 (39.8%), 99/234 (42.3%), 82/180 (45.6%), and 115/230 patients (46.0%) in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups reported treatment-emergent adverse events (TEAEs), respectively. Of these, 26 (11.1%), 33 (13.5%), 27 (11.5%), 40 (22.2%), and 46 patients (18.4%) in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively, were considered to be drug-related. Overall, the percentage of subjects with serious TEAEs was similar in the edoxaban (53/893; 5.9%) and warfarin (11/250; 4.4%) treatment groups.

The study was not powered for major adverse cardiovascular events, and few events were reported (Table 4). These included stroke (one, two, one, and one in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, and 60 mg bid groups, respectively, and three in the warfarin group), all of which were confirmed by computed tomography (CT) or autopsy, two transient ischaemic attacks (TIA) (one each in the edoxaban 60 mg bid and warfarin groups), both of which were
confirmed by a neurologist, and SEE (one each in the edoxaban 30 mg qd and 30 mg bid groups).

There were no differences in the incidence of abnormal hepatic function tests across treatment groups during treatment and follow-up periods. The proportion of patients with elevated ALT or AST (≥3 times ULN) were 3/230 (1.3%), 2/235 (0.9%), 7/229 (3.1%), 3/172 (1.7%), and 4/245 (1.6%) in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively. The proportion of patients with elevated bilirubin levels (≥2 times ULN) were 2/230 (0.9%), 3/235 (1.3%), 1/229 (0.4%), 5/172 (2.9%), and 4/245 (1.6%) in the edoxaban 30 mg qd, 30 mg bid, 60 mg qd, 60 mg bid, and warfarin treatment groups, respectively. There were two subjects (one each in the edoxaban bid groups) who experienced concomitant, but not persistent, elevations of ALT or AST ≥3 times ULN and total bilirubin ≥2 times ULN. Along with elevated ALT/AST and bilirubin, both subjects also had levels of alkaline phosphatase > 3 times ULN, suggesting cholestasis rather than drug-induced hepatocellular injury. Based on additional investigations, one subject was diagnosed with acute cholecystitis, while the abnormalities in the other were attributed to chronic heart failure with dilated bile ducts.

**Edoxaban PK**

The median (lower and upper quartiles) of edoxaban exposure parameters, Cmin, ss, AUCss, and Cmax, ss and the percentage of subjects with bleeding event by dose regimen are presented in Figure 2. Although all exposure parameters and bleeding rates increased with higher total daily doses of edoxaban, the frequency of bleeding correlated most closely with Cmin, ss. With the same total daily dose of 60 mg, both Cmin, ss and bleeding frequency were higher with the 30 mg bid regimen than with the 60 mg qd regimen.

**Biomarkers of activation of coagulation**

D-dimer is an indirect marker of increased activation of coagulation. As indicated in Figure 3, in warfarin naïve patients, D-dimer levels decreased from baseline in all treatment groups. The decrease was less apparent in warfarin experienced patients because baseline D-dimer levels were lower in these individuals. Notwithstanding the variability in this decrease, no significant differences were detected across treatment groups. Similar results
were observed with F$_{1+2}$, a marker of prothrombin activation (data not shown).

Discussion

The purpose of phase II trials is to identify drug doses that can safely be carried forward into phase III – a goal that was achieved by the current study. In this 12-week study, at doses of 30 or 60 mg qd, the rate of bleeding with edoxaban is similar to or less than that with warfarin. Therefore, these are the edoxaban doses that are being compared with warfarin for stroke prevention in AF in the phase III, ENGAGE AF-TIMI 48 trial (trial registration number: NCT00781391).

The higher bleeding rates observed with bid edoxaban dose regimens were an unexpected finding. Current thinking is that peak drug concentrations are an important contributor to bleeding (17, 18). Therefore, bid dose regimens are used to reduce the difference between peak and trough drug levels. However, the results of this study suggest that bleeding correlates better with trough edoxaban concentrations than it does with peak concentrations (19). This observation raises the possibility that there is a threshold of anticoagulant activity with edoxaban, which, if exceeded, can lead to bleeding. The trough edoxaban concentrations are higher with bid dose regimens than they are with qd regimens. Consequently, this threshold may only be transiently exceeded with qd edoxaban dosing regimens. A threshold of anticoagulation is also observed with warfarin where INR values > 4 are associated with an exponential increase in the risk of bleeding. FXa inhibitors provide more targeted anticoagulation than VKAs, which reduce the levels of all of the vitamin K-dependent coagulation factors. Nonetheless, like the situation with VKAs, time above a threshold level of anticoagulation with edoxaban also appears to result in a non-linear increase in bleeding relative to daily dose as evidenced by the trend for more bleeding with the 30 mg bid regimen than with the 60 mg qd regimen. Regardless of the mechanism responsible for this phenomenon, this study suggests that the risk of bleeding is lower with qd edoxaban regimens than it is with bid regimens.

Whether the link between the dose regimen and bleeding observed with edoxaban also occurs with other oral FXa inhibitors is unknown. Similar, large phase II studies were not performed with rivaroxaban or apixaban in patients with AF. However, when qd and bid rivaroxaban or apixaban regimens were evaluated for other indications, no major differences in the rates of bleeding were detected (13, 20–22). In the ongoing phase III trials comparing these agents with warfarin for stroke prevention in AF, rivaroxaban is administered qd, whereas apixaban is given bid. Dabigatran etexilate, an oral thrombin inhibitor, was evaluated in a phase II program in patients with AF. In this study, bid dabigatran etexilate dose regimens were more effective than qd regimens, but were associated with a small increase in bleeding – findings consistent with the results of the current study (23). However, when compared with warfarin in a large phase III trial, dabigatran 110 mg bid was associated with similar rates of stroke and systemic embolism as warfarin and significantly lower rates of major haemorrhage, whereas dabigatran 150 mg bid was associated with significantly lower rates of stroke and systemic embolism and a similar rate of major haemorrhage (14). Considering all the available data, therefore, it is unclear whether the findings with edoxaban can be translated to other oral FXa or thrombin inhibitors. However, because the pharmacological features of edoxaban are similar to those of other FXa inhibitors, it is unlikely that the relationship between dosing regimen and bleeding is unique to edoxaban.

