ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Edoxaban is a direct oral factor Xa inhibitor with proven antithrombotic effects. The long-term efficacy and safety of edoxaban as compared with warfarin in patients with atrial fibrillation is not known.

METHODS

We conducted a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

RESULTS

The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), as compared with 1.18% with high-dose edoxaban (hazard ratio, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority) and 1.61% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban versus warfarin (hazard ratio, 0.87; 97.5% CI, 0.73 to 1.04; P=0.08) and an unfavorable trend with low-dose edoxaban versus warfarin (hazard ratio, 1.13; 97.5% CI, 0.96 to 1.34; P=0.10). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The corresponding annualized rates of death from cardiovascular causes were 3.17% versus 2.74% (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), and 2.71% (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.008), and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (hazard ratio, 0.87; 95% CI, 0.78 to 0.96; P=0.005), and 4.23% (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; P=0.32).

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

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EDOXABAN IS AN ORAL, REVERSIBLE, DI-rect factor Xa inhibitor with a linear and predictable pharmacokinetic profile and 62% oral bioavailability.[1] It achieves maximum concentrations within 1 to 2 hours, and 50% is excreted by the kidney.[2] A randomized, dose-ranging, warfarin-controlled, phase 2 study involving 1146 patients with atrial fibrillation showed that once-daily doses of edoxaban (60 mg or 30 mg) were safer than twice-daily doses.[3] Pharmacokinetic modeling and simulation showed that patients with low body weight, moderate-to-severe renal dysfunction, or concomitant use of a potent P-glycoprotein inhibitor should have the edoxaban dose reduced by 50%.[4] A phase 3 study involving 8292 patients with acute venous thromboembolism showed that once-daily edoxaban at a dose of 60 mg (reduced to 30 mg in selected patients) was as effective as warfarin for the prevention of recurrent symptomatic venous thromboembolism and was associated with a significantly lower rate of bleeding.[5] We compared two dose regimens of once-daily edoxaban with warfarin in patients with atrial fibrillation who were at moderate-to-high risk for stroke.

METHODS

STUDY OVERSIGHT

The trial was designed and led by an executive committee, in coordination with an international steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol and amendments were approved by the ethics committee at each participating center. All the patients provided written informed consent. An independent data and safety monitoring committee performed multiple safety reviews. The Thrombolysis in Myocardial Infarction Study Group coordinated the trial and performed all the analyses independently using raw data. Quintiles, a contract research organization, managed the database and monitored the study sites. All the authors participated in the design of the trial and in the analysis of the data. The first author wrote the first draft of the manuscript, and all the authors participated in subsequent drafts and made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol,

which is available at NEJM.org. There were no contractual agreements with the sponsor that could have denied the investigators the right to examine the data independently or submit the manuscript for publication without consent of the sponsor.

TRIAL DESIGN

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial was a three-group, randomized, double-blind, double-dummy trial comparing two dose regimens of edoxaban with warfarin. We conducted the trial at 1393 centers in 46 countries (see the Supplementary Appendix). Patients were enrolled during the period from November 19, 2008, through November 22, 2010. The protocol and statistical analysis plan have been described previously.[6]

STUDY POPULATION

Eligible patients were 21 years of age or older and had atrial fibrillation documented by means of an electrical tracing within the 12 months preceding randomization, a score of 2 or higher on the $CHADS_2$ risk assessment, and anticoagulation therapy planned for the duration of the trial.[7] Scores on the $CHADS_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or transient ischemic attack is assigned 2 points. Key exclusion criteria were atrial fibrillation due to a reversible disorder; an estimated creatinine clearance of less than 30 ml per minute; a high risk of bleeding; use of dual antiplatelet therapy; moderate-to-severe mitral stenosis; other indications for anticoagulation therapy; acute coronary syndromes, coronary revascularization, or stroke within 30 days before randomization; and an inability to adhere to study procedures.[6]

RANDOMIZATION AND STUDY DRUGS

Patients were randomly assigned, in a 1:1:1 ratio, to receive warfarin, dose-adjusted to achieve an international normalized ratio (INR) of 2.0 to 3.0, or to receive high-dose or low-dose edoxaban. Randomization was performed with the use of a central, 24-hour, interactive, computerized response system. Patients who were already taking

a vitamin K antagonist underwent randomization after the INR was 2.5 or less. Randomization was stratified according to the following characteristics: CHADS$_2$ score of 2 or 3 versus a score of 4, 5, or 6 and status with respect to the need for a reduction in the edoxaban dose.[6]

The high-dose edoxaban group received 60 mg, and the low-dose group 30 mg. For patients in either group, the dose was halved if any of the following characteristics were present at the time of randomization or during the study: estimated creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less, or the concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors). A protocol amendment on December 22, 2010, mandated similar dose modifications in the case of concomitant use of dronedarone. After randomization, standard dosing was resumed if verapamil, quinidine, or dronedarone was discontinued and if there had been no other reason for a reduction of the edoxaban dose. Each patient received two sets of study drugs: either active edoxaban and a placebo matching warfarin, or a placebo matching edoxaban and active warfarin.

