ORIGINAL ARTICLE

Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease

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ABSTRACT

BACKGROUND

Despite consistent recommendations from clinical guidelines, data from randomized trials on a long-term antithrombotic treatment strategy for patients with atrial fibrillation and stable coronary artery disease are still lacking.

METHODS

We conducted a multicenter, open-label, adjudicator-masked, randomized trial comparing edoxaban monotherapy with dual antithrombotic therapy (edoxaban plus a single antiplatelet agent) in patients with atrial fibrillation and stable coronary artery disease (defined as coronary artery disease previously treated with revascularization or managed medically). The risk of stroke was assessed on the basis of the CHA_2DS_2-VASc score (scores range from 0 to 9, with higher scores indicating a greater risk of stroke). The primary outcome was a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, and major bleeding or clinically relevant nonmajor bleeding at 12 months. Secondary outcomes included a composite of major ischemic events and the safety outcome of major bleeding or clinically relevant nonmajor bleeding.

RESULTS

We assigned 524 patients to the edoxaban monotherapy group and 516 patients to the dual antithrombotic therapy group at 18 sites in South Korea. The mean age of the patients was 72.1 years, 22.9% were women, and the mean CHA_2DS_2-VASc score was 4.3. At 12 months, a primary-outcome event had occurred in 34 patients (Kaplan–Meier estimate, 6.8%) assigned to edoxaban monotherapy and in 79 patients (16.2%) assigned to dual antithrombotic therapy (hazard ratio, 0.44; 95% confidence interval [CI], 0.30 to 0.65; P<0.001). The cumulative incidence of major ischemic events at 12 months appeared to be similar in the trial groups. Major bleeding or clinically relevant nonmajor bleeding occurred in 23 patients (Kaplan–Meier estimate, 4.7%) in the edoxaban monotherapy group and in 70 patients (14.2%) in the dual antithrombotic therapy group (hazard ratio, 0.34; 95% CI, 0.22 to 0.53).

CONCLUSIONS

In patients with atrial fibrillation and stable coronary artery disease, edoxaban monotherapy led to a lower risk of a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding at 12 months than dual antithrombotic therapy. (Funded by the CardioVascular Research Foundation and others; EPIC-CAD ClinicalTrials.gov number, NCT03718559.)

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*A full list of the investigators in the EPIC-CAD trial is provided in the Supplementary Appendix, available at NEJM.org.

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This article was published on September 1, 2024, at NEJM.org.

DOI: 10.1056/NEJMoa2407362

Atrial fibrillation is common among patients with atherosclerotic coronary artery disease, but choosing the appropriate antithrombotic therapy for patients with both conditions is challenging.[1,2] Patients with atrial fibrillation need oral anticoagulants to prevent stroke or systemic embolism, whereas antiplatelet therapy is indicated to prevent ischemic events in patients with coronary artery disease. However, the combined use of an antiplatelet regimen and an anticoagulant regimen in patients with atrial fibrillation and concomitant coronary artery disease increases the risk of bleeding.[3,4]

Over the past decade, several clinical trials have evaluated various non–vitamin K oral anticoagulants for patients with atrial fibrillation immediately after percutaneous coronary intervention (PCI) or an acute coronary syndrome.[5-8] On the basis of these trials, contemporary clinical guidelines recommend the combined use of a direct oral anticoagulant and a P2Y12 inhibitor as the most favorable treatment option for 6 to 12 months after the index PCI or cardiac event.[9-14] Moreover, these guidelines uniformly recommend the use of monotherapy with oral anticoagulants after the early period of dual antithrombotic treatment; however, there is limited supporting evidence from randomized trials.[15,16]

Two trials that have evaluated long-term antithrombotic strategies (one with warfarin and one with rivaroxaban) in patients with atrial fibrillation and stable coronary artery disease showed a lower incidence of bleeding with oral anticoagulant monotherapy than with combination therapy including a single antiplatelet agent.[15,16] However, both trials were terminated prematurely,[15,16] and the trial of rivaroxaban did not use the globally approved standard dose of the drug.[16] We conducted the Edoxaban versus Edoxaban with Antiplatelet Agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease (EPIC-CAD) trial to assess whether the incidence of adverse clinical events is lower with standard-dose edoxaban monotherapy than with dual antithrombotic therapy consisting of edoxaban plus a single antiplatelet agent in patients with atrial fibrillation and stable coronary artery disease that had previously been treated with revascularization or managed medically.

METHODS

TRIAL DESIGN AND OVERSIGHT

EPIC-CAD was a multicenter, open-label, adjudicator-masked, randomized trial. The trial rationale and design have been published previously.[17] Details regarding the participating investigators and trial organization are provided in the Supplementary Appendix (available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) and subsequent amendments were approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent before enrollment.