It is not possible to assess the efficacy of edoxaban in this study because the number of patients is small, follow-up is short, and event rates are low. However, two lines of evidence support the effectiveness of the 30 and 60 mg qd dose regimens. First, when used for thromboprophylaxis in patients undergoing elective knee or hip surgery, both the 30 and the 60 mg qd dose reduced the rate of venous thromboembolism compared with placebo or dalteparin, respectively, without a significant increase in bleeding (9, 10). Second, both of these doses of edoxaban reduced plasma D-dimer and F$_{1+2}$ levels (biomarkers of ongoing activation of coagulation) to a

Figure 3: Median D-dimer values by treatment and by time in warfarin-naive and warfarin-experienced patients. BID, twice daily; QD, once daily.
What is known about this topic?
- Atrial fibrillation (AF) affects over 3 million people in the United States and 4.5 million in the European Union.
- Vitamin K antagonists (VKAs), such as warfarin, reduce the risk of stroke and death in patients with AF.
- VKAs have numerous limitations, which has prompted the development of new oral anticoagulants.

What does this paper add?
- Edoxaban is a new oral factor Xa inhibitor in development for stroke prevention.
- This phase II dose-finding study demonstrates that once-daily regimens of edoxaban (30 and 60 mg) have a safety profile similar to that of dose-adjusted warfarin.
- In contrast, twice-daily edoxaban regimens (30 and 60 mg) were associated with more bleeding than warfarin.

The focus of this study was on safety; the study was not powered to assess the efficacy of edoxaban. Suboptimal warfarin management may have limited the effectiveness of warfarin, leading to an overestimate of the efficacy of edoxaban. Nonetheless, the efficacy of edoxaban relative to warfarin will be established in the ongoing phase III trial.

In summary, edoxaban is a promising new oral FXa inhibitor that has potential in patients with AF. This phase II dose-finding study indicates that in this 12-week study, the 30 and 60 mg qd edoxaban regimens have a safety profile similar to that of dose-adjusted warfarin. Therefore, both doses are being carried forward into a randomised, double-blind, phase III trial where they are being compared with dose-adjusted warfarin for stroke prevention in patients with AF. Education of investigators and continuous monitoring of the quality of anticoagulation control at each study site have been implemented to ensure that the overall time in therapeutic range with warfarin is over 60% in this trial. By including daily doses that differ by two-fold, this phase III trial will define the therapeutic window for edoxaban.

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Disclosures
Jeffrey I. Weitz, MD, has been a consultant for and received honoraria from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer Ingelheim, Takeda, sanofi-aventis, and The Medicines Company. Dr Weitz was also a member of the Data Safety Monitoring Board for this study and received fees for this service from Daiichi Sankyo. Stuart J. Connolly, MD, has received consulting fees, lecture fees, and grant support from Boehringer Ingelheim. Dr Connolly was also a member of the Data Safety Monitoring Board for this study and received fees for this service from Daiichi Sankyo. Daniel Salazar, PhD, Jeanne Mendell, PhD, James Jin, PhD, Shashank Rohatagi, PhD, Indravadan Patel, MD, and Satoshi Kunitada, PhD, are full-time employees of Daiichi Sankyo. Helen Kastrissios, PhD, is an employee of Pharsight Corporation and has been a consultant for Daiichi Sankyo.

similar extent as warfarin. How these dose regimens of edoxaban will compare with warfarin for stroke prevention in AF remains to be established in the ongoing phase III trial.

The low stroke rate has deterred many experts from conducting phase II dose-finding studies with new oral anticoagulants in patients with AF. Nonetheless, the primary goal of phase II studies is to identify drug doses that can safely be carried forward into phase III. This study clearly identified edoxaban regimens that were associated with more bleeding than warfarin. Thus, the rate of bleeding was higher with the bid edoxaban regimens than it was with the qd regimens.

Effective stroke prevention with warfarin requires a time in therapeutic INR range of at least 60% (24). We did not achieve this goal, which highlights the problems that can occur when the majority of patients are enrolled in countries where VKAs other than warfarin are used, and where anticoagulation management is often suboptimal. Enrollment of predominantly warfarin-naïve patients also complicates anticoagulation management because such patients are slower and less likely to achieve a therapeutic INR. Thus, in the RE-LY trial (13), 61% of warfarin-naïve patients had their INR values within the target therapeutic range compared with 67% of those who were warfarin experienced.

What is the impact of suboptimal warfarin management on the results of this study? In effect, because only about half the patients had INR values within the therapeutic range, the various doses of edoxaban were compared with a subtherapeutic dose of warfarin. Consequently, we may be underestimating the risk of bleeding associated with warfarin therapy. In contrast, because fixed doses of edoxaban produce predictable levels of anticoagulation, the bleeding rates with edoxaban seen in this study are likely to be representative of what will be observed in the larger phase III trial. If the rates of bleeding with the 30 or 60 mg qd edoxaban regimens are similar to that observed with subtherapeutic warfarin doses, they should be at least the same, or even lower, than that with therapeutic doses of warfarin.
References