The INR was measured at least monthly with the use of an encrypted point-of-care device. To maintain blinding, sham INR values were generated for patients who were randomly assigned to edoxaban. The time in the therapeutic range in the warfarin group was calculated by means of linear interpolation,[8] with INR values rounded to the nearest 0.1.[9] Study visits were scheduled on days 8, 15, 29, and 60, at month 3, and at least every 3 months thereafter.

At the end of the trial, patients made the transition to open-label oral anticoagulation therapy with the use of a detailed plan (see the study protocol). Patients who made the transition from edoxaban to an open-label vitamin K antagonist received both active low-dose edoxaban and an open-label vitamin K antagonist until the INR reached 2.0 or for 2 weeks (whichever came first). At least three INR measurements were mandated between days 4 and 14 of the transition period; the use of an approved dosing algorithm for the vitamin K antagonist was required.

STUDY END POINTS

The primary efficacy end point was the time to the first adjudicated stroke (ischemic or hemorrhagic) or systemic embolic event. The principal safety end point was adjudicated major bleeding during treatment, as defined by the International Society on Thrombosis and Haemostasis.[10] Key secondary composite end points included the following: stroke, systemic embolic event, or death from cardiovascular causes (including bleeding); myocardial infarction, stroke, systemic embolic event, or death from cardiovascular causes; and stroke, systemic embolic event, or death from any cause. Net clinical end points included composites of stroke, systemic embolic event, major bleeding, or death; disabling stroke, life-threatening bleeding, or death; and stroke, systemic embolic event, life-threatening bleeding, or death.

An independent clinical end-point committee, whose members were unaware of the study assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, bleeding events, and hepatic events. Details of the definitions used by the clinical end-point committee are provided in the protocol.

STATISTICAL ANALYSIS

The primary efficacy analysis, which tested whether either dose regimen of edoxaban was noninferior to warfarin, was performed with the use of a Cox proportional-hazards model that included treatment groups and the two randomization stratification factors. This analysis included data from patients who underwent randomization and received at least one dose of the study drug during the treatment period (modified intention-to-treat population). The treatment period 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 the double-blind therapy (whichever came first), with interval censoring of events during study-drug interruptions that lasted more than 3 days. To satisfy noninferiority, the upper boundary of the one-sided 97.5% confidence interval for the hazard ratio of the primary efficacy end point comparing edoxaban with warfarin could not exceed 1.38, which was an estimate that preserved at least 50% of the benefit of warfarin over placebo.[11,12]

If an edoxaban dosing regimen met the prespecified criteria for noninferiority, that dose

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	Warfarin (N = 7036)	High-Dose Edoxaban (N = 7035)	Low-Dose Edoxaban (N = 7034)
Age — yr			
Median	72	72	72
Interquartile range	64–78	64–78	64–78
Female sex — no. (%)	2641 (37.5)	2669 (37.9)	2730 (38.8)
Region — no. (%)			
North America	1562 (22.2)	1559 (22.2)	1560 (22.2)
Latin America	888 (12.6)	886 (12.6)	887 (12.6)
Western Europe	1078 (15.3)	1079 (15.3)	1079 (15.3)
Eastern Europe	2381 (33.8)	2383 (33.9)	2380 (33.8)
Asia–Pacific region and South Africa	1127 (16.0)	1128 (16.0)	1128 (16.0)
Paroxysmal atrial fibrillation — no. (%)	1778 (25.3)	1753 (24.9)	1835 (26.1)
Qualifying risk factor — no. (%)			
Age ≥75 yr	2820 (40.1)	2848 (40.5)	2806 (39.9)
Prior stroke or transient ischemic attack	1991 (28.3)	1976 (28.1)	2006 (28.5)
Congestive heart failure	4048 (57.5)	4097 (58.2)	3979 (56.6)
Diabetes mellitus	2521 (35.8)	2559 (36.4)	2544 (36.2)
Hypertension requiring treatment	6588 (93.6)	6591 (93.7)	6575 (93.5)
CHADS$_2$ score†	2.8±1.0	2.8±1.0	2.8±1.0
≤3 — no. (%)	5445 (77.4)	5422 (77.1)	5470 (77.8)
4–6 — no. (%)	1591 (22.6)	1613 (22.9)	1564 (22.2)
Dose reduction at randomization — no. (%)‡	1787 (25.4)	1784 (25.4)	1785 (25.4)
Creatinine clearance ≤50 ml/min	1361 (19.3)	1379 (19.6)	1334 (19.0)
Weight ≤60 kg	701 (10.0)	684 (9.7)	698 (9.9)
Use of verapamil or quinidine	243 (3.5)	258 (3.7)	260 (3.7)
Previous use of vitamin K antagonist for ≥60 days — no. (%)	4138 (58.8)	4140 (58.8)	4163 (59.2)
Medication at time of randomization — no. (%)			
Aspirin	2092 (29.7)	2070 (29.4)	2018 (28.7)
Thienopyridine	164 (2.3)	174 (2.5)	149 (2.1)
Amiodarone	827 (11.8)	866 (12.3)	799 (11.4)
Digoxin or digitalis preparation	2176 (30.9)	2078 (29.5)	2073 (29.5)