The trial was funded by an investigator-initiated grant from the CardioVascular Research Foundation (South Korea) under a contract with Daiichi Sankyo and Daewoong Pharmaceutical. The funders had no role in the design or conduct of the trial, analysis of the data, or preparation of the manuscript. An independent data and safety monitoring board reviewed unblinded patient-level data at regular intervals. All the authors vouch for the adherence of the trial to the protocol. The first, second, and last two authors wrote the first draft of the manuscript and vouch for the accuracy and completeness of the data.

TRIAL POPULATION

Patients at least 18 years of age who had prevalent or paroxysmal atrial fibrillation and concomitant stable coronary artery disease were eligible for enrollment. Patients with atrial fibrillation were screened with the use of the CHA_2DS_2-VASc score (scores range from 0 to 9, with higher scores indicating a greater risk of stroke),[18] and patients considered to be at high risk for thromboembolism (as defined by a CHA_2DS_2-VASc score of 2 or more) were enrolled. Stable coronary artery disease was defined as a chronic coronary syndrome previously treated with PCI or coronary-artery bypass grafting (CABG) at least 6 months before enrollment, an acute coronary syndrome previously treated with PCI or CABG at least 12 months before enrollment, or anatomically confirmed coronary artery disease (≥50% stenosis of a major epicardial coronary artery on cardiac catheterization or coronary computed tomographic angiog-

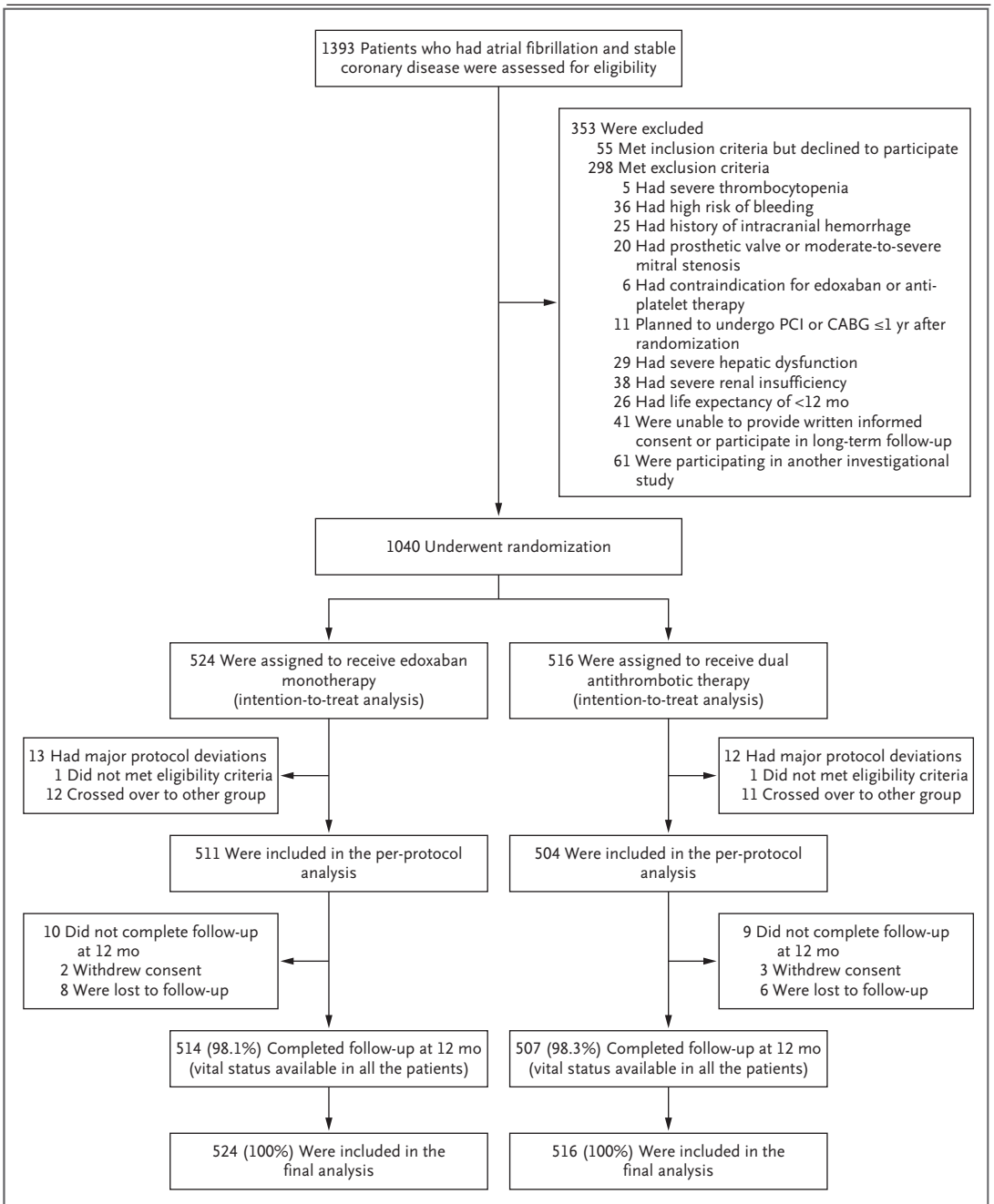


Figure 1. Enrollment, Randomization, and Follow-up.

Patients were randomly assigned in a 1:1 ratio to receive edoxaban monotherapy or dual antithrombotic therapy consisting of edoxaban plus a single antiplatelet agent (either aspirin or a P2Y12 inhibitor). CABG denotes coronary-artery bypass grafting, and PCI percutaneous coronary intervention.

raphy) managed with the use of medical therapy alone. We also evaluated the bleeding risk at baseline as defined by the HAS-BLED score, which ranges from 0 to 9, with higher scores indicating a greater risk.[19]

Key exclusion criteria were contraindications for antithrombotic drugs, including severe coexisting conditions or a high risk of bleeding, a history of intracranial hemorrhage, prosthetic heart valves or moderate-to-severe mitral stenosis, and severe hepatic dysfunction or severe renal insufficiency. Details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)
Age — yr	71.7±8.0	72.5±8.4
Male sex — no. (%)	396 (75.6)	406 (78.7)
Weight — kg	68.3±11.8	68.9±11.2
Body-mass index†	25.3±3.3	25.4±3.3
Diabetes mellitus — no. (%)	224 (42.7)	197 (38.2)
Hypertension — no. (%)	423 (80.7)	422 (81.8)
Hyperlipidemia or statin use — no. (%)	490 (93.5)	482 (93.4)
Current smoker — no. (%)	37 (7.1)	50 (9.7)
Previous myocardial infarction — no. (%)	79 (15.1)	92 (17.8)
Congestive heart failure — no. (%)	96 (18.3)	109 (21.1)
History of cerebrovascular disease — no. (%)	77 (14.7)	77 (14.9)
History of peripheral artery disease — no. (%)	33 (6.3)	45 (8.7)
Creatinine clearance — ml/min‡	67.0±23.6	66.0±21.4
Type of atrial fibrillation — no. (%)		
Paroxysmal	292 (55.7)	283 (54.8)
Persistent or permanent	232 (44.3)	233 (45.2)
CHA_2DS_2-VASc score§		
Mean	4.3±1.6	4.4±1.5
Median (IQR)	4 (3–5)	4 (3–5)
$CHADS_2$ score¶		
Mean	2.1±1.2	2.2±1.2
Median (IQR)	2 (1–3)	2 (1–3)
HAS-BLED score‖		
Mean	2.1±0.8	2.2±0.8
Median (IQR)	2 (2–3)	2 (2–3)
Obstructive coronary artery disease — no. (%)**	188 (35.9)	169 (32.8)
Previous coronary revascularization — no. (%)	336 (64.1)	347 (67.2)
Previous percutaneous coronary intervention		
Overall — no. (%)	308 (58.8)	318 (61.6)
Drug-eluting stent — no./total no. (%)	251/308 (81.5)	267/318 (84.0)
Bare-metal stent — no./total no. (%)	13/308 (4.2)	7/318 (2.2)
Both stent types — no./total no. (%)	8/308 (2.6)	4/318 (1.3)
Unknown stent type — no./total no. (%)	36/308 (11.7)	40/318 (12.6)

Table 1. (Continued.)

Characteristic	Edoxaban Monotherapy (N = 524)	Dual Antithrombotic Therapy (N = 516)
Previous CABG — no. (%)	41 (7.8)	36 (7.0)
Previous or concomitant PPI use — no. (%)	59 (11.3)	74 (14.3)
Indication for dose adjustment of edoxaban — no. (%)††	178 (34.0)	168 (32.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CABG denotes coronary-artery bypass grafting, IQR interquartile range, and PPI proton-pump inhibitor.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Creatinine clearance was assessed with the Cockcroft–Gault formula.
§ The CHA_2DS_2-VASc score is a measure of the risk of stroke among persons with atrial fibrillation. Scores are weighted on the basis of the presence of congestive heart failure, hypertension, diabetes mellitus, and vascular disease; a history of stroke or transient ischemic attack; an age of 65 to 74 years or 75 years or older; and sex. Scores range from 0 to 9, with higher scores indicating a greater risk.[18]
¶ The $CHADS_2$ score is a measure of the risk of stroke among persons with atrial fibrillation. Scores are weighted on the basis of the presence of congestive heart failure, hypertension, and diabetes mellitus; an age of 75 years or older; and a history of stroke or transient ischemic attack. Scores ranges from 0 to 6, with higher scores indicating a greater risk.[27]
‖ The HAS-BLED score is a measure of the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy. Scores are weighted on the basis of the presence of hypertension, abnormal renal function, and abnormal liver function; a history of stroke or bleeding; the labile international normalized ratio; an age of 65 years or older; and the use of medications or consumption of alcohol at a level that increases the risk of bleeding. Scores range from 0 to 9, with higher scores indicating a greater risk.[19]
** Obstructive coronary artery disease was managed with the use of medical therapy alone and was confirmed anatomically on the basis of at least 50% stenosis of major epicardial vessels on coronary angiography in 165 patients (46.2%) and on coronary computed tomographic angiography in 192 patients (53.7%).
†† Indications for adjustment of the edoxaban dose included a creatinine clearance rate of 50 ml or less per minute, a body weight of 60 kg or less, and concomitant therapy with a P-glycoprotein inhibitor.