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups in any of the characteristics listed.
† Scores on the CHADS$_2$ range from 0 to 6, with higher scores indicating a greater risk of stroke; congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point, and prior stroke or transient ischemic attack is assigned 2 points.
‡ Patients with a creatinine clearance of 50 ml per minute or less, those with a body weight of 60 kg or less, and those who were receiving the concomitant potent P-glycoprotein inhibitors verapamil or quinidine at randomization received a dose of edoxaban that was reduced by 50% to maintain an exposure level similar to that of patients who did not have any of these three factors. Patients may have had more than one reason for dose adjustment.

was then compared with warfarin in a test of superiority with the use of data from the intention-to-treat population, with all primary-endpoint events that occurred during the overall study period (i.e., from randomization to the end of the treatment period) considered in the analysis. To control the overall rate of a type I error with a two-sided alpha significance level of

0.025 for superiority, sequential multiplicity-adjustment procedures (closed testing) were used in a hierarchical fashion to test secondary end points in the intention-to-treat population (Fig. S1 in the Supplementary Appendix). We calculated that with approximately 672 primary-end-point events, the study would have more than 87% power to reject the null hypothesis that edoxaban was inferior to warfarin.[6]

RESULTS

PATIENTS AND FOLLOW-UP

The characteristics of the patients at baseline were well balanced (Table 1). Complete information on the primary end point was ascertained for 99.5% of the total 56,346 patient-years of potential follow-up (Fig. S2 in the Supplementary Appendix). One patient was lost to follow-up, and 244 patients withdrew consent to follow-up; 182 of these patients had no known primary-end-point event and were not known to be dead.

STUDY DRUGS

A total of 21,105 patients underwent randomization, of whom 21,026 (99.6%) received the study drug. A total of 5330 patients (25.3%) received a reduced dose of edoxaban or matching placebo at randomization, with similar rates in the three treatment groups. After randomization, dose reductions occurred in 7.1% of the patients, and dose increases in 1.2%, with similar rates in the three treatment groups. The median duration of treatment exposure was 907 days, excluding interruptions; the median follow-up was 1022 days (2.8 years).

Fewer patients in the warfarin group than in either edoxaban group completed the study without drug interruption (2421 in the warfarin group, as compared with 2621 in the high-dose edoxaban group and 2673 in the low-dose edoxaban group; P<0.001 for the comparisons of each dose of edoxaban with warfarin). Premature permanent discontinuation of the study drugs occurred in 2417 patients, 2415 patients, and 2309 patients in the three groups, respectively (Table S1 in the Supplementary Appendix). In the warfarin group, the median time in the therapeutic range was 68.4% of the treatment period (interquartile range, 56.5 to 77.4), and the mean (±SD) time in the therapeutic range was 64.9±18.7% of the treatment period; the INR was between 1.8 and 3.2 for 83.1% of the treatment period.

PRIMARY END POINT

During the treatment period, a stroke or systemic embolic event occurred in 232 patients in the warfarin group (representing a rate of 1.50% per year), as compared with 182 patients in the high-dose edoxaban group (a rate of 1.18% per year; hazard ratio vs. warfarin, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority, P=0.02 for superiority) and 253 patients in the low-dose edoxaban group (a rate of 1.61% per year; hazard ratio vs. warfarin, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority, P=0.44 for superiority) (Table 2).

In the prespecified superiority analysis for efficacy that was performed in the intention-to-treat population with data from the overall study period, the annualized rate of the primary end point was 1.80% in the warfarin group, as compared with 1.57% in the high-dose edoxaban group (hazard ratio vs. warfarin, 0.87; 97.5% CI, 0.73 to 1.04; P=0.08) and 2.04% in the low-dose edoxaban group (hazard ratio vs. warfarin, 1.13; 97.5% CI, 0.96 to 1.34; P=0.10) (Table 2 and Fig. 1A). The annualized rate of hemorrhagic stroke was 0.47% with warfarin, as compared with 0.26% with high-dose edoxaban (hazard ratio, 0.54; 95% CI, 0.38 to 0.77; P<0.001) and 0.16% with low-dose edoxaban (hazard ratio, 0.33; 95% CI, 0.22 to 0.50; P<0.001). The rate of ischemic stroke was 1.25% with warfarin as compared with 1.25% with high-dose edoxaban (hazard ratio, 1.00; 95% CI, 0.83 to 1.19; P=0.97) and 1.77% with low-dose edoxaban (hazard ratio, 1.41; 95% CI, 1.19 to 1.67; P<0.001).

At the end of the trial, seven primary-end-point events occurred in each treatment group during the 30-day transition period from treatment with the blinded study drug to receipt of an open-label anticoagulant agent. The rates of major bleeding and death were also similar among treatment groups during this transition period.

BLEEDING

The annualized rate of major bleeding events was 3.43% with warfarin, as compared with 2.75% with high-dose edoxaban (hazard ratio, 0.80; 95%

Table 2. Efficacy End Points.*

End Point	Warfarin (N=7036)		High-Dose Edoxaban (N=7035)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7034)		Low-Dose Edoxaban vs. Warfarin	
	no. of patients with event	% of patients/yr	no. of patients with event	% of patients/yr	Hazard Ratio (95% CI)	P Value	no. of patients with event	% of patients/yr	Hazard Ratio (95% CI)	P Value
Primary end point										
Modified intention-to-treat population in the treatment period†	232	1.50	182	1.18	0.79 (0.63–0.99)‡	<0.001	253	1.61	1.07 (0.87–1.31)‡	0.005
Intention-to-treat population in the overall study period§	337	1.80	296	1.57	0.87 (0.73–1.04)‡	0.08	383	2.04	1.13 (0.96–1.34)‡	0.10
Event during the 30-day transition¶	7	—	7	—	—	—	7	—	—	—
Stroke	317	1.69	281	1.49	0.88 (0.75–1.03)	0.11	360	1.91	1.13 (0.97–1.31)	0.12
Hemorrhagic	90	0.47	49	0.26	0.54 (0.38–0.77)	<0.001	30	0.16	0.33 (0.22–0.50)	<0.001
Ischemic	235	1.25	236	1.25	1.00 (0.83–1.19)	0.97	333	1.77	1.41 (1.19–1.67)	<0.001
Nondisabling and nonfatal‖	190	1.01	154	0.81	0.80 (0.65–0.99)	0.044	214	1.13	1.12 (0.92–1.36)	0.26
Disabling or fatal‖	135	0.71	132	0.69	0.97 (0.76–1.23)	0.81	152	0.80	1.11 (0.89–1.40)	0.36
Fatal	86	0.45	80	0.42	0.92 (0.68–1.25)	0.61	73	0.38	0.84 (0.61–1.15)	0.27
Systemic embolic event	23	0.12	15	0.08	0.65 (0.34–1.24)	0.19	29	0.15	1.24 (0.72–2.15)	0.43
Key secondary end points										
Stroke, systemic embolic event, or death from cardiovascular causes	831	4.43	728	3.85	0.87 (0.78–0.96)	0.005	796	4.23	0.95 (0.86–1.05)	0.32
Major adverse cardiac event**	926	4.98	827	4.41	0.88 (0.81–0.97)	0.01	913	4.90	0.98 (0.90–1.08)	0.69
Stroke, systemic embolic event, or death	1046	5.57	949	5.01	0.90 (0.82–0.98)	0.02	985	5.23	0.94 (0.86–1.02)	0.13

Other end points									
Death or intracranial hemorrhage	926	4.88	817	4.27	0.87 (0.79–0.96)	0.004	773	4.03	0.82 (0.75–0.90)	<0.001
Death or disabling stroke	878	4.61	812	4.24	0.92 (0.83–1.01)	0.08	794	4.15	0.90 (0.81–0.99)	0.02
Death									
Any cause	839	4.35	773	3.99	0.92 (0.83–1.01)	0.08	737	3.80	0.87 (0.79–0.96)	0.006
Cardiovascular causes	611	3.17	530	2.74	0.86 (0.77–0.97)	0.013	527	2.71	0.85 (0.76–0.96)	0.008
Myocardial infarction	141	0.75	133	0.70	0.94 (0.74–1.19)	0.60	169	0.89	1.19 (0.95–1.49)	0.13