RANDOMIZATION AND TRIAL REGIMEN

Trial participants were randomly assigned in a 1:1 ratio to receive either monotherapy with standard-dose (60 mg once daily) edoxaban or dual antithrombotic therapy that included standard-dose edoxaban plus a single antiplatelet agent (either aspirin or a P2Y12 inhibitor, according to the discretion of the treating physician). Indications for dose adjustment of edoxaban to 30 mg once daily were a creatinine clearance of 15 to 50 ml per minute (as assessed with the Cockcroft–Gault formula), a body weight of 60 kg or less, and the use of certain P-glycoprotein inhibitors. Randomization was performed by means of a central, Web-based interactive response system with block sizes of 4 or 6, stratified according to the participating site. Details regarding the randomization procedure and administration of the trial regimens are provided in the Supplementary Appendix.

Follow-up assessments were performed at baseline and 6 and 12 months after randomization. At each visit, all information regarding clinical events and concomitant cardiovascular medications was systematically collected. Cross-validation of survival status was performed with the use of the Korean National Health Insurance database.[20]

OUTCOMES

The primary outcome was net adverse clinical events (i.e., efficacy and safety outcomes), defined as a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (as defined by the International Society on Thrombosis and Haemostasis),[21] at 12 months after randomization. The secondary outcomes included individual components of the primary outcome; stent thrombosis; a composite of major ischemic events (death from any cause, myocardial infarction, ischemic stroke, or systemic embolism); a composite of major bleeding or clinically relevant nonmajor bleeding; fatal bleeding; major bleeding; and any bleeding event. Bleeding was also classified according to the Bleeding Academic Research Consortium definition and the Throm-

bolysis in Myocardial Infarction definition.[22,23] A detailed list of the trial outcomes is provided in the Supplementary Appendix.

Prespecified, standard definitions were used for the assessment of each clinical outcome (see the Supplementary Appendix). All clinical outcomes were adjudicated by an independent clinical events committee, whose members were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

The primary hypothesis was that edoxaban monotherapy would be superior to dual antithrombotic therapy with respect to the primary net clinical outcome. On the basis of previous trials,[24,25] we assumed that the incidence of the primary outcome at 12 months would be 13% in the edoxaban monotherapy group and 18% in the dual antithrombotic therapy group. We estimated that the enrollment of 1038 patients would provide the trial with 80% power to detect a relative reduction of 30% in the incidence of a primary outcome event in the monotherapy group as compared with the dual therapy group at a significance level of 0.05 on the basis of a two-sided log-rank test of survival. In this final sample-size calculation, we assumed a 6% incidence of attrition (with loss to follow-up occurring in 3.0% of the patients and nonadherence or crossover occurring in 3.0%) and 3 years of total trial time, including the 2-year recruitment period. Additional details regarding estimation of the sample size are provided in the Supplementary Appendix.

All analyses were performed in the intention-to-treat population. Cumulative-event probabilities were estimated by means of the Kaplan–Meier method and were compared with the use of the log-rank test. Treatment effects were estimated with Cox proportional-hazards regression and are presented as hazard ratios with 95% confidence intervals. The difference in cumulative incidence and the associated 95% confidence interval for trial outcomes at 12 months were calculated with the use of Kaplan–Meier estimates and Greenwood standard errors.[26] Sensitivity analyses were performed in the per-protocol population, which included patients who underwent randomization and had no major protocol deviations. Subgroup analysis of the primary outcome was performed according to the prespecified clinical factors. No imputation methods were used to infer missing values of baseline variables.

The confidence intervals have not been adjusted for multiple comparisons; thus, these intervals should not be used to infer definitive treatment effects. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software, version 4.3 (R Foundation for Statistical Computing). Additional details regarding the statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From May 14, 2019, through September 19, 2022, a total of 1393 patients were assessed for eligibility, of whom 1040 underwent randomization at 18 sites in South Korea (Fig. 1). The baseline characteristics of the patients appeared to be well balanced between the two groups (Table 1 and Table S1 in the Supplementary Appendix). The mean (±SD) age of the patients was 72.1±8.2 years, and 22.9% of the patients were women. Of the patients who underwent randomization, 683 (65.7%) had previously undergone coronary revascularization (isolated PCI in 88.7%, isolated CABG in 8.3%, and both PCI and CABG in 2.9%), and 357 (34.3%) had anatomically confirmed coronary artery disease that was medically managed only. A total of 55.3% of the patients had paroxysmal atrial fibrillation, and 44.7% had prevalent (persistent or permanent) atrial fibrillation. The mean CHA_2DS_2-VASc score was 4.3±1.5 points, and the mean HAS-BLED score was 2.2±0.8 points.