*   Data are from the intention-to-treat cohort during the overall study period with 95% confidence intervals and P values for superiority, unless otherwise indicated. Patients in the modified intention-to-treat population received at least one dose of study drug.
†   Data are from noninferiority analyses of the primary end point. P values are in reference to the noninferiority boundary of 1.38. The P values for superiority were 0.02 for the comparison of high-dose edoxaban with warfarin and 0.44 for the comparison of low-dose edoxaban with warfarin. The analysis of the modified intention-to-treat population included data from 7012 patients in the warfarin group, 7012 in the high-dose edoxaban group, and 7002 in the low-dose edoxaban group.
‡   A 97.5% confidence interval was used.
§   Hazard ratios and confidence intervals were derived from a Cox model that included only patients who received the randomly assigned treatment; P values were calculated with the use of the log-rank test. All other analyses were performed with the use of a Cox model adjusted for the variables that were used to stratify randomization. This analysis represents the primary prespecified analysis for superiority.
¶   Data are from the 30-day period after the conclusion of the double-blind treatment phase; included are data from patients who were receiving the study treatment at the end of the double-blind treatment phase.
‖   Stroke severity was assessed by means of the Rankin score (with scores ranging from 0 to 6 and higher scores indicating greater severity). A score of 0, 1, or 2 indicated a nondisabling stroke, and a score of 3, 4, or 5 a nonfatal disabling stroke. A score of 6 indicated a fatal stroke.
** A major adverse cardiac event was defined as myocardial infarction, stroke, systemic embolic event, or death due to cardiovascular cause (including bleeding).

CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001) (Table 3 and Fig. 1B). The rates of life-threatening bleeding, intracranial bleeding, and major bleeding plus clinically relevant nonmajor bleeding were 0.78%, 0.85%, and 13.02%, respectively, with warfarin, as compared with 0.40%, 0.39%, and 11.10%, respectively, with high-dose edoxaban and 0.25%, 0.26%, and 7.97%, respectively, with low-dose edoxaban (P<0.001 for the comparison of warfarin with each dose of edoxaban). The annualized rate of major gastrointestinal bleeding was higher with high-dose edoxaban than with warfarin (1.51% vs. 1.23%), but the rate was lowest with low-dose edoxaban (0.82%).
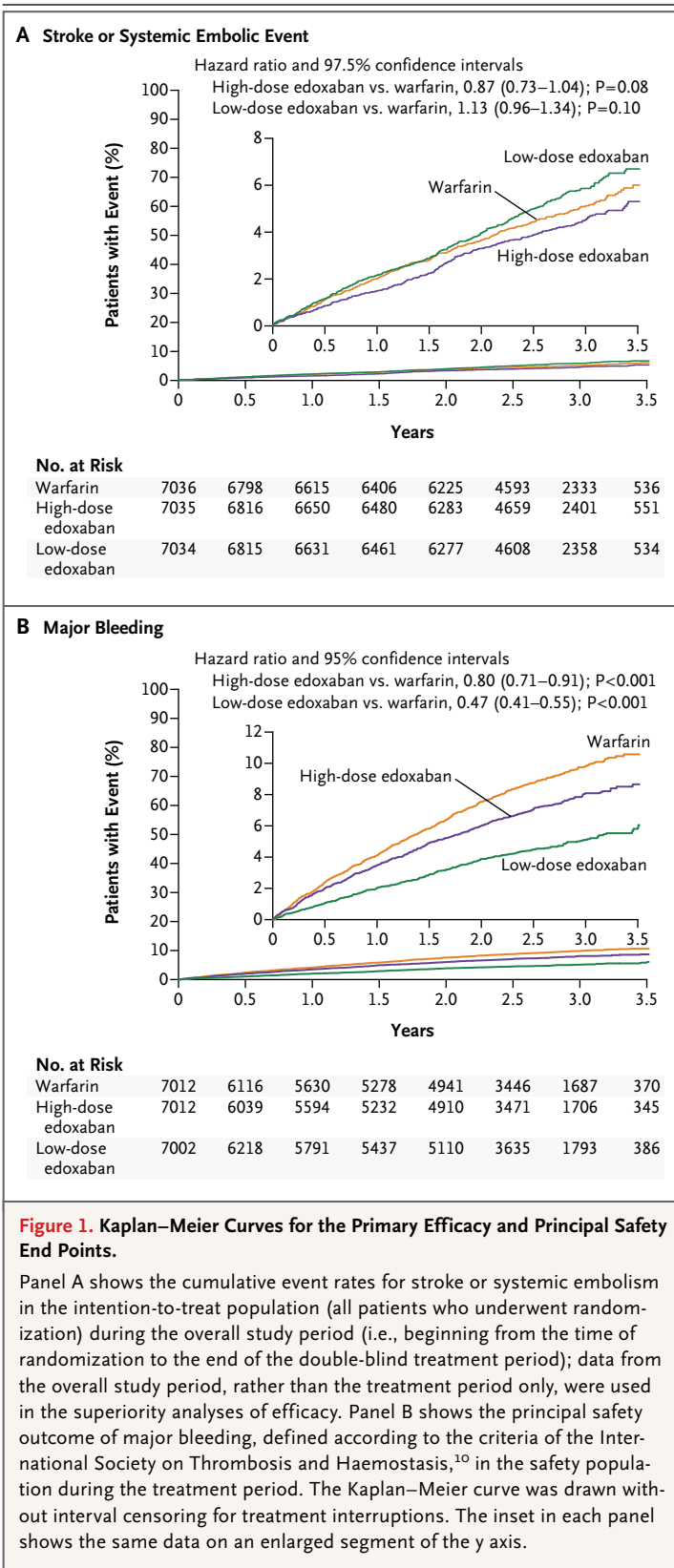
SECONDARY AND OTHER EFFICACY OUTCOMES

The rates of all three prespecified secondary composite outcomes were significantly lower with high-dose edoxaban than with warfarin (Table 2); there were no significant differences between low-dose edoxaban and warfarin in the rates of those outcomes. Treatment with edoxaban was associated with lower annualized rates of death from cardiovascular causes than was warfarin: 3.17% with warfarin, as compared with 2.74% with high-dose edoxaban (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01) and 2.71% with low-dose edoxaban (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.008), with findings in a similar direction for the rate of death from any cause.

The annualized rate of the primary net clinical outcome (death from any cause, stroke, systemic embolic event, or major bleeding) was significantly lower with both edoxaban regimens than with warfarin: 8.11% with warfarin, as compared with 7.26% with high-dose edoxaban (hazard ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.003) and 6.79% with low dose-edoxaban (hazard ratio, 0.83; 95% CI, 0.77 to 0.90; P<0.001) (Table 3). Similarly, as compared with warfarin, both edoxaban regimens were associated with significantly lower rates of the secondary net clinical outcome of death from any cause, disabling stroke, or life-threatening bleeding, and the tertiary net clinical outcome of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.

SUBGROUPS

In subgroup analyses of the primary efficacy end point, there were significant interactions

A Stroke or Systemic Embolic Event

Hazard ratio and 97.5% confidence intervals
High-dose edoxaban vs. warfarin, 0.87 (0.73–1.04); P=0.08
Low-dose edoxaban vs. warfarin, 1.13 (0.96–1.34); P=0.10

No. at Risk

Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

B Major Bleeding

Hazard ratio and 95% confidence intervals
High-dose edoxaban vs. warfarin, 0.80 (0.71–0.91); P<0.001
Low-dose edoxaban vs. warfarin, 0.47 (0.41–0.55); P<0.001

No. at Risk

Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

Figure 1. Kaplan–Meier Curves for the Primary Efficacy and Principal Safety End Points.

Panel A shows the cumulative event rates for stroke or systemic embolism in the intention-to-treat population (all patients who underwent randomization) during the overall study period (i.e., beginning from the time of randomization to the end of the double-blind treatment period); data from the overall study period, rather than the treatment period only, were used in the superiority analyses of efficacy. Panel B shows the principal safety outcome of major bleeding, defined according to the criteria of the International Society on Thrombosis and Haemostasis,[10] in the safety population during the treatment period. The Kaplan–Meier curve was drawn without interval censoring for treatment interruptions. The inset in each panel shows the same data on an enlarged segment of the y axis.

(at P<0.05) between treatment and subgroups defined according to status with respect to previous receipt of a vitamin K antagonist (warfarin vs. both edoxaban groups), concurrent aspirin use (warfarin vs. low-dose edoxaban group), and concurrent amiodarone use (warfarin vs. low-dose edoxaban group) (Fig. S3 in the Supplementary Appendix). The reduction in major bleeding with edoxaban as compared with warfarin was significantly greater among patients who received a dose reduction at randomization than among those who did not receive a dose reduction (Fig. S4 in the Supplementary Appendix).

OTHER SAFETY OUTCOMES

The rates of adverse events and serious adverse events were similar in the three groups (Table S1 in the Supplementary Appendix). The proportions of patients with an elevated level of liver enzymes or with hepatocellular injury were also similar in the three groups.