TREATMENTS AND FOLLOW-UP

Details regarding the antithrombotic regimens used before randomization and the trial drugs used after randomization are summarized in Table S2. Before randomization, 44.6% of the patients were receiving dual antithrombotic therapy, 45.2% were receiving oral anticoagulants alone, and 8.9% were receiving antiplatelet therapy alone. After randomization, 521 of 524 patients (99.4%) in the edoxaban monotherapy group and 514 of 516 patients (99.6%) in the dual antithrombotic therapy group started their assigned antithrombotic treatment. Edoxaban doses of 60 mg and

Table 2. Primary and Secondary Outcomes at 12 Months after Randomization.*

Outcome	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)	Difference, Dual Therapy vs. Monotherapy (95% CI)	Hazard Ratio, Monotherapy vs. Dual Therapy (95% CI)
	no. of patients (estimated %)		*percentage points*	
Primary outcome				
Net adverse clinical events†	34 (6.8)	79 (16.2)	9.41 (5.40 to 13.42)	0.44 (0.30 to 0.65)
Secondary outcomes				
Efficacy				
Death				
Any cause	3 (0.6)	3 (0.7)	0.08 (–0.97 to 1.13)	1.29 (0.29 to 5.76)
Cardiovascular cause	2 (0.4)	1 (0.2)	–0.17 (–0.86 to 0.52)	1.66 (0.16 to 17.14)
Noncardiovascular cause	1 (0.2)	2 (0.5)	0.25 (–0.55 to 1.05)	1.02 (0.14 to 7.22)
Stroke				
Any event	7 (1.4)	4 (0.8)	–0.60 (–1.89 to 0.69)	NR‡
Ischemic event	5 (1.0)	3 (0.6)	–0.41 (–1.53 to 0.70)	1.82 (0.46 to 7.14)
Hemorrhagic event	2 (0.4)	1 (0.2)	–0.19 (–0.84 to 0.47)	1.64 (0.16 to 17.00)
Systemic embolic event	0	0	NA	NA
Myocardial infarction	0	2 (0.5)	0.46 (–0.18 to 1.11)	NR‡
Unplanned urgent revascularization	7 (1.4)	6 (1.4)	0.0 (–1.50 to 1.50)	1.00 (0.35 to 2.85)
Stent thrombosis§	0/308	0/318	NA	NA
Composite of major ischemic events¶	8 (1.6)	8 (1.8)	0.13 (–1.52 to 1.78)	1.23 (0.48 to 3.10)
Composite of any ischemic events‖	15 (3.0)	11 (2.4)	–0.55 (–2.63 to 1.53)	1.40 (0.67 to 2.93)
Safety**				
Major bleeding or clinically relevant nonmajor bleeding	23 (4.7)	70 (14.2)	9.58 (5.92 to 13.24)	0.34 (0.22 to 0.53)
Fatal bleeding	0	0	NA	NA
Major bleeding	6 (1.3)	22 (4.5)	3.12 (0.99 to 5.25)	0.32 (0.14 to 0.73)
Clinically relevant nonmajor bleeding	18 (3.5)	52 (10.6)	7.08 (3.89 to 10.27)	0.36 (0.21 to 0.59)
Any bleeding	49 (9.9)	99 (20.1)	10.20 (5.73 to 14.67)	0.48 (0.35 to 0.67)
Intracranial hemorrhage	2 (0.4)	3 (0.6)	0.21 (–0.65 to 1.06)	0.70 (0.12 to 4.16)
Gastrointestinal hemorrhage	8 (1.6)	13 (2.6)	1.03 (–0.75 to 2.81)	NR‡

* The number of patients with events and estimated percentages were calculated with the use of a Kaplan–Meier survival analysis of data in the intention-to-treat population; therefore, the percentages may not reflect the ratio of the numerator and the denominator. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons, and therefore inferences drawn from these intervals may not be reproducible. NA denotes not available.

† Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (according to the International Society on Thrombosis and Haemostasis [ISTH] definition). P<0.001 for superiority of edoxaban monotherapy to dual antithrombotic therapy.

‡ Hazard ratios were not reported (NR) for outcomes that did not appear to satisfy the proportional-hazards assumption.

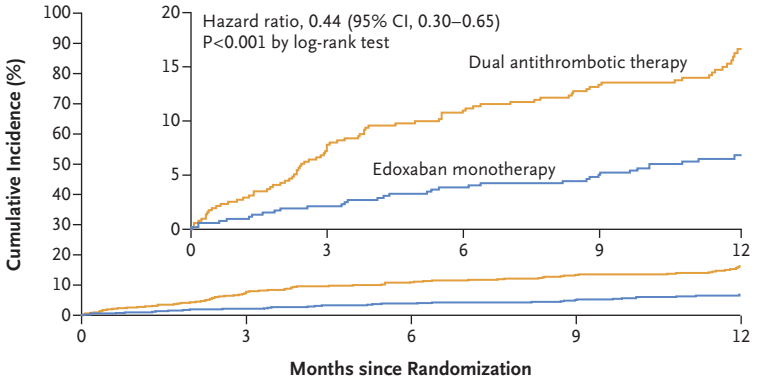
§ Stent thrombosis (definite or probable) was assessed in patients who underwent coronary stenting.