COMPARISON OF EDOXABAN REGIMENS

In the intention-to-treat analysis, the rate of stroke or systemic embolic event was lower with high-dose edoxaban than with low-dose edoxaban (P<0.001); this difference was driven by a relative reduction in the incidence of ischemic stroke of 29% with high-dose edoxaban (236 vs. 333 events), which more than offset a higher incidence of hemorrhagic stroke (49 events, vs. 30 events with low-dose edoxaban), although the hemorrhagic strokes had more severe sequelae than the ischemic strokes. As compared with high-dose edoxaban, low-dose edoxaban was associated with significantly lower rates of bleeding, including major bleeding, intracranial bleeding, and major or clinically relevant nonmajor bleeding. There were no significant differences between the two edoxaban groups in the rates of death from cardiovascular causes and death from any cause.

DISCUSSION

In this trial, both edoxaban regimens were noninferior to well-managed warfarin (median time in the therapeutic range, 68.4% of the treatment period) for the prevention of stroke or systemic embolic event; the high-dose edoxaban regimen tended to be more effective than warfarin. The rate of ischemic stroke was similar with high-

Table 3. Safety and Net Clinical End Points.*

Outcome	Warfarin (N=7012)		High-Dose Edoxaban (N=7012)		High-Dose Edoxaban vs. Warfarin		Low-Dose Edoxaban (N=7002)		Low-Dose Edoxaban vs. Warfarin	
	no. of patients with event	% of patients/yr	no. of patients with event	% of patients/yr	Hazard Ratio (95% CI)	P Value	no. of patients with event	% of patients/yr	Hazard Ratio (95% CI)	P Value
Major bleeding	524	3.43	418	2.75	0.80 (0.71–0.91)	<0.001	254	1.61	0.47 (0.41–0.55)	<0.001
Fatal	59	0.38	32	0.21	0.55 (0.36–0.84)	0.006	21	0.13	0.35 (0.21–0.57)	<0.001
Bleeding into a critical organ or area	211	1.36	108	0.70	0.51 (0.41–0.65)	<0.001	69	0.44	0.32 (0.24–0.42)	<0.001
Overt bleeding with blood loss of ≥2 g/dl	327	2.13	317	2.08	0.98 (0.84–1.14)	0.78	187	1.19	0.56 (0.47–0.67)	<0.001
Any intracranial bleeding	132	0.85	61	0.39	0.47 (0.34–0.63)	<0.001	41	0.26	0.30 (0.21–0.43)	<0.001
Fatal intracranial bleeding	42	0.27	24	0.15	0.58 (0.35–0.95)	0.03	12	0.08	0.28 (0.15–0.53)	<0.001
Gastrointestinal bleeding	190	1.23	232	1.51	1.23 (1.02–1.50)	0.03	129	0.82	0.67 (0.53–0.83)	<0.001
Upper gastrointestinal tract	111	0.71	140	0.91	1.27 (0.99–1.63)	0.06	88	0.56	0.78 (0.59–1.03)	0.08
Lower gastrointestinal tract	81	0.52	96	0.62	1.20 (0.89–1.61)	0.23	44	0.28	0.54 (0.37–0.77)	<0.001
Bleeding in other location	211	1.37	131	0.85	0.62 (0.50–0.78)	<0.001	87	0.55	0.40 (0.31–0.52)	<0.001
Bleeding during transition to open-label oral anticoagulation therapy										
Day 1–14	6	—	4	—	—	—	5	—	—	—
Day 15–30	5	—	6	—	—	—	13	—	—	—
Life-threatening bleeding	122	0.78	62	0.40	0.51 (0.38–0.70)	<0.001	40	0.25	0.32 (0.23–0.46)	<0.001
Clinically relevant nonmajor bleeding	1396	10.15	1214	8.67	0.86 (0.79–0.93)	<0.001	969	6.60	0.66 (0.60–0.71)	<0.001
Minor bleeding	714	4.89	604	4.12	0.84 (0.76–0.94)	0.002	533	3.52	0.72 (0.65–0.81)	<0.001
Major or clinically relevant nonmajor bleeding	1761	13.02	1528	11.10	0.86 (0.80–0.92)	<0.001	1161	7.97	0.62 (0.57–0.67)	<0.001
Any overt bleeding	2114	16.40	1865	14.15	0.87 (0.82–0.92)	<0.001	1499	10.68	0.66 (0.62–0.71)	<0.001
Net clinical outcome†										
Primary	1462	8.11	1323	7.26	0.89 (0.83–0.96)	0.003	1248	6.79	0.83 (0.77–0.90)	<0.001
Secondary	987	5.23	883	4.64	0.88 (0.81–0.97)	0.008	837	4.38	0.83 (0.76–0.91)	<0.001
Tertiary	1123	6.02	999	5.30	0.88 (0.81–0.96)	0.003	1010	5.37	0.89 (0.82–0.97)	0.007

* Data are from the safety cohort during the treatment period (which began when the first dose of study drug was administered), with interval censoring of events during study-drug interruptions that lasted more than 3 days, except for net clinical outcomes, which are presented for the overall treatment period (which began at the time of randomization).