¶ The composite of major ischemic events was defined as a composite of death from any cause, myocardial infarction, ischemic stroke, or systemic embolism.

‖ The composite of any ischemic events was defined post hoc as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic embolism, or unplanned urgent revascularization.

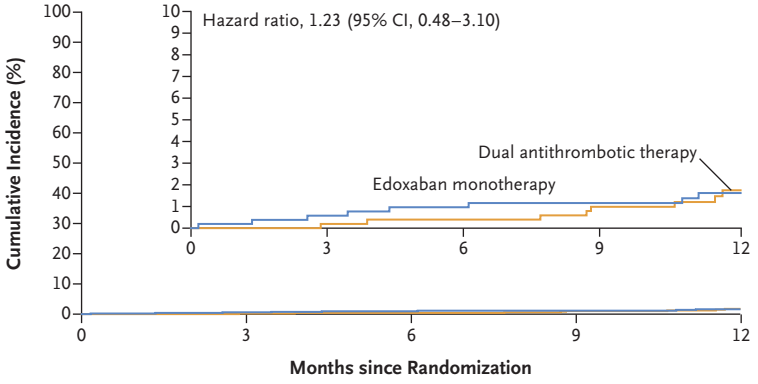
** Bleeding events were assessed primarily according to the ISTH definition. Bleeding was also classified according to the Bleeding Academic Research Consortium definition and the Thrombolysis in Myocardial Infarction definition (see Table S4).

A Net Adverse Clinical Events



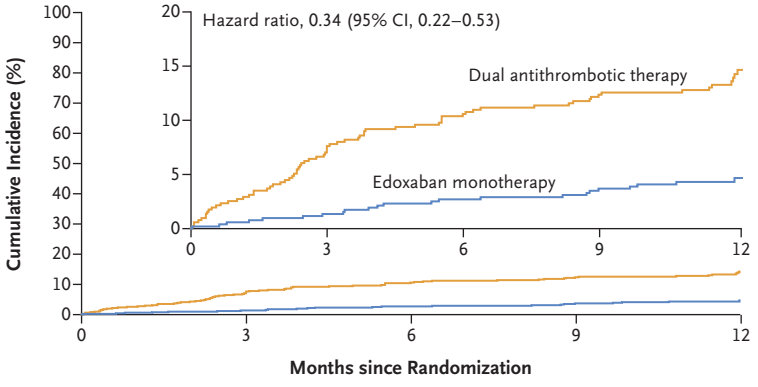
No. at Risk					
Dual antithrombotic therapy	516	475	452	437	391
Edoxaban monotherapy	524	508	495	487	409

B Major Ischemic Events



No. at Risk					
Dual antithrombotic therapy	516	510	505	499	446
Edoxaban monotherapy	524	516	510	506	428

C Major Bleeding or Clinically Relevant Nonmajor Bleeding



No. at Risk					
Dual antithrombotic therapy	516	475	453	441	393
Edoxaban monotherapy	524	512	500	492	414

Figure 2 (facing page). Kaplan–Meier Analysis of the Primary Outcome and Key Ischemic and Bleeding Events in the Intention-to-Treat Population.

Shown are the incidence at 12 months of net adverse clinical events (primary outcome), defined as a composite of death from any cause, myocardial infarction, stroke, systemic thromboembolic event, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding (as defined by the International Society on Thrombosis and Haemostasis [ISTH]) (Panel A); a composite of major ischemic events (death from any cause, myocardial infarction, ischemic stroke, or systemic embolism (Panel B); and major bleeding or clinically relevant nonmajor bleeding (as defined by the ISTH) (Panel C). The percentages are Kaplan–Meier estimates. The hazard ratios are for edoxaban monotherapy as compared with dual antithrombotic therapy. In each panel, the inset shows the same data on an expanded y axis.

30 mg were used in 57.5% and 42.5% of the enrolled patients, respectively. In the dual antithrombotic therapy group, 319 patients (61.8%) received aspirin, and 195 (37.8%) received clopidogrel.

Details regarding medication use at randomization and during follow-up are provided in Table S3. Ascertainment of the primary and secondary outcomes at 12 months was completed in 98.2% of the patients, and data on vital status were obtained for all the patients (Fig. 1).

PRIMARY AND SECONDARY OUTCOMES

At 12 months after randomization, a primary-outcome event had occurred in 34 of 524 patients (Kaplan–Meier estimate, 6.8%) in the edoxaban monotherapy group and in 79 of 516 patients (Kaplan–Meier estimate, 16.2%) in the dual antithrombotic therapy group (hazard ratio, 0.44; 95% confidence interval [CI], 0.30 to 0.65; P<0.001) (Table 2 and Fig. 2A). The number needed to treat to avoid one primary-outcome event at 12 months with edoxaban monotherapy as compared with dual antithrombotic therapy was 10.6 (95% CI, 6.1 to 15.2).

The cumulative incidence of individual components of the primary outcome appeared to be similar in the two groups. The cumulative incidence of major ischemic events (a composite of death, myocardial infarction, ischemic stroke, or systemic embolism) at 12 months was estimated to be 1.6% in the edoxaban monotherapy group and 1.8% in the dual antithrombotic therapy group (hazard ratio, 1.23; 95% CI, 0.48 to 3.10) (Table 2 and Fig. 2B). The cumulative incidence of any ischemic event at 12 months also appeared to be similar in the trial groups.

The estimated cumulative incidence of major bleeding or clinically relevant nonmajor bleeding at 12 months was 4.7% in the edoxaban monotherapy group and 14.2% in the dual antithrombotic therapy group (hazard ratio, 0.34; 95% CI, 0.22 to 0.53) (Table 2 and Fig. 2C). The estimated cumulative incidence of major bleeding at 12 months was 1.3% in the edoxaban monotherapy group and 4.5% in the dual antithrombotic therapy group (hazard ratio, 0.32; 95% CI, 0.14 to 0.73). Detailed information regarding the severity of bleeding according to different bleeding criteria and bleeding sites is summarized in Table S4.

SENSITIVITY AND SUBGROUP ANALYSES

Overall findings for the primary outcome and key major ischemic and bleeding events in the per-protocol population were consistent with those in the intention-to-treat population (Table S5 and Fig. S1). With respect to the primary outcome, the treatment effect of edoxaban monotherapy as compared with dual antithrombotic therapy appeared to be consistent across all prespecified subgroups (Fig. 3). In a post hoc analysis, the treatment effect with respect to a composite of major ischemic events (Fig. S2) and a composite of major bleeding or clinically relevant nonmajor bleeding (Fig. S3) was similar across all prespecified subgroups. Findings for the primary outcome were consistent irrespective of past use of antithrombotic therapy, the appropriateness of the edoxaban dose, and the combination of antiplatelet agents (Fig. S4).

DISCUSSION

In this multicenter, randomized trial that assessed two long-term antithrombotic strategies in patients with atrial fibrillation and stable coronary artery disease, the risk of the primary net clinical outcome — a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor

Subgroup	Patients	Edoxaban Monotherapy	Dual Antithrombotic Therapy	Hazard Ratio (95% CI)
	%	*estimated %*		
Overall	100	6.8	16.2	0.44 (0.30–0.65)
Age				
≥75 yr	42.2	5.3	18.7	0.31 (0.17–0.59)
<75 yr	57.8	7.8	14.2	0.56 (0.35–0.92)
Sex				
Male	77.1	6.0	17.4	0.37 (0.23–0.58)
Female	22.9	9.4	12.1	0.81 (0.39–1.72)
Creatinine clearance				
≥50 ml/min	75.8	5.2	14.5	0.41 (0.25–0.66)
<50 ml/min	24.2	12.1	21.7	0.53 (0.28–0.99)
Type of most recent revascularization				
Percutaneous coronary intervention	59.1	6.4	17.1	0.43 (0.26–0.70)
CABG	6.5	7.4	20.6	0.46 (0.13–1.67)
Medical treatment alone	34.3	7.1	13.7	0.50 (0.26–0.99)
Edoxaban dose				
60 mg/day	57.5	6.5	16.4	0.46 (0.28–0.75)
30 mg/day	42.5	7.5	16.1	0.44 (0.24–0.79)
CHA_2DS_2-VASc score				
≥4	67.3	6.1	16.2	0.39 (0.24–0.63)
<4	32.7	8.2	16.3	0.57 (0.31–1.05)
HAS-BLED score				
≥3	31.8	7.7	15.1	0.48 (0.25–0.93)
<3	68.2	6.5	16.9	0.43 (0.27–0.69)

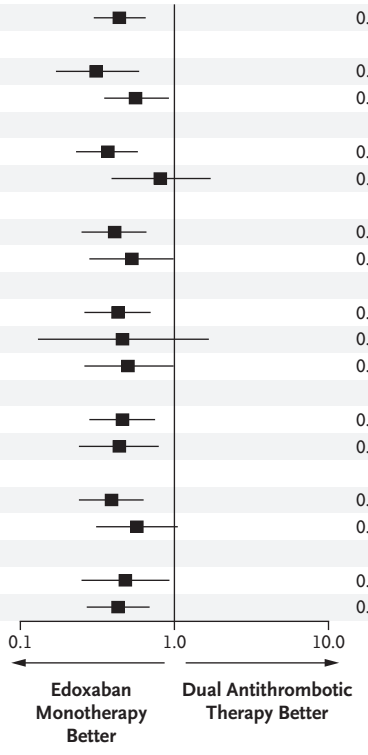


Figure 3. Subgroup Analyses of the Primary Outcome in the Intention-to-Treat Population.