† The primary net clinical outcome was a composite of stroke, systemic embolic event, major bleeding, or death from any cause. The secondary net clinical outcome was a composite of disabling stroke, life-threatening bleeding, or death from any cause. The tertiary net clinical outcome was an exploratory composite of stroke, systemic embolic event, life-threatening bleeding, or death from any cause.

dose edoxaban and warfarin but was higher with the low-dose edoxaban regimen. The incidence of hemorrhagic stroke and the rate of death from cardiovascular causes were significantly lower with both edoxaban regimens than with warfarin.

As compared with warfarin, edoxaban was associated with consistently lower, dose-related rates of all types of bleeding, including major bleeding, intracranial bleeding, and life-threatening bleeding. The single exception was gastrointestinal bleeding, which occurred more frequently with high-dose edoxaban but less frequently with low-dose edoxaban than it did with warfarin. The rates of net clinical outcomes, which were composites of cardiovascular events, death from any cause, or bleeding, were significantly lower with both edoxaban regimens than with warfarin. The very low rate of missing data (0.5%) underscores the robustness of these observations.[13,14]

The primary efficacy and safety findings were consistent across major subgroups, including those defined according to demographic characteristics of the patients, risk of stroke (as defined by the CHADS$_2$ score), and geographic region, with three notable exceptions. First, patients who had not previously received a vitamin K antagonist had significantly fewer stroke or systemic embolic events with high-dose edoxaban than with warfarin, whereas the rates were similar among patients who had previously received a vitamin K antagonist. Second, the concomitant use of amiodarone and low-dose edoxaban, as well as the concomitant use of aspirin and low-dose edoxaban, appeared to increase the treatment effect of low-dose edoxaban — a finding that was possibly related to a modest increase in edoxaban levels with amiodarone[15] and enhanced stroke prevention with aspirin.[11] Third, a reduction in the edoxaban dose in patients with moderate renal impairment, a body weight of 60 kg or less, or the concomitant use of P-glycoprotein inhibitors was associated with a decreased risk of bleeding with both regimens. Subgroup analyses exploring relationships among safety, efficacy, and dose reduction (as compared with no dose reduction) showed an even greater reduction in bleeding with edoxaban as compared with warfarin among patients who underwent dose reduction, without an apparent loss in efficacy (Fig. S3 and S4 in the Supplementary Appendix). In addition, dose modifications were permitted after randomization, since factors that affect drug clearance may vary over time.

Edoxaban appeared to be safe, had no unexpected side effects, had fewer side effects than warfarin (as managed with a median time in the therapeutic range of 68.4% of the treatment period), and had a favorable net clinical outcome. Although no specific antidote for edoxaban is currently available, hemostatic agents reverse its anticoagulant effect.[16] The availability of a reliable factor Xa assay[17] and specific reversal strategies[18] in urgent clinical situations could potentially improve the safety profile of edoxaban, but no particular strategy is well accepted in practice at this time. The rate of myocardial infarction was not altered with edoxaban, and there was no increase in the risk of stroke or bleeding when patients in the edoxaban groups made the transition to open-label anticoagulant therapy at the end of the study.

In previous studies involving patients with atrial fibrillation, dabigatran, rivaroxaban, and apixaban were at least as efficacious as warfarin and were associated with lower rates of intracranial bleeding.[19-21] Similar to edoxaban, these drugs can be given in fixed doses without routine laboratory monitoring and have fewer drug–drug and food–drug interactions than vitamin K antagonists. Although there may be subtle differences among the new anticoagulant agents with respect to the prevention of ischemic stroke, myocardial infarction, bleeding, or death,[22] direct comparative studies are needed to determine whether these are real differences in clinical efficacy and safety or whether they reflect differences in the pharmacologic properties, the doses used, the patient populations, the quality of warfarin management, or other aspects of the trial designs.[23]

Strengths of the ENGAGE AF-TIMI 48 trial include the large sample size, long follow-up, minimal amount of missing data, greater-than-average time in the therapeutic range in the warfarin group, and the inclusion of multiple once-daily doses[24,25] of a new anticoagulant agent ranging from 15 to 60 mg with dynamic dose modification. In addition, the implementation of a comprehensive transition plan to open-label anticoagulation therapy resulted in a low and evenly distributed number of events after the discontinuation of study therapy. This finding

makes it unlikely that there is a rebound activation of coagulation after the discontinuation of edoxaban.

In conclusion, both once-daily regimens of edoxaban were noninferior to warfarin for the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

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