Shown are hazard ratios (edoxaban monotherapy vs. dual antithrombotic therapy) for the primary outcome according to prespecified subgroups. The CHA_2DS_2-VASc score is a measure of the risk of stroke among persons with atrial fibrillation (scores range from 0 to 9, with higher scores indicating a greater risk). The HAS-BLED score is a measure of the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy (scores range from 0 to 9, with higher scores indicating a greater risk). The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

bleeding — was lower with standard-dose edoxaban monotherapy than with dual antithrombotic treatment with edoxaban plus a single antiplatelet agent. This result appeared to be driven mainly by a lower incidence of bleeding events. The incidence of ischemic events and mortality appeared to be similar in the trial groups.

The antithrombotic strategy recommended by current guidelines for use immediately after PCI or an acute coronary syndrome in patients with atrial fibrillation has been supported by multiple randomized trials.[5-8] These trials assessed the combination of standard-dose direct oral anticoagulants for the prevention of stroke in patients with atrial fibrillation who were receiving antiplatelet therapy (with variability in treatment duration and various P2Y12 inhibitors). These trials were designed to assess safety outcomes (i.e., bleeding events) but not to reliably assess between-group differences in ischemic outcomes. Nevertheless, clinical guidelines recommend the use of direct oral anticoagulants plus a P2Y12 inhibitor after PCI or an acute coronary syndrome as the preferred antithrombotic regimen in such high-risk patients.[9-14]

By contrast, few clinical trials have included patients with atrial fibrillation and concomitant coronary artery disease in the chronic stabilized phase.[15,16] Given that the relative risk of ischemic and bleeding events after PCI or an acute coronary syndrome is temporally dynamic,[28] a different antithrombotic strategy with the clinical imperative of lowering the risk of bleeding while preserving ischemic benefit would be needed for

this group of patients. The OAC-ALONE (Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stent) trial failed to show noninferiority of oral anticoagulants alone as compared with combined use of oral anticoagulants and antiplatelet therapy.[15] Furthermore, warfarin was predominantly used, and results of the trial were inconclusive owing to its premature termination. The AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban) trial showed that rivaroxaban monotherapy was noninferior to combination therapy with rivaroxaban plus antiplatelet therapy for ischemic outcomes and superior for bleeding outcomes.[16] However, although the AFIRE trial included more patients than our trial and had a different primary end point, it evaluated predominantly low-risk patients and used a locally approved but nonstandard dose of rivaroxaban (15 mg or 10 mg once daily with dose-reduction criteria), which limits the generalizability of the trial results to other clinical practice settings.

Similar to previous trials, the current trial showed that edoxaban monotherapy was superior to dual antithrombotic therapy with respect to the cumulative incidence of net adverse clinical events at 12 months. Our approach provided a clinical benefit of fewer bleeding events without an apparent difference in major ischemic events between the trial groups. However, none of the available trials, including the EPIC-CAD trial, were designed to assess meaningful differences in clinically relevant ischemic events and mortality. Nonetheless, given that none of the contemporary trials that assessed the appropriate antithrombotic strategy in patients with atrial fibrillation and coronary artery disease enrolled a large enough sample to detect a meaningful reduction in the incidence of ischemic events,[5-8,15,16] conducting new trials with a sufficient sample size to determine the true efficacy of an antithrombotic strategy would not be feasible (see the Supplementary Appendix).

Several limitations of the current trial should be considered. First, our trial had an open-label design that entailed a risk of reporting bias or ascertainment bias. However, we minimized the risk of bias by conducting an outcome analysis with precisely defined prespecified criteria and using an independent committee to adjudicate the events. Second, our trial was not designed to detect potential differences in less common but clinically relevant ischemic outcomes. Third, our trial used net adverse clinical events as the primary outcome. Because of the relatively higher incidence of bleeding events than ischemic events, the use of net clinical outcomes might bias results in favor of the less potent antithrombotic strategy.[29,30] However, this aggregate of ischemic and bleeding outcomes is important to patients and clinicians in shared decision making about the appropriate antithrombotic strategy. In addition, major bleeding or clinically relevant nonmajor bleeding events have been widely adopted as an end point in relevant clinical trials.[7,8] Fourth, dynamic changes in risks of bleeding and ischemic events (as assessed with the HAS-BLED score and the CHA_2DS_2-VASc score, respectively) over time were not captured in our trial.[12,31] Fifth, our trial includes an East Asian population, which is known to have a different propensity for ischemic or bleeding complications than Western populations,[32,33] and women were underrepresented in our trial population, which may limit the generalizability of our findings (Table S6).

In this trial involving patients with atrial fibrillation and stable coronary artery disease, edoxaban monotherapy was associated with a lower risk of a composite of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding than dual antithrombotic therapy at 12 months.

Supported by the CardioVascular Research Foundation, Daiichi Sankyo, and Daewoong Pharmaceutical.